

***Endovascular
treatments for
intracranial
aneurysms***

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Assessment Report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Contents

Contents	iii
List of Tables	v
List of Figures	viii
Executive Summary	ix
Introduction	1
Background	2
Endovascular treatments for intracranial aneurysm	8
Existing procedures	12
Comparator.....	13
Choosing between endovascular and surgical treatments.....	13
Clinical need/burden of disease.....	17
Marketing status of the device/technology.....	19
Current reimbursement arrangement.....	19
Approach to assessment	20
Review of literature.....	20
Inclusion criteria.....	21
Methods of the review.....	22
Description and methodological quality of included studies.....	23
Expert advice	23
Results of assessment	25
Studies included in the review	25
Ruptured aneurysms	43
Comparison 1: Endovascular coiling versus surgical clipping.....	43
Comparison 2: Endovascular versus surgical treatment.....	66
Comparison 3: Endovascular versus conservative treatment.....	71
Unruptured aneurysms.....	73
Comparison 1: Endovascular coiling versus surgical clipping.....	73
Comparison 2: Endovascular versus surgical treatment.....	77
Comparison 3: Endovascular versus conservative treatment.....	82
Economic considerations.....	83
Discussion	90
Conclusions	94
Recommendation	95
Appendix A MSAC terms of reference and membership	96
Appendix B Advisory Panel	98
Appendix C Case reports	100
Ruptured aneurysms	100
Unruptured aneurysms	102

Appendix D Grading and outcome scales	104
Abbreviations	105
References	107

List of Tables

Table 1: Risk of rupture for unruptured intracranial aneurysms.....	8
Table 2: Endovascular devices for aneurysm treatment registered on ARTG.....	19
Table 3: Inclusion and exclusion criteria	21
Table 4: Evidence dimensions.....	23
Table 5: Designations of levels of evidence*	23
Table 6: Summary of studies included in the review.....	26
Table 7: Allocation and follow-up in non-randomised comparative studies of ruptured aneurysms	30
Table 8: Allocation and follow-up in non-randomised comparative studies of unruptured aneurysms.....	33
Table 9: Allocation and follow-up in non-randomised comparative studies of ruptured and unruptured aneurysms.....	34
Table 10: Allocation and follow-up in non-randomised comparative studies of endovascular versus surgical treatments.....	36
Table 11: Allocation and follow-up in non-randomised comparative studies of endovascular versus conservative treatments	38
Table 12: Neuropsychological tests employed in randomised and non-randomised comparative studies.....	40
Table 13: Allocation and follow-up in included registry studies	42
Table 14: Safety outcomes in patients undergoing coiling or clipping for ruptured aneurysms.....	43
Table 15: Neuropsychological outcomes in patients undergoing coiling or clipping for ruptured aneurysms in Koivisto et al. (2000)	44
Table 16: Crossover and retreatment for patients undergoing coiling or clipping for ruptured aneurysms.....	45
Table 17: Functional outcomes in patients undergoing coiling or clipping for ruptured aneurysms	46
Table 18: Causes of death at follow-up in Molyneux et al. (2005).....	47
Table 19: Angiographic outcomes in patients undergoing coiling or clipping for ruptured aneurysms	48
Table 20: Perioperative mortality rates in patients undergoing coiling or clipping for ruptured aneurysms.....	49
Table 21: Vasospasm in patients undergoing coiling or clipping for ruptured aneurysms.....	50
Table 22: Intraoperative rupture in patients undergoing coiling or clipping for ruptured aneurysms	50
Table 23: Delayed ischaemic neurological deficit in patients undergoing coiling or clipping for ruptured aneurysms.....	51

Table 24: Intracranial infarction in patients undergoing coiling or clipping for ruptured aneurysms	51
Table 25: Thromboembolic complications in patients undergoing coiling or clipping for ruptured aneurysms.....	52
Table 26: Procedure-related complications in patients undergoing coiling or clipping for ruptured aneurysms.....	52
Table 27: Neurological complications in patients undergoing coiling or clipping for ruptured aneurysms.....	53
Table 28: Conversions to surgery in patients undergoing coiling for ruptured aneurysms.....	53
Table 29: Degree of aneurysm occlusion in patients undergoing coiling or clipping for ruptured aneurysms.....	54
Table 30: Impairment and disability at discharge in patients undergoing coiling or clipping for ruptured aneurysms.....	56
Table 31: Impairment and disability at follow-up in patients undergoing coiling or clipping for ruptured aneurysms.....	58
Table 32: Aneurysm recurrence or enlargement in patients undergoing coiling or clipping for ruptured aneurysms.....	59
Table 33: Aneurysm retreatment in patients undergoing coiling or clipping for ruptured aneurysms	60
Table 34: Aneurysm rebleeding in patients undergoing coiling or clipping for ruptured aneurysms	60
Table 35: Mortality at follow-up in patients undergoing coiling or clipping for ruptured aneurysms	61
Table 36: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Bellebaum et al. (2004).....	62
Table 37: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Chan et al. (2002).....	63
Table 38: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Fontanella et al. (2003).....	64
Table 39: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Hadjivassilou et al. (2001).....	65
Table 40: Perioperative mortality in patients undergoing endovascular or surgical treatments for ruptured aneurysms.....	66
Table 41: Intraoperative rupture in patients undergoing endovascular or surgical treatments for ruptured aneurysms	67
Table 42: Impairment and disability in patients undergoing endovascular, surgical or conservative treatment for ruptured aneurysms.....	70

Table 43: Perioperative mortality in patients undergoing endovascular or conservative treatment for ruptured aneurysms.....	71
Table 44: Perioperative mortality in patients undergoing coiling or clipping for unruptured aneurysms.....	73
Table 45: Intraoperative rupture in patients undergoing coiling or clipping for unruptured aneurysms.....	73
Table 46: Intracranial or ischaemic infarction in patients undergoing coiling or clipping for unruptured aneurysms.....	74
Table 47: Procedure-related complications in patients undergoing coiling or clipping for unruptured aneurysms.....	74
Table 48: Conversions to surgery in patients undergoing endovascular treatment for unruptured aneurysms.....	75
Table 49: Length of hospital stay in patients undergoing coiling or clipping for unruptured aneurysms.....	75
Table 50: Degree of aneurysm occlusion in patients undergoing coiling or clipping for unruptured aneurysms.....	76
Table 51: Degree of aneurysm occlusion in patients undergoing endovascular or surgical treatment for unruptured aneurysms.....	78
Table 52: Perioperative mortality in patients undergoing endovascular or surgical treatment for unruptured aneurysms.....	80
Table 53: Complications in patients undergoing endovascular or surgical treatment for unruptured aneurysms in Barker et al. (2004).....	80
Table 54: Length of hospital stay in patients undergoing endovascular or surgical treatment for unruptured aneurysms.....	81
Table 55: Death or discharge to nursing home in patients undergoing endovascular or surgical treatment for unruptured aneurysms.....	81
Table 56: Sources for the costs associated with the treatment of ruptured and unruptured aneurysms.....	85
Table 57: Unit costs for the base case for treatment of ruptured aneurysms.....	86
Table 58: Unit costs for the base case for the treatment of unruptured aneurysms.....	89
Table D1: Hunt and Hess Classification of Subarachnoid Haemorrhage.....	104
Table D2: Glasgow Outcome Scale.....	104
Table D3: Modified Rankin Scale.....	104

List of Figures

Figure 1: Cerebral arteries	4
Figure 2: Coils being placed into an aneurysm	10
Figure 3: Titanium clips for aneurysm surgery and a clipped aneurysm	12
Figure 4: Clinical decision pathway for the treatment of intracranial aneurysms	15

Executive Summary

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team of evaluators was engaged to conduct a systematic review of literature on endovascular treatments for intracranial aneurysms. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of endovascular treatments for intracranial aneurysms

Background

At least 75% of all spontaneous subarachnoid haemorrhages are the result of rupture of an intracranial aneurysm (small weaknesses in intracranial blood vessels). While treatment and management is essentially for the effects due to the underlying subarachnoid haemorrhage, the aneurysm must be occluded in some way. Endovascular approaches have become alternatives to surgical management of intracranial aneurysms. The most common form of endovascular treatment is coiling where the aneurysm is filled with platinum coils to prevent further, or future, rupture and bleeding.

Objectives

The objective of this committee was to assess the safety, effectiveness and cost-effectiveness of endovascular approaches (mostly coiling) compared with surgical approaches (mostly clipping) for treating ruptured intracranial aneurysms. Also, to assess endovascular approaches (mostly coiling) compared with surgical approaches (mostly clipping) or conservative treatment for unruptured aneurysms.

Methods

The evidence for endovascular treatment of intracranial aneurysms was systematically assessed. MEDLINE, EMBASE, and a number of other databases were searched from January 1990 to July 2005. Results for ruptured and unruptured aneurysms were analysed and presented separately.

Results

A total of 182 studies were included. For ruptured aneurysms, 34 comparative studies (including two randomised controlled trials (RCTs) of coiling versus clipping) were located. For unruptured aneurysms, 14 comparative studies (no RCTs) were identified. Thus most of the evidence base consisted of lower level evidence with very little data available for some comparisons such as endovascular versus conservative treatment for unruptured aneurysms.

Both RCTs recruited patients who were suitable for either endovascular or surgical treatment and so these results are applicable only to certain groups of patients with ruptured aneurysms.

Ruptured aneurysms

Safety

Complication rates were generally similar for coiling or clipping in both the randomised and non-randomised comparative studies, although the rates of vasospasm and seizure were significantly higher for clipping than for coiling.

Effectiveness

In one large RCT, functional outcome was significantly better for coiling than for clipping (relative risk reduction of 23.9% (95% CI 12.4 to 33.9 in Modified Rankin score 3-6 (death or dependency)); absolute risk difference of 7% in favour of coiling). This RCT also found a small but significant survival advantage (up to seven years follow-up). The other smaller RCT found no differences in functional outcome (measured by the Glasgow Outcome Score) between coiling and clipping. Coiling may need more retreatment than clipping.

Cost effectiveness

Assuming a 7% risk difference in favour of coiling for functional outcome and a similar length of hospital stay, the incremental cost effectiveness ratio (for each additional death or dependency avoided) was estimated to be \$43 414 to \$57 770. In various sensitivity analyses, this ranged from about \$18 000 to \$136 000.

Unruptured aneurysms

For unruptured aneurysms, results were only available from nonrandomised studies. These indicated similar outcomes for coiling and clipping, although some studies reported significantly higher complication rates and hospital stay for clipping.

Conclusions

In certain types of patients, coiling for ruptured aneurysms is more effective than surgical clipping, and for other patients clipping is the more suitable choice. Therefore it is imperative for treatment to be optimised for each patient, ideally through assessment in a multidisciplinary setting which offers expertise in both coiling and clipping.

Compared with clipping, coiling is more expensive but it has a relatively low cost per death or dependency avoided. No conclusions can be drawn about the effect of aneurysm location or size or the patient's preoperative neurological status on outcome.

For unruptured aneurysms, the evidence is less clear about whether coiling is more effective than clipping.

Recommendation

Available evidence suggests that endovascular treatment of intracranial aneurysms using coils is as safe and effective as surgical clipping for appropriately selected patients. The procedure is also cost effective when compared to surgery. MSAC recommended public funding for this procedure.

The Minister for Health and Ageing accepted this recommendation on 6 June 2006.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of endovascular therapeutic technologies for intracranial aneurysms. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are given in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for endovascular treatments in treating intracranial aneurysms.

Background

Endovascular treatments for intracranial aneurysms include coiling, stenting and balloon occlusion, alone or in combination. Endovascular approaches were originally developed to provide treatment options for patients who were unsuitable for surgical management of intracranial aneurysms but have been accepted in some settings as an alternative to surgical treatment for many aneurysms (Dovey *et al.* 2001; Maurice-Williams & Lafuente 2003) and in some centres as the treatment of choice (Johnston *et al.* 2002). The most commonly used endovascular treatment for intracranial aneurysm is coiling with detachable platinum coils, in which the aneurysm is filled with coils to remove it from the circulation with the aim of preventing future rupture. Stents and sometimes balloons are also used, often in combination with coiling, to treat aneurysms which could not be adequately treated with coils alone because of the location, size or morphology of the aneurysm. Occasionally aneurysms, or the parent artery rather than the aneurysm sac, are occluded with liquid embolic material.

Intracranial aneurysms

Intracranial aneurysms are dilations of the intracranial vasculature of pathological or traumatic origin which are prone to rupture (Vega, Kwoon & Lavine 2002; Liebeskind 2004; Soliman 2004). Spontaneous rupture of intracranial aneurysms most commonly causes subarachnoid haemorrhage (SAH), which may lead to stroke, coma and sometimes death. Intracranial aneurysms can occur in any part of the intracranial vasculature but are most common in the walls of the major intracranial arteries (Vega, Kwoon & Lavine 2002).

Pathophysiology of intracranial aneurysms

Intracranial aneurysms result from structural defects of the cerebrovasculature with multiple possible causes which are not clearly understood (Krex, Schackert & Schackert 2001). A normal cranial artery wall consists of an innermost endothelial layer – the intima; a middle layer of smooth muscle – the tunica media; and an outer layer of connective tissue – the adventitia. The intima and tunica media are separated by an elastic membrane. Aneurysms typically occur when the internal elastic membrane of the artery wall is either damaged or absent and the tunica media also has defects (Krex, Schackert & Schackert 2001; Vega, Kwoon & Lavine 2002). Haemodynamic stress causes formation and growth of aneurysms and thrombosis, and can result in aneurysm rupture (Inci & Spezler 2000; Krex, Schackert & Schackert 2001). There may also be atherosclerotic changes in the parent artery (Krex, Schackert & Schackert 2001). It is probable that the additional haemodynamic stress occurring at arterial bifurcations (resulting from turbulence, abnormal shear stresses and changes in normal arterial wall architecture) account for the large number of aneurysms which occur at bifurcations (Rhoton 2002). Vasospasm is a common complication of aneurysm rupture which causes significant SAH-related morbidity and mortality. Vasospasm occurs subsequent to SAH when an inflammatory reaction to the bleeding causes narrowing and hardening of the vessel walls leading to ischaemic events (Liebeskind 2004). The effect of endovascular treatments on the occurrence (or prevention) of vasospasm is not clear (Dovey *et al.* 2001).

Types of aneurysm

Aneurysms are classified as either true or false. True aneurysms involve the outpouching of all layers of the vessel wall and include saccular and fusiform aneurysms. False aneurysms occur when the wall of the artery is disrupted and a second lumen is created contained either by a layer of the arterial wall or a haematoma. Infectious or mycotic, traumatic and dissecting aneurysms are considered to be false aneurysms (Lazinski *et al.* 2000).

True aneurysms

The most common type of aneurysm is the saccular aneurysm, which is a rounded berry-like outpouching arising at arterial bifurcations (Vega, Kwoon & Lavine 2002). Up to 90% of aneurysms are saccular aneurysms and the majority (85% to 95%) are found in the anterior circulation. Around 20% to 30% of patients have multiple saccular aneurysms (Vega, Kwoon & Lavine 2002). Rhoton (2002) notes four anatomical characteristics of saccular aneurysms: they arise at the site of a branching of the parent artery, either at a side branch or a bifurcation of the main arterial trunk; they arise at a turn or curve in the artery which causes alterations in the local haemodynamic stresses at that point; they point in the direction the blood would flow if not for the curve or turn in the artery (i.e. in the direction of maximal haemodynamic thrust in the parent artery); there are a constantly occurring set of perforating arteries at the site of each aneurysm.

Around 7% of aneurysms are fusiform atherosclerotic aneurysms (Liebeskind 2004). These aneurysms are characterised by stretching and elongation of the arterial wall from severe atherosclerosis, usually in the proximal arteries (Liebeskind 2004; Soliman 2004). They are primarily found in the vertebrobasilar system and may not have a true aneurysm neck (Liebeskind 2004). They are more common in older patients and may exert a mass effect putting pressure on brain structures in the immediate area causing brainstem compression and cranial neuropathies or blocking the flow of cerebrospinal fluid out of the brain (Liebeskind 2004). Fusiform aneurysms often contain clots and these may thrombose resulting in infarct (Soliman 2004).

False aneurysms

Dissecting aneurysms result in the creation of a false lumen from arterial necrosis or a traumatic arterial tear (Vega, Kwoon & Lavine 2002). Dissecting aneurysms tend to arise on straight, non-branching sections of arterial wall with the aneurysm sac pointing in the same direction as the blood flow (Rhoton 2002). Infectious and traumatic aneurysms are typically dissecting in nature.

Infectious or mycotic aneurysms arise on the distal branches of the middle intracranial artery in around 75% to 80% of cases (van Gijn & Rinkel 2001) and account for less than 1% of all aneurysms (Liebeskind 2004). These aneurysms are embolic in origin and can occur in patients with subacute bacterial endocarditis who suffer cardioembolism of septic material and other patients with congenital heart disease. These aneurysms may also occur in the basal circulation in patients with meningitis and have also been documented in children and adults with HIV (van Gijn & Rinkel 2001).

Aneurysms of traumatic origin are rare (less than 1%; Aarabi 1995, Krex, Schackert & Schackert 2001) and occur secondary to skull fracture from penetrating or closed head injury. Aneurysms may also arise at the skull base after intramural haemorrhage leading to

the compression of cranial nerves and possibly distal embolisation. Carotid-cavernous fistulae may result from the rupture of the internal carotid artery after trauma (Liebeskind 2004).

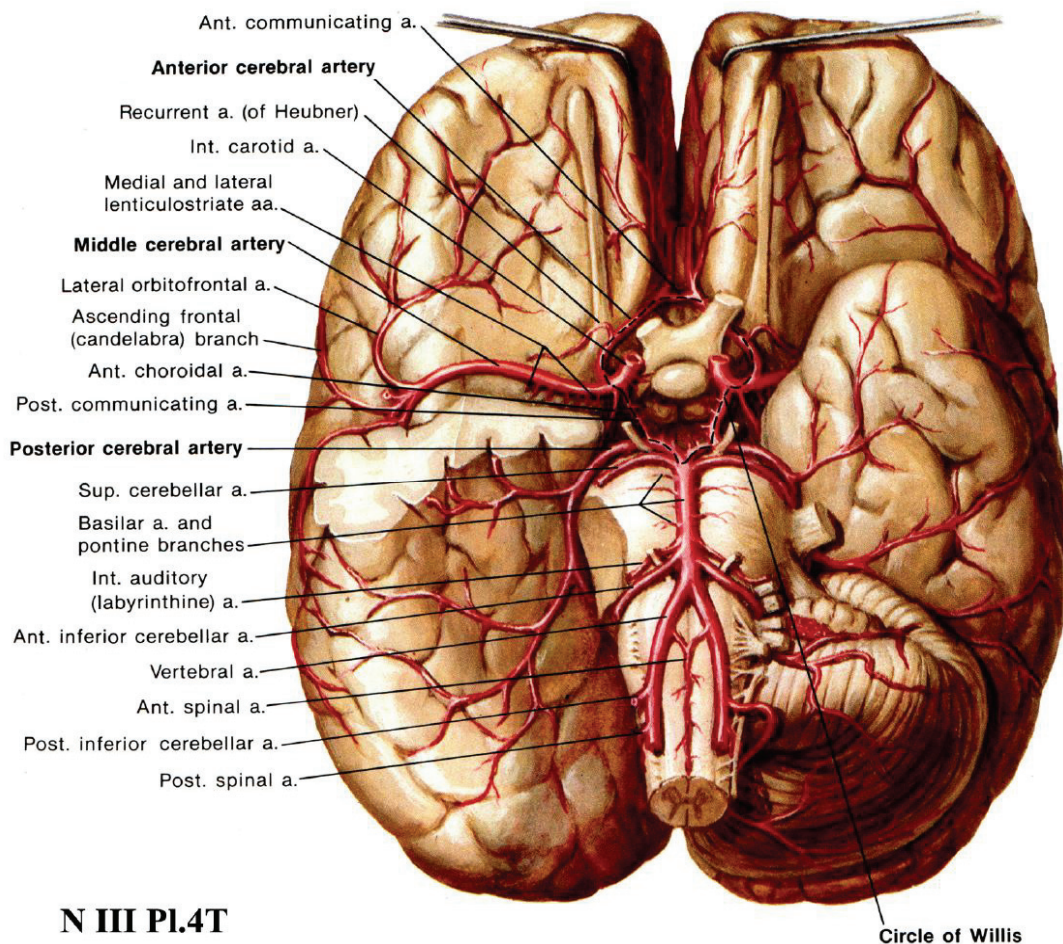
Location of aneurysms

The majority (around 85%) of all aneurysms arise in the anterior circulation with the remainder in the posterior (vertebrobasilar) circulation. Most saccular aneurysms arise on the Circle of Willis or in the middle intracranial artery bifurcation (Vega, Kwoon & Lavine 2002; See Figure 1).

In the anterior circulation, around 30% to 35% of aneurysms arise in the anterior communicating artery, with another 30% to 35% on the internal carotid artery, and around 20% at the middle intracranial artery bifurcation (Rhoton 2002; Liebeskind 2004; Soliman 2004).

In the posterior circulation around two thirds of aneurysms arise at the basilar artery bifurcation or basilar tip (i.e. 5% of all aneurysms; Rhoton 2002), with the remainder arising in other posterior fossa vessels such as the superior cerebellar artery, vertebral artery at the origin of the posterior inferior cerebellar artery and, rarely, at the anterior inferior cerebellar artery (Liebeskind 2004; Soliman 2004).

Figure 1: Cerebral arteries



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Source: <http://cns.georgetown.edu/medneuro/lab1/secii10.jpg>

Size and morphology of aneurysms

Aneurysms are also classified according to their size, with giant aneurysms being greater than 25mm in diameter, large aneurysms greater than 10mm in diameter and small aneurysms having a dome size of less than 10mm. The neck of the aneurysm is considered small if it is less than 4mm, and wide if it is greater than 4mm or the neck to body ratio is greater than 1:2 (American Society of Interventional and Therapeutic Neuroradiology 2001).

Risk factors for aneurysms

Intracranial aneurysms have been found to be associated with hypertension, ischaemic heart disease, diabetes mellitus, hyperlipidaemia, arteriosclerosis, smoking, alcohol consumption, and some medications (Krex, Schackert & Schackert 2001; Bendo 2002; Vega, Kwoon & Lavine 2002; Weir 2002; Feigin *et al.* 2005a; Feigin *et al.* 2005b). They have also been associated with a number of inherited disorders and syndromes including Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease, Noonan's syndrome, and neurofibromatosis types I and II, although the strength and nature of these relationships is not entirely clear (Krex, Schackert & Schackert 2001; van Gijn & Rinkel 2001; Vega, Kwoon & Lavine 2002; Weir 2002; Mitchell *et al.* 2004). There appears to be an increased risk in people with first and possibly second degree relatives with symptomatic aneurysm but the magnitude of this risk is unclear (Wardlaw & White 2000).

Unruptured aneurysms

Unruptured aneurysms are defined as “those lesions with no historical or pathological evidence of a complete breach through the artery walls” (Weir 2002). There is considerable uncertainty regarding the prevalence and incidence of unruptured aneurysms, the benefit of screening for unruptured aneurysms, factors associated with the risk of rupture, and the appropriate treatment modalities for individual patients or groups of patients with a particular aneurysm characteristic or risk factor.

For these reasons unruptured aneurysms present a management challenge. The management of a patient with an unruptured aneurysm may depend on whether the aneurysm is symptomatic or asymptomatic, the size and location of the aneurysm, a history of previous SAH or previous ruptured aneurysm, and the age of the patient; all of which may impact on the likelihood that the aneurysm will rupture. In order to recommend active treatment of any kind the risk of rupture needs to outweigh the risks associated with the treatment.

Prevalence of unruptured aneurysms

The prevalence of unruptured aneurysms has been estimated from data gathered at autopsy and from studies using angiography. However, estimates differ depending on which source of data is used. Retrospective autopsy studies may underestimate aneurysm rates because of their reliance on retrospective data collection, whereas prospective autopsy studies may produce lower estimates than prospective angiography studies because patients with a familial history of SAH, polycystic kidney disease or atherosclerosis are screened more often for aneurysm than other patients (Rinkel *et al.* 1998). Keeping these issues in mind, the prevalence of unruptured aneurysms has been estimated at 0.4% (95% CI: 0.4 to 0.5) in retrospective autopsy studies, 3.6% (95% CI: 3.1 to 4.1) in prospective

autopsy studies, 3.7% (95% CI: 3.0 to 4.4) in retrospective angiography studies, and 6.0% (95% CI: 5.3 to 6.8) in prospective angiography studies (Rinkel *et al.* 1998). Taking these difference into account, a prevalence rate of between 3% and 6% is usually quoted (White & Wardlaw 2003; Donnan & Davis 2005) although some authors quote lower rates of between 1% and 2% (probably basing their estimates on autopsy data) (Bladin 2000; Dorsch & Jacobson 2000; Weir 2002; Winn *et al.* 2002; Mitchell *et al.* 2004).

The prevalence of unruptured aneurysm has been found to increase with age and vary in different populations, being higher among women, the Japanese and Finnish populations, in patients who are currently smoking, in patients with autosomal polycystic kidney disease (prevalence of aneurysms estimated to be 10-15%), and in patients with first or second degree relatives with aneurysm (9.8% in families with two or more affected members and 4.5% for families with one affected member) (Wardlaw & White 2000; Mitchell *et al.* 2004). The prevalence of unruptured intracranial aneurysm has been estimated to be around 2% for patients with no known risk factors (Rinkel *et al.* 1998).

Rupture of aneurysms

Rupture of intracranial aneurysm most commonly causes SAH - bleeding into the subarachnoid space in the brain. Around 70% to 80% of spontaneous SAH are caused by the rupture of intracranial aneurysms (Liebeskind 2004). SAH is characterised by a history of unusually severe headache of sudden onset (Bendo 2002). In approximately 50% of patients who suffer a SAH, headache onset after aneurysm rupture is immediate; although a more gradual onset of seconds to minutes has also been described. Furthermore, only around 10% of patients with a history of explosive headache are found to have SAH. Other presenting symptoms of SAH may be epileptic seizure, confusion, focal deficits, and coma (van Gijn & Rinkel 2001). To confirm a diagnosis of SAH patients need to have a CT scan which will identify extravasated blood in the basal cisterns. For patients with negative brain imaging, lumbar puncture may be required to exclude a diagnosis of SAH (van Gijn & Rinkel 2001). To accurately determine the location, size and morphology of aneurysms, intra-arterial digital subtraction angiography, MR angiography or CT angiography is necessary (Wardlaw & White 2000; Vega, Kwoon & Lavine 2002; Mitchell *et al.* 2004). SAH is associated with 25% to 50% case fatality and 30% to 50% long-term disability and dependence in survivors due to brain damage (White & Wardlaw 2003).

Risk of aneurysm rupture

A systematic review in 1998 of 495 patients with unruptured aneurysms and 3907 patient-years of follow-up (Rinkel *et al.* 1998) found an annual rupture rate of 1.9% (95% CI: 1.5 to 2.4). Women had a higher risk of rupture (RR 2.1, 95% CI: 1.1 to 3.9), as did patients aged 60-79 years (RR 1.7, 95% CI: 0.7 to 4.0). Symptomatic aneurysms were more likely to rupture than asymptomatic (RR 8.2, 95% CI: 3.9 to 17.0), as were aneurysms of the posterior circulation (RR 4.1, 95% CI: 1.5 to 11.0). Aneurysms smaller than 10mm were less likely to rupture than large aneurysms (RR 5.5, 95% CI: 3.3 – 9.5). However, the largest study to consider this question, the International Study of Unruptured Intracranial Aneurysms (ISUIA; The International Study of Unruptured Intracranial Aneurysms Investigators 1998) found somewhat different results.

The first phase of the ISUIA (ISUIA-1) used retrospectively collected data on 1449 patients with 12 023 patient-years of follow-up (mean 8.3 years). The ISUIA-1 study found overall rupture rate of 0.3% compared to 1.9% in the systematic review. Controversially,

the rupture rate for small aneurysms (less than 10mm in diameter) reported in ISUIA-1 was 0.05% compared to 0.7% in the systematic review, and 0.5% for larger aneurysms compared to 4% (ISUIA 1998; Rinkel *et al.* 1998).

Wardlaw & White (2000) suggest that differences in the duration of follow-up may account for the discrepancy between the two sources of data. Furthermore, the retrospective nature of data collection and reliance on complete angiographic records for included patients may have introduced selection bias.

The second phase of the ISUIA (ISUIA-2) (Wiebers *et al.* 2003) followed 1692 patients prospectively for a mean of 4.1 years (6544 patient years).

Table 1 (adapted from Wardlaw & White 2000; White & Wardlaw 2003) compares

- the risk of rupture for different subgroups of patients reported in the Rinkel *et al.* (1998) systematic review;
- two phases of the ISUIA; although
 - for some subgroups the ISUIA did not report data for risk of rupture and Although much of the data from the ISUIA-2 was not reported in such a way that it can be directly compared to the other data sets;
 - it appeared that the overall rate of rupture annually had increased from 0.3% in ISUIA-1 to 0.8% in ISUIA-2, and in particular that the rate of small aneurysm rupture was significantly higher (0.05% in ISUIA-1 to 0.1% in ISUIA-2);
 - ISUIA-2 also found that larger aneurysms were more likely to rupture than aneurysms less than 7mm in diameter (For aneurysms 7-12mm RR: 3.3, 95% CI: 1.3-8.2, and for aneurysms 12mm in diameter RR: 17.0, 95% CI: 8.0 – 36.1).
 - At this time, there is still uncertainty about the true incidence of aneurysm rupture for aneurysms of different sizes and locations, and disagreement about appropriate management (Donnan & Davis 2005).

Table 1: Risk of rupture for unruptured intracranial aneurysms

	Rinkel <i>et al.</i> 1998	ISUIA -1 (1998)	ISUIA-2 (2003)
Number of patients	495	1449	1692
Number of aneurysms	-	1937	2686
Duration of follow-up (px yrs)	3907 (mean FU 5.5 yrs)	12 023 (mean FU 8.3 yrs)	6544 (mean FU 4.1 years)
Number of ruptured aneurysms	75	32	51
Cumulative rupture rate	10% per decade	0.5-5% per decade	0.7-1.5% per decade*
Aneurysm rupture rate (% pa)			
overall	1.9 (95% CI: 1.5 – 2.4)	0.27 (32 in 12 023 yrs)	0.8 (51 in 6544)
aneurysms <10mm	0.7 (95% CI: 0.5 – 1.0)	0.05	0.07* (<7mm no previous SAH) 0.41* (< 7mm previous SAH)
aneurysms >10mm	4.0 (95% CI: 2.7 – 5.8)	0.5	0.15* (>7mm)
symptomatic aneurysm	6.5 (95% CI:4.4 – 9.1)	-	-
asymptomatic aneurysm	0.8 (95% CI: 0.4 – 1.5)	-	<7mm 0.07* >7mm 2.1*
additional aneurysm	1.4 (0.9 – 2.0)	-	0.36*
posterior circulation aneurysm	4.4 (2.7 – 6.8)	-	0.5 (<7mm) to 10 (>24mm)*
age 20 – 39 years	0.0 (0.0 – 13.0)	-	-
age 40 – 59 years	3.5 (1.4 – 7.0)	-	-
age 60 – 70 years	5.7 (3.4 – 9.0)	-	-

* this data extrapolated from Wiebers *et al.* 2003 by White & Wardlaw 2003

Endovascular treatments for intracranial aneurysm

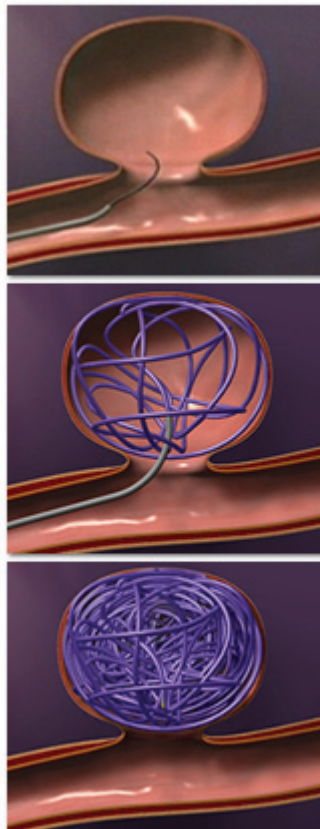
In endovascular treatments a guide catheter is introduced through the femoral artery in the groin and advanced under angiographic imaging to the carotid or vertebral artery using flexible guidewires (Qureshi 2004). A microcatheter, assisted by a flexible microguidewire is advanced through the guiding catheter and the tip of the microcatheter located within the aneurysm. The embolisation agent or device is then deployed and the microcatheter is removed. Endovascular treatment was first developed for the deployment of detachable balloons placed into the parent artery or the fundus of the aneurysm but these techniques were not particularly successful (Tong, Cloft & Dion 2000; Johnston *et al.* 2002). Coil embolisation was developed in the late 1980s largely replacing balloon embolisation. However, as experience with coiling has grown it has become apparent that large, wide-necked, and fusiform aneurysms are not easily treated with coiling alone, and thus stent or balloon-assisted coiling techniques have developed to enable endovascular treatment for some of these types of aneurysms (Bendok, Hanel & Hopkins 2003). More recently, the use of flexible stents or stent grafts alone has been used with some difficult-to-treat aneurysms (Hurst *et al.* 1998; Tsuura *et al.* 1999; Islak *et al.* 2002; Felber *et al.* 2004). Rarely, liquid embolics are used to occlude the aneurysm sac (Leonardi, Simonetti & Andreoli 2001; Molyneux *et al.* 2004; Lubicz *et al.* 2005). Occlusion of the parent artery, with coils, balloons, or liquid embolic has also been used to exclude giant and wide-necked aneurysms from the circulation (Larrazabal *et al.* 2001; Horowitz *et al.* 2002b).

Coiling

From the literature, the most common type of coil in use is the Guglielmi Detachable Coil (GDC, Boston Scientific Corporation, USA). The GDC operates on the principle that the coil is not detached from the delivery mechanism until it has been correctly placed, and may be repositioned or retrieved if it is not achieving appropriate occlusion of the aneurysm (Tong, Cloft & Dion 2000). The coiling technique consists of the placement of multiple detachable coils through a microcatheter, the tip of which is located within the neck or fundus of the aneurysm. A large bore guiding catheter, inserted into the femoral artery is advanced into the internal carotid or vertebral artery. A microguidewire or microcatheter combination is introduced into the aneurysm through the guide catheter. Once the microcatheter is in place, the guide catheter is removed. Both the guide catheter and microcatheter are continuously infused with heparinised saline to prevent thromboembolism and to ensure that the coil does not become damaged by static blood in the microcatheter. Digital subtraction angiography (DSA) is used throughout the process to ensure accurate placement. Individual platinum coils are placed into the aneurysm and detached one at a time until the aneurysm is filled with coils and thus excluded from the normal circulation (embolised). The coils are detached from the pusher wire by the introduction of a small electrical current after the microcatheter and coils are appropriately aligned. The size of coil used is determined by the characteristics of the aneurysm, in particular the neck diameter, as the first coil used needs to be wider than the neck of the aneurysm to avoid herniation into the parent artery. The coils are placed in such a way that a basket of loops within the fundus of the aneurysm creates a structure into which subsequent coils can be added (Figure 2). Throughout the process and after its completion care is taken not to dislodge any of the coils (Tong, Cloft & Dion 2000; Bendok, Hanel & Hopkins 2003).

For some aneurysms that have a wide neck it is possible that the coils might herniate into the artery and thus a balloon or flexible stent may be placed over the aneurysm neck in the parent artery to allow coiling of the aneurysm sac without herniation. In balloon remodelling an inflatable balloon, sized to fit over the aneurysm neck creating a seal, is inflated to almost match the diameter of the parent artery. The aneurysm sac is filled with coils with intermittent inflation of the balloon, with flow arrest for no more than 2-3 minutes at any given time. Once the aneurysm sac is completely filled with coils, the deflated balloon is removed (Johnston *et al.* 2001; Bendok, Hanel & Hopkins 2003). The use of a flexible stent allows circulation to continue during the placement of the coils and the stent is left in place after the treatment providing a supportive structure for the coil-filled aneurysm. To avoid thromboembolic complications associated with stents, premedication with antiplatelet agents is used. However, it may not be possible to use stents if the aneurysm is located in an area with tortuous vascular anatomy (Horowitz *et al.* 2001, Bendok, Hanel & Hopkins 2003). Recently a flexible microstent designed for use in the intracranial vasculature has been developed (the Neuroform Stent, Boston Scientific Corporation, USA) which is purported to be effective for the treatment of aneurysms located in tortuous intracranial vasculature (Fiorella *et al.* 2004b).

Figure 2: Coils being placed into an aneurysm



Source: www.brainaneurysm.com

Stenting

Although stenting is usually used as an additional technique to support or enable coiling, it is possible to use a stent or stent graft alone to treat some aneurysms which would not be suitable for endovascular treatment with coils or for surgical clipping. Such aneurysms include dissecting cervical internal carotid artery aneurysms (Hurst *et al.* 1998; Tsuura *et al.* 1999), intracranial vertebral artery aneurysms (Felber *et al.* 2004) and giant and fusiform aneurysms (Benndorf *et al.* 2002; Islak *et al.* 2002; Felber *et al.* 2004). The aim of stenting in these cases is to reduce blood flow without permanently occluding the parent artery into the aneurysm and to redirect the blood flow to the unaffected contralateral artery (Islak *et al.* 2002). Stent grafts have a coating of autologous tissue (such as saphenous vein) or biocompatible membrane (such as polytetrafluoroethylene, PTFE) which seals over the aneurysm neck and prevents aneurysmal inflow (Felber *et al.* 2004).

Liquid embolics

Liquid embolics are an alternative to mechanical occlusion of aneurysms. An occlusive liquid is delivered to the aneurysm sac via a microcatheter with balloon occlusion of the aneurysm neck during the procedure. Liquid embolic materials include histoacryl glue, or *n*-butylcyanoacrylate (*n*-BCA). Recently an alternative material has been developed – Onyx Liquid Embolic Material (Micro Therapeutics Inc., Irvine, California). Rather than being a cyanoacrylate, Onyx is an ethylene vinyl alcohol copolymer which is dissolved in dimethyl sulfoxide and opacified with tantalum powder (Molyneux 2002). Liquid

embolics are typically used when other forms of treatment (particularly coiling) are not indicated, such as for giant and wide-necked aneurysms (Molyneux 2002).

Parent artery occlusion

Parent artery occlusion is an option for treating giant aneurysms and other aneurysms that cannot be treated effectively using conventional surgical clipping or endovascular coiling (Johnston *et al.* 2002). The aim of parent artery occlusion is to induce thrombosis in the aneurysm and relieve the symptoms of mass effect (Boardman & Byrne 1998; Lubicz *et al.* 2004b) by obliterating the aneurysm and excluding it from systemic flow (Numagami *et al.* 1999). Prior to permanent occlusion most patients have a test occlusion with non-detachable balloons to confirm that the intracranial blood flow continues via unoccluded arteries. Test occlusion takes up to 30 minutes and may be done with the patient conscious so that neurological condition can be monitored (Lubicz *et al.* 2004b). The permanent occlusion is performed under continuous heparinisation and is achieved via endovascular access and placement of detachable coils, detachable balloons or liquid embolics.

Intended purpose

The primary goal of treatment for unruptured intracranial aneurysms is to prevent future rupture (Johnston *et al.* 2002). Endovascular treatments aim to prevent the flow of blood into the aneurysm sac by either inducing a thrombus through occlusion of the aneurysm with coils or liquid embolics (Dovey *et al.* 2001), or by isolating the aneurysm from intracranial blood flow using parent artery occlusion (Lubicz *et al.* 2004b).

Potential complications of endovascular approaches

Although endovascular approaches are less invasive than open surgical approaches for the treatment of intracranial aneurysms there are a number of potential complications.

Perforation of the aneurysm during the coiling process, thromboembolic complications resulting from thrombus formation on the catheters, guide-wires and coils during or after treatment, and damage to coils are common potential complications of coiling (Tong, Cloft & Dion 2000). The detached coils may also herniate through the aneurysm neck into the parent artery resulting in partial occlusion and increasing the risk of thromboembolic complications (Tong, Cloft & Dion 2000), the risk of such complications may be minimised for patients with unruptured aneurysm by treating with anticoagulants prior to coiling (Bendok, Hanel & Hopkins 2003). Rebleeding from partially occluded aneurysms or aneurysms with residual necks or dog-ears is also a potential problem, which could lead to future rupture (Dovey *et al.* 2001).

Inflammatory reactions causing vessel hyperplasia, ischaemic neurological and thromboembolic complications, and bleeding resulting from the use of anticoagulants are all potential problems with stenting (Tsuura *et al.* 1999; Islak *et al.* 2002; Fiorella *et al.* 2004a). The primary risks associated with liquid embolics are thromboembolic complications due to the irritation which may be caused by the presence of a foreign body in the circulation, through migration or leaking of embolic material into the parent artery during the injection process. There may also be toxicity associated with the use of the solvent although this has not yet been clarified (Mawad *et al.* 2002; Molyneux 2002).

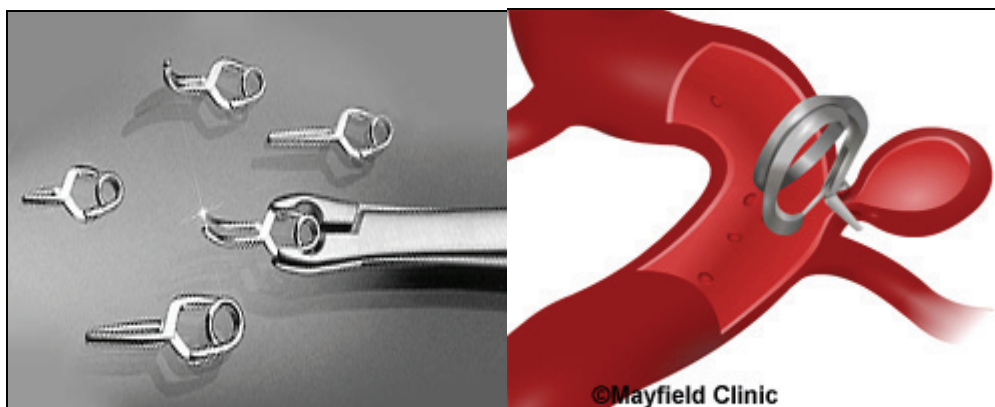
Intracranial infarct caused by a thromboembolic event or occlusion of a perforating artery is the most common complication after parent artery occlusion (Lubicz *et al.* 2004b). Immediate or delayed ischaemic events can also occur which may lead to neurological deficit and sometimes death (Boardman & Byrne 1998). There is also the possibility of recanalisation of the occluded artery (Numagami *et al.* 1999).

Existing procedures

Surgical clipping (ruptured and unruptured aneurysms)

The standard treatment for ruptured and unruptured aneurysms is surgical clipping (van Gijn & Rinkel 2001; Wijndicks *et al.* 2005). Under general anaesthesia the site of the aneurysm is accessed via a craniotomy. The aneurysm is exposed and focal circulatory arrest in local vessels is obtained by proximal clip placement. By reducing aneurysmal flow the aneurysm dome is softened and easier to manipulate and blood flow is easier to control if there is premature rupture. Focal circulatory arrest provides a safe interval for clip placement but increases the risk of ischaemic injury; techniques such as induced hypotension to improve perfusion in adjacent vasculature, and the use of barbiturate medications or mild hypothermia to slow brain metabolism may be used to manage this risk (Bendo 2002; Barrow & Cawley 2004; Ellegala & Day 2005). The aneurysm neck is dissected away from surrounding connective tissue taking care to isolate perforating arteries, and one or more titanium clips are placed over the aneurysm neck (see Figure 3). The goal of clip placement is to isolate the aneurysm from the normal circulation without compromising parent artery flow (Barrow & Cawley 2004). Isolation may be confirmed by puncturing the aneurysm dome or by intraoperative angiography. After ensuring that the clip is not obstructing the parent artery, the wound is closed with sutures (Ellegala & Day 2005).

Figure 3: Titanium clips for aneurysm surgery and a clipped aneurysm



Source: <http://www.mayfieldclinic.com/PE-Clipping.htm>

For some aneurysms where surgical clipping is not appropriate, for example wide-necked and giant aneurysms, clipping may be combined with aneurysm wrapping or endovascular therapy. Aneurysm wrapping was developed in the 1930s but has largely fallen out of favour as a primary surgical treatment for ruptured aneurysms due to concerns over efficacy and complications (Choudhari 2004). In this technique the aneurysm is wrapped externally, usually in fine cotton gauze (muslin) or occasionally in autologous tissue (muscle, fascia or dura) or sometimes by covering with a liquid

adhesive coating. A primary risk of this technique is the possibility of rupture during the wrapping procedure (Choudhari 2004).

Safety and efficacy of surgical clipping of aneurysms

A large population-based study of surgical clipping in 3527 patients in one US state found a survival rate of 82.1% after one year for ruptured aneurysms and 77.6% after five years. Survival rates for unruptured aneurysms were 91.5% at one year and 86.6% after five years. A meta-analysis of 61 studies published between 1966 and 1996 found mortality after surgical clipping of unruptured aneurysms to be 2.6% (95% CI: 2.0% to 3.3%) and morbidity 10.9% (95% CI: 9.6% to 12.2%). Poor outcome was associated most strongly with posterior circulation aneurysms and giant aneurysm size (Raaymakers *et al.* 1998). Morbidity and mortality were higher in earlier published studies but the effect was not as significant as aneurysm characteristics in terms of outcome.

Outcomes for treatment of ruptured aneurysm are known to depend on the clinical grade of the patient after SAH, the location and size of the aneurysm, the presence of multiple aneurysms, the timing of surgery, the presence of comorbidities and the age of the patient (Bryan, Rigamonti & Mathis 1997; Wijndicks *et al.* 2005). It is generally agreed that outcomes will be poorer for patients with a worse clinical grade prior to treatment and for those with posterior circulation or multiple aneurysms. However the effect of the presence of comorbidities, the effect of increasing age and the timing of aneurysm treatment have not yet been clearly defined (de Gans *et al.* 2002; Wijndicks *et al.* 2005).

Best medical treatment (unruptured aneurysms)

Aneurysm rupture and SAH are associated with a number of modifiable risk factors including smoking, substance abuse and hypertension (Juvola 2004). Best medical treatment for unruptured aneurysms therefore focuses on reducing or eliminating these risk factors and hence the risks of aneurysm rupture. Aggressive control of blood pressure and programs aimed at smoking cessation and moderating alcohol intake may all reduce the risk of rupture of an unruptured aneurysm to a level that is substantially lower than the risks associated with active treatment (Pfohman & Criddle 2001).

Comparator

For the treatment of both ruptured and unruptured aneurysms the primary comparator to endovascular treatments is surgical clipping. However, for unruptured aneurysms best medical treatment or no treatment may also be appropriate comparators.

Choosing between endovascular and surgical treatments

The clinical decision pathway for the treatment of intracranial aneurysm is shown in Figure 4. The decision about whether to treat a patient with an endovascular or surgical approach is complex and takes into consideration:

- the characteristics of the aneurysm including the type, size, location and morphology of the aneurysm;

- whether the patient is symptomatic i.e. has either SAH if the aneurysm is ruptured or symptoms of mass effect if the aneurysm is unruptured;
- for unruptured aneurysm the risk of rupture compared to the risks of treatment;
- patient characteristics such as patient grade on presentation (using a scale such as the Hunt and Hess grading scale), age, presence of comorbidities; and
- the endovascular and surgical experience of the team treating the aneurysm.

Although the decision pathway in Figure 4 shows the most likely treatment to be selected according to the expert opinion of the Advisory Panel for this review, it is possible in some cases that an alternative treatment will be chosen for a particular patient. The clinical pathway is not intended to imply that such decisions are not appropriate.

Figure 4: Clinical decision pathway for the treatment of intracranial aneurysms

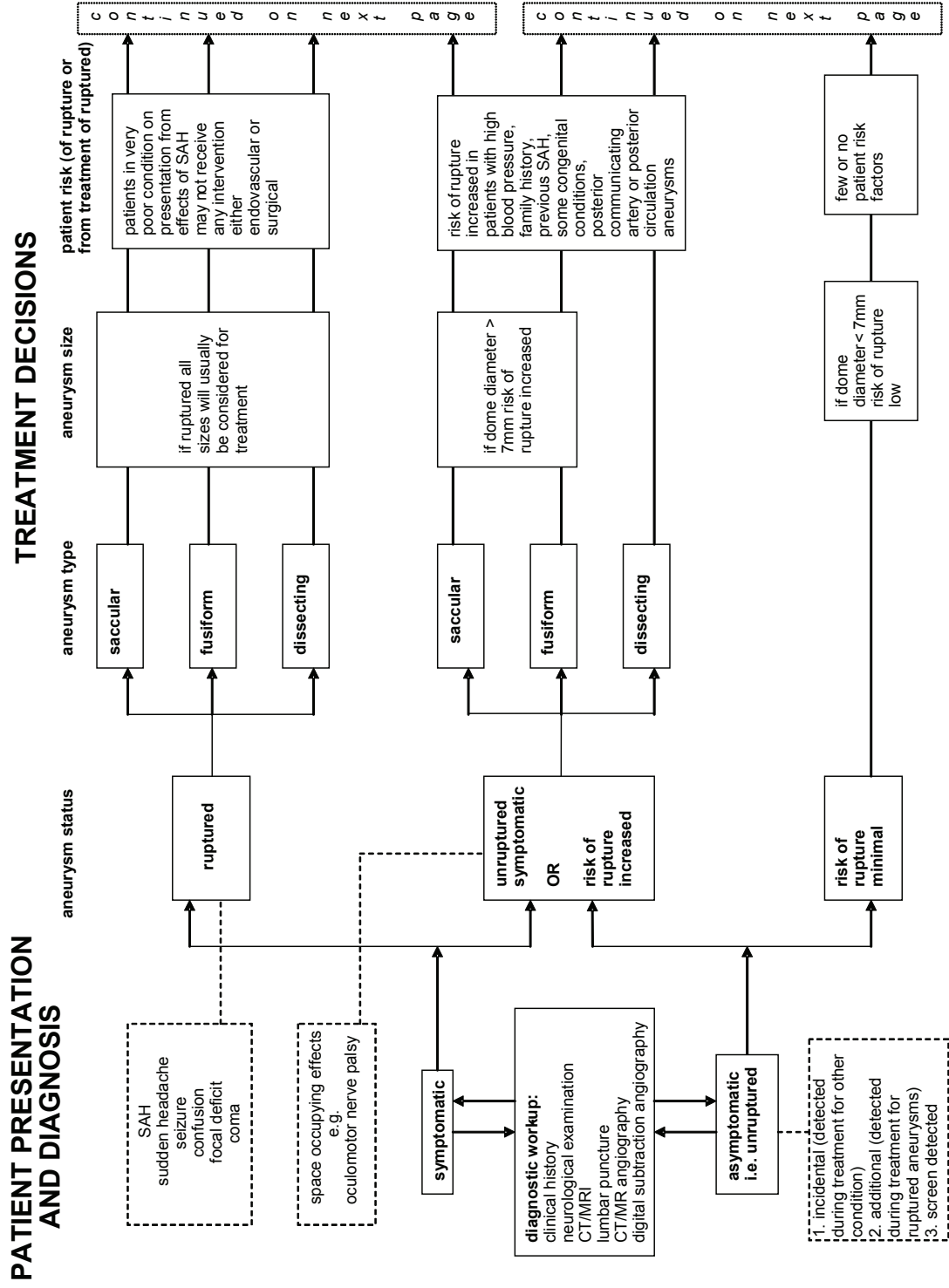
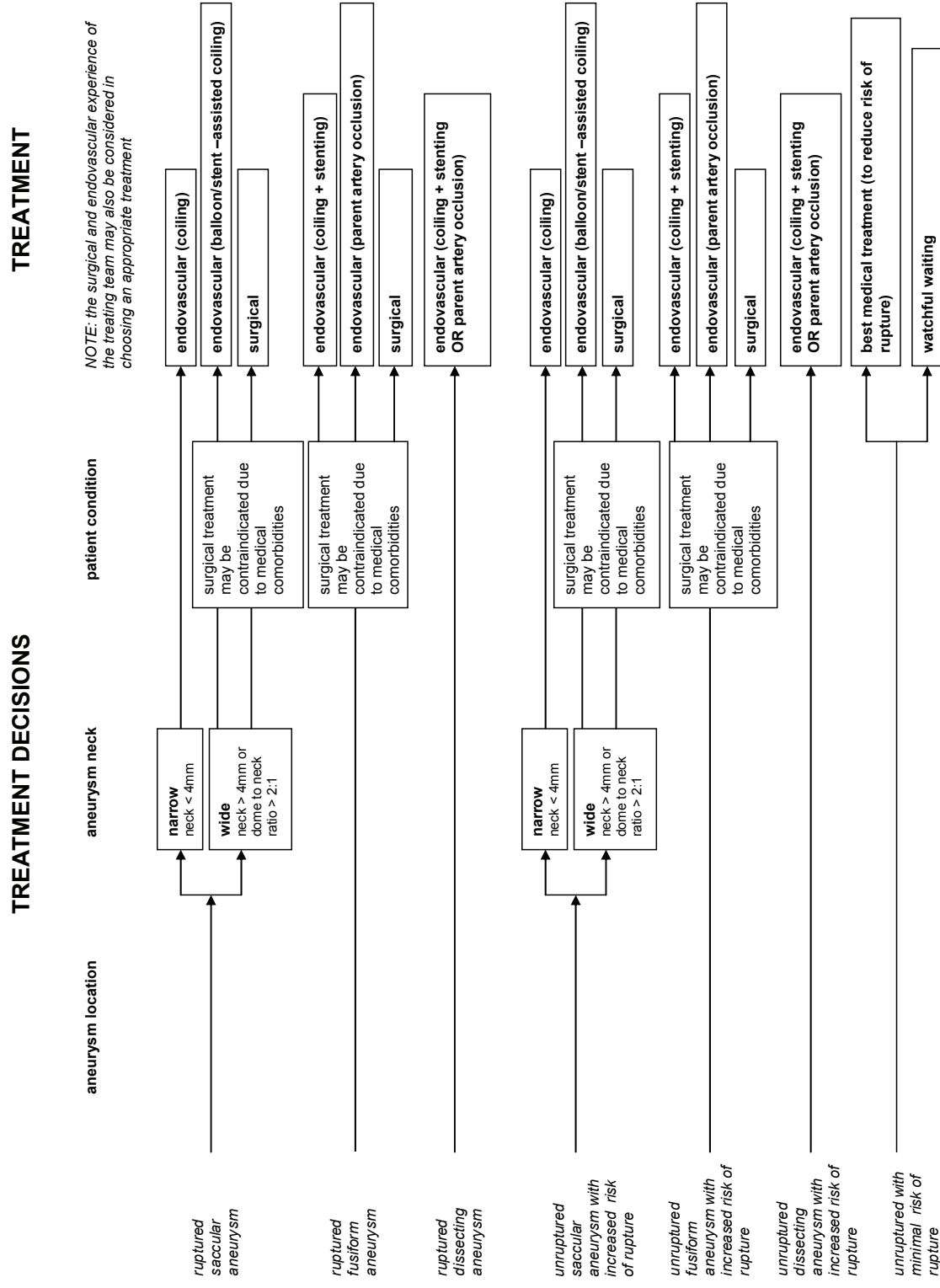


Figure 4: Clinical decision pathway for the treatment of intracranial aneurysms *continued*



Clinical need/burden of disease

Incidence of SAH and ruptured intracranial aneurysm

Subarachnoid haemorrhage is thought to account for around 4% of all strokes (ACROSS Group 2000) and probably 75% or more of all SAH are caused by rupture of an intracranial aneurysm (Liebeskind 2004). Frequently data regarding the prevalence and incidence of stroke are not reported separately for strokes caused by SAH and ischaemic strokes. However, it may be possible to estimate the rate of SAH from stroke statistics.

Australian data

In Australia, there have been a number of epidemiological studies focused on either stroke or SAH. The Australasian Cooperative Research on Subarachnoid Haemorrhage Study (ACROSS) studied the incidence of SAH in Australia and New Zealand from data in four population-based registers between 1995 and 1998. Out of a total population in the four cities of 2.8 million, 436 cases of SAH were identified with a mean age of 57 [SD 17] years (range 16 to 94 years) and 62% female. The age and sex-adjusted annual incidence rate for first ever SAH (1996-1998) was 6.5 (95% CI: 5.8 to 7.2) per 100 000 but was higher in New Zealand (9.9 per 100 000 95% CI: 7.9 to 12.4) reflecting higher rates of SAH in the Maori and Pacific populations. Overall 28-day case fatality was 39% (170/436). The incidence of SAH increased with age continuously for females up to around the age of 55 but then tapered off, whereas for males the incidence appeared to be bimodal, peaking at around 35-55 years and again for those aged over 85 years (ACROSS Group 2000). Of the 436 patients with SAH, 76% (330/436) were found to have a ruptured aneurysm.

Truelsen *et al.* (1998) found that the age-standardized incidence of SAH in the New Zealand population decreased from 14.6 per 100 000 for 1981-1983 to 11.3 per 100 000 for 1991-1993. However, 28-day case fatality did not differ significantly between the two periods. Mortality from SAH declined from around 12 to around 8 per 100 000 for women and from around 8 to around 6 per 100 000 for men over the same 10 year period.

A study of stroke survival in Western Australia between 1995 and 1998 found SAH responsible for 807/7784 (4%) hospital admissions for stroke. The mean age of these patients was 54.3 years (range 52.3 to 56.3) and 57.5% female. Over the study period 66.5% of these patients survived for an average of 835 (range 770 to 900) days. Survival after 7 days was 82% (95% CI: 78 to 86) and 28-day survival was 72% (95% CI: 67 to 77) (Lee, Somerford & Yau 2003). This is consistent with the 30-day case fatality for SAH of 38% reported in Perth Community Stroke Study (372 cases of stroke in a population of 138 708 people from 1989 to 1990; Hankey *et al.* 2000).

The North East Melbourne Stroke Incidence Study (NEMESIS) reported incidence of stroke among a population of 133 816 residents of one area of Melbourne between 1996 and 1997. The age adjusted annual incidence of first ever stroke was 100 (95% CI: 80 to 119) per 100 000 (Thrift, Dewey & Macdonell 2000). Assuming that around 4% of these strokes were SAH, the estimated incidence would be 4 in 100 000 which is consistent with the ACROSS data.

International data

The World Health Organisation Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases or MONICA study found age-adjusted mean annual SAH rates of between 2.0 (95% CI: 1.6 to 2.4) per 100 000 in China to 22.5 (95% CI: 20.9 to 24.1) per 100 000 in Finland. The MONICA study obtained data from China, Denmark, Finland, East Germany, Italy, Lithuania, Poland, Russia, Sweden and Yugoslavia between 1982 and 1986. There were 3368 SAH events and a 41.7% case fatality at 28-days, although the case-fatality rate varied from 23% in China to 62% in Yugoslavia. Patients were much more likely to die within the first week after SAH (75%) than later. In patients who received medical attention the 28-day case fatality ranged from 23% in China to 51% in Russia. Mean age at onset of SAH was 49.0 [SD 10.0]. The MONICA investigators suggested that differences across countries may be related to the prevalence of risk factors in each country (Ingall *et al.* 2000).

A systematic review of case-fatality rates after SAH (Hop *et al.* 1997) identified 21 studies published between 1960 and 1992. Case fatality rates varied between 23% and 67%.

Quality of life among survivors of SAH

Patients who survive SAH (with or without interventional treatments) are usually left with a range of neurological, cognitive and psychosocial problems which may vary from mild to severe. These problems are likely to impact on ability to function in everyday life and may result in vocational and social disability and reduced quality of life (Saciri & Kos 2005). It has been noted that while neurological deficits (as measured by a scale such as the Glasgow Outcome Scale or Rankin scale) may not be severe, and patients may be considered to be independent in activities of daily living, such patients may still experience significant cognitive impairment and/or decline in quality of life (Hop *et al.* 1997, Powell *et al.* 2002). Furthermore, even patients with no significant cognitive impairment may report psychosocial distress and reduced social independence (Powell *et al.* 2002), with these problems estimated to affect between one third and one half of all survivors of SAH (Politynska, Berrios & Lewko 1995).

The Hop *et al.* (1997) systematic review found that between 10% and 20% of patients were disabled and or dependent after SAH. Quality of life was found to be significantly reduced for patients who remained independent 4 months after SAH and although this improved considerably after 18 months, around two-thirds of patients still reported reduced quality of life (van Gijn & Rinkel 2001).

The ACROSS study reported health outcomes one year after SAH (Hackett & Anderson 2000). Nearly half (46%) of those patients who were still alive after one year reported continuing problems with memory (50%), mood (39%), speech (14%) and self-care (10%). Health-related quality of life (HRQL) was significantly lower than for the Australian population particularly in the domains of role limitations due to physical or emotional problems. Patients who reported a complete recovery had higher HRQL than patients who reported an incomplete recovery (Hackett & Anderson 2000).

Prevalence of unruptured aneurysm

Specific Australian data on the prevalence of unruptured aneurysms was not identified. However, as noted in the discussion of unruptured aneurysms, the prevalence of unruptured aneurysms is thought to be between 3% and 6% including patients with

known risk factors and perhaps 2% in patients with no known risk factors (White & Wardlaw 2003, Rinkel *et al.* 1998). If this data is applied to the Australian population of approximately 20 million, this equates to between 400 000 and 1.2 million people who may be living with an unruptured aneurysm.

Marketing status of the device/technology

Endovascular devices for treating aneurysms listed on the Australian Register of Therapeutic Goods (ARTG) are shown in Table 2.

Table 2: Endovascular devices for aneurysm treatment registered on ARTG

Description	Sponsor	ARTG number
Detachable Platinum Coils		
Guglielmi detachable coils (various sizes)	Boston Scientific	48608 (Product ID 102803)
Vortex-35 fibered platinum coil (various sizes)	Boston Scientific	48608 (Product ID 114478)
GDC trispan coils (various sizes)	Boston Scientific	48608 (Product ID 142198)
Matrix SR detachable coils	Boston Scientific	114316 (Product ID 193870)
Trufill DCS detachable coil (various models)	Johnson & Johnson Medical	56630 (Product ID 146748)
Micro Plex coil systems (various)	N. Stenning & Co.	83194 (Product ID 155089)
Hydro Coil system (various)	N. Stenning & Co.	83194 (Product ID 161446)
Micrus platinum microcoil delivery system (various sizes and configurations)	Medtel	78178 (Product ID 147307)
Sapphire detachable coil	Device Technologies Australia	77883 (Product ID 146944)
Detachable embolisation coils (various)	William A Cook Australia	21823 (Product ID 144500)
Stents		
Neuroform 2 stent	Boston Scientific	94705 (Product ID 165341)
Microballoon catheters		
Occlusion balloon catheter (various) – Hyperform and Hyperglide	Device Technologies Australia	71132 (Product ID 136224)
Sentry occlusion balloon catheter (various sizes)	Boston Scientific	58842 (Product ID 142197)
Liquid embolics		
Onyx system	Device Technologies Australia	71300 (Product ID 136502)

Current reimbursement arrangement

There is currently no MBS item number for endovascular treatments for intracranial aneurysms.

Approach to assessment

Review of literature

MEDLINE, EMBASE, Current Contents, PubMed and the Cochrane Library were searched to identify relevant studies. The searches were date restricted from January 1990 to July 2005 to ensure that only currently available endovascular treatments were included. The York (UK) Centre for Reviews and Dissemination (CRD) databases, Clinicaltrials.gov, National Research Register, relevant online journals and the Internet were also searched. Searches were conducted without language restriction.

Search strategy

for MEDLINE

1. ((exp *INTRACRANIAL ANEURYSM/ or exp *ANEURYSM, RUPTURED/ or exp *ANEURYSM, UNRUPTURED/ or exp *ANEURYSM, DISSECTING/ or exp *ANEURYSM, INFECTED/ or exp *ANEURYSM/ or exp *ANEURYSM, FALSE) or aneurysm\$.mp)) OR exp *Subarachnoid Hemorrhage/

for EMBASE

1. (exp *SACCULAR ANEURYSM/or exp *BRAIN ARTERY ANEURYSM/or exp *ANEURYSM/ or exp *INTRACRANIAL ANEURYSM/ or exp *ANEURYSM RUPTURE/ or exp *MYCOTIC ANEURYSM/ or exp *FALSE ANEURYSM/ or exp *BRAIN ARTERY ANEURYSM RUPTURE/ or exp *DISSECTING ANEURYSM/) OR aneurysm\$.mp OR exp *Subarachnoid Hemorrhage/ OR (ruptur\$ or unrupt\$)

for Current Contents

1. aneurysm\$

for all three databases listed above

2. cerebral or intracerebral or intracranial or parenchymal or cerebellar or brain\$ or verterbrobasilar
3. 1 and 2
4. endovasc\$.mp OR (coil\$ or stent\$ or balloon or liquid embol\$.mp)
5. 3 and 4

for PubMed

((intracranial OR cerebral) and aneurysm\$) and (endovasc\$ OR (coil\$ OR stent\$ OR balloon OR liquid embol\$))

for The Cochrane Library and CRD Databases

(intracranial or cerebral) and aneurysm\$

Inclusion criteria

The inclusion and exclusion criteria for the review are shown in Table 3.

Table 3: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Participants	<p>human studies of patients (children and adults) with ruptured and unruptured intracranial aneurysms regardless of how the aneurysm was diagnosed</p> <ul style="list-style-type: none"> - including saccular, berry, fusiform, dissecting, traumatic, infectious, peripheral and extradural aneurysms - including multiple aneurysms <p>NOTE: patients were considered to have a ruptured aneurysm if it was so stated, or where there was both an identified aneurysm and a subarachnoid haemorrhage</p>	<p>results for patients with ruptured and unruptured aneurysm could not be separated</p> <p>subarachnoid haemorrhage from a cause other than rupture of aneurysm</p>
New intervention	<p>coiling (with detachable coils of any type) with or without stent or balloon-assistance</p> <p>stenting or stent graft</p> <p>liquid embolic</p> <p>parent artery occlusion (with coils, stents, balloons or liquid embolic)</p>	<p>endovascular treatments combined with surgical clipping</p> <p>second order endovascular treatments</p> <p>aneurysm treatment combined with treatment for another condition (e.g. tumour excision)</p>
Comparative intervention	<p>surgical clipping or wrapping</p> <p>best medical treatment</p> <p>no treatment</p>	-
Outcomes	<p>peri and postoperative morbidity and mortality</p> <p>efficacy and durability of treatment, including but not limited to:</p> <ul style="list-style-type: none"> - degree of aneurysm occlusion/obliteration - rebleeds, recanalisation, reopening or regrowth of aneurysm - technical complications (such as coil compaction) - reoperation/retreatment rate <p>patient-relevant outcomes, including but not limited to:</p> <ul style="list-style-type: none"> - survival - functional and neurological outcomes (including symptom relief of mass effect) - cognitive outcomes - psychological and psychosocial outcomes - quality of life - return to work/normal activities <p>cost and resource use issues</p>	technical not clinical outcomes
Types of studies	<p>randomised and non-randomised comparative studies</p> <p>case series and case reports were included if they reported durability of endovascular treatments (rebleeding including fatal rerupture, recanalisation, retreatment, reopening or regrowth of aneurysm) (for case series only) or adverse events</p>	<p>case series and case reports that did not report durability or adverse events were excluded except if they reported an aneurysm, patient, condition, treatment or device (or combinations) which was not reported in comparative studies</p>
Language	<p>searches were conducted without language restriction, however only English language studies were included in the review</p>	-

Methods of the review

Articles were retrieved when they were judged to possibly meet the selection criteria. Retrieved articles were checked against the selection criteria. Articles that did not meet the inclusion criteria were excluded from the review. The reasons were documented when that occurred. The bibliographies of all publications retrieved were manually searched for relevant references that may have been missed in the database search (pearling). Data were extracted by one researcher and checked by a second using standardised data extraction tables developed *a priori*.

Meta-analysis

Where outcomes from randomised controlled trials (RCTs) could be sensibly combined (outcomes measured in comparable ways and no apparent heterogeneity), relative risks with 95% confidence intervals (CI) were calculated for dichotomous outcomes and weighted mean differences (WMD) with 95% CIs were calculated for continuous outcomes (using RevMan 4.2, Update Software).

Subgroup analyses were planned; however insufficient data were available to perform any of the following subgroup analyses:

- aneurysm status (ruptured vs unruptured)
- aneurysm size
- aneurysm location
- aneurysm type
- patients in poor grade (using Hunt and Hess or similar grading scheme)
- older patients
- patients with significant comorbidities

To avoid the introduction of bias, data was only extracted from studies where such results were stated explicitly, and a zero occurrence of events was not imputed from a lack of comment on such events.

Included studies were given a study identifier in the form [first author; date of most recent paper] e.g. Alberts 2001. This was done so that if there was more than one paper relating to a particular study, these could be listed together in the list of references of included studies.

Handling of non-randomised data

Where statistical pooling was not possible, medians of rates (for dichotomous outcomes) or medians of means (for continuous outcomes) for all studies reporting the outcome was calculated. The data is presented according to the comparison (e.g. coiling alone vs clipping alone) or endovascular intervention (for case series and case reports). Results for ruptured and unruptured aneurysms have been reported separately.

Description and methodological quality of included studies

The evidence presented in the selected studies has been assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 4) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 4: Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 5

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 5.

Table 5: Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC 1999.

Expert advice

An advisory panel with expertise in neurology, neurosurgery and interventional neuroradiology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to

approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the advisory panel is provided in Appendix B.

Results of assessment

Studies included in the review

One hundred and eighty two studies were identified for inclusion in this assessment of the safety and effectiveness of endovascular treatments for the treatment of intracranial aneurysms (Table 6). The main comparison was between endovascular coiling and surgical clipping (Comparison 1), with safety and effectiveness outcomes for ruptured and unruptured aneurysms extracted from two RCTs and 44 non-randomised comparative studies. Safety and effectiveness outcomes were also extracted from 63 case-series, 69 case reports, and 4 registry studies of endovascular coiling and other endovascular techniques.

The following subsidiary analyses were also performed:

- Endovascular versus surgical treatment (Comparison 2)
- Endovascular versus conservative treatment (Comparison 3)

Excluded studies

One thousand and sixty studies were excluded from this review for a variety of reasons, including the fact that they were non-English language, did not report adverse events or durability outcomes, did not separate outcomes for ruptured and unruptured aneurysms, or described surgical interventions only.

Table 6: Summary of studies included in the review

Comparative studies				Non-comparative studies			
Intervention	RCTs (Level II)	Non-randomised comparative studies (Level III)	Registry studies	Intervention	Case series (Level IV)	Case reports (Level IV)	
Coiling versus clipping	2	32	3	Coiling	51	43	
Ruptured aneurysm	2	24	2	Ruptured aneurysm	43	26	
Unruptured aneurysm		9	2	Unruptured aneurysm	37	19	
Unspecified aneurysm type		5		Coiling + balloon	2	6	
				Ruptured aneurysm	2	4	
				Unruptured aneurysm	1	2	
Endovascular versus surgical		7	1	Coiling + stent		7	
Ruptured aneurysm		4		Ruptured aneurysm		3	
Unruptured aneurysm		4	1	Unruptured aneurysm		4	
				Balloon	5	11	
				Ruptured aneurysm	4	3	
				Unruptured aneurysm	4	9	
Endovascular versus conservative		5		Stent	3	1	
Ruptured aneurysm		4		Ruptured aneurysm	3	1	
Unruptured aneurysm		1		Unruptured aneurysm	3		
				Liquid embolic	2	1	
				Ruptured aneurysm	2		
				Unruptured aneurysm	2	1	
Subtotal	2	44	4		63	69	
Total number of included studies: 182							

Critical appraisal

Randomised controlled trials

Two RCTs (Koivisto *et al.* 2002 and Molyneux *et al.* 2005) compared endovascular coiling with surgical clipping for the treatment of ruptured aneurysms. Koivisto *et al.* (2002) was a single centre prospective study from eastern Finland. Molyneux *et al.* (2005) was a multicentre randomised trial from Europe, commonly known as the International Subarachnoid Aneurysm Trial (ISAT).

Inclusion and exclusion criteria

In both studies, patients were included where the aneurysm causing SAH was confirmed by CT, lumbar puncture or angiogram, and if the aneurysm was suitable for endovascular or surgical treatment. Both studies required consent from patients or their next of kin and both had ethics approval.

Of the 321 patients admitted with primary SAH in Koivisto *et al.* (2002), the condition was confirmed via angiography in 242 consecutive patients. After applying the exclusion criteria, 111/321 patients (34%) were entered into the trial (52 coiling, 57 surgical clipping). An additional 2 patients were excluded after randomisation because they were incorrectly assessed for eligibility. The basis for inclusion and endovascular treatment in this study was the morphology of the aneurysm that had most probably ruptured, which was confirmed by CT scan. The surgical teams at each centre determined the treatment pathway. Patients were excluded if they were older than 75 years of age, had a SAH less than three days prior to surgery, and if they were not suitable candidates for both endovascular and surgical treatment.

Overall, ISAT (Molyneux *et al.* 2005) included 2143/9559 patients (22.4%) who met their stringent selection criteria (1073 coiling, 1070 surgical clipping), excluding 7416/9559 patients (671 refused and 6745 were excluded for 'other' reasons). These 'other' reasons were not specified, although clinician preference is likely to have been a common reason. The ISAT inclusion criteria specified that the clinician must have been uncertain about whether to undertake coiling or clipping in order for a patient to be included.

Randomisation and allocation concealment

Koivisto *et al.* (2002) randomised consecutive patients via sealed envelopes to either endovascular treatment or neurosurgery. Patients were stratified based on their Hunt and Hess grade on presentation. Hunt and Hess grades were pooled for allocation (I-II, III and IV-V) in order to balance the treatment groups.

Randomisation of consecutive patients in the ISAT cohort occurred after the provision of key baseline data by a 24-hr telephone randomisation service provided by the Clinical Trials Service Unit at the University of Oxford (Molyneux *et al.* 2005). A minimisation algorithm ensured a balance in cohort allocation.

Losses to follow-up

Koivisto *et al.* (2002) reported no losses to follow-up, although the results of three patients were excluded because they crossed over to surgery immediately after coiling due to failed embolisation. One patient had crossover treatment prior to a second SPECT analysis and

five patients had crossover treatment before the 12-month examination. According to the authors, exclusion of these crossover patients did not significantly alter the results.

ISAT reported losses to follow-up as those 'ineligible for analyses, measuring the primary endpoint event in terms of the Modified Rankin Scale (MRS) or Oxford Handicap Scale (OHS)'.

Both studies reported using an 'intention-to-treat-analysis' where patients who crossed over to another treatment were analysed in the group to which they were originally allocated.

Sample size

Koivisto *et al.* (2002) did not report a power calculation. ISAT reported that the trial aimed to recruit 2500 patients for a 90% power ($p < 0.01$), to detect a reduction in the proportion of patients dead or dependent at one year from 24% to 19%, reflecting a 25% improvement in the outcomes for endovascular patients.

Endpoints

Koivisto *et al.* (2002) reported that the primary endpoints of the study were rebleeding of the aneurysm or death of the patient. The secondary endpoint was refilling of the aneurysm, which indicated a need for retreatment.

The primary objective reported by ISAT was to determine whether endovascular treatment when compared with neurosurgical treatment reduced the proportion of patients' dependent or dead (classified by the MRS 3-6) at one year by 25%. The secondary objective was to assess the difference between endovascular coiling and neurosurgery, with regard to their ability to prevent rebleeding, reflected as a better quality of life at one year as assessed by the Euroqol health state questionnaire; and whether endovascular coiling was more effective than the comparator in improving neuropsychological outcomes at one-year follow-up. As a tertiary objective, ISAT sought to assess the long-term outcomes of treatment (initially planned for at least 5 years, but has been extended to 7 years), with particular focus on the frequency of further haemorrhage and the long-term significance of radiological results. The decision to include MRS 3 in the composite measure of dead or dependent can be questioned since MRS 3 patients are unlikely to be completely dependent.

Outcome analysis

Blinding to assessment was not reported in ISAT or Koivisto *et al.* (2002) however in the latter study, the outcomes at 3 and 12 months were assessed by the neurosurgeons that performed the procedures.

Initial follow-up periods ranged from 2 months (ISAT) to 3 months (Koivisto *et al.* 2002), however both studies undertook a 12-month follow-up.

Neuropsychological outcomes

Neuropsychological outcomes were reported in one study (Koivisto *et al.* 2002), in which patients underwent testing 3 and 12 months after treatment.

Non-randomised comparative studies

Forty-four non-randomised comparative studies were included in this review (Tables 7 and 8). There were 32 non-randomised comparative studies comparing surgical clipping with endovascular coiling, consisting of thirty level III-1 studies and two level III-2 studies. Endovascular versus surgical clipping was examined in eight studies consisting of four level III-2 studies, three level III-2/3 studies and one level III-3 study. Endovascular versus conservative treatment was reported in five studies, four level III-2 studies and one level III-3 study. Neuropsychological outcomes were reported in four level III-2 studies.

Coiling versus clipping

Ruptured aneurysms

The majority of studies reported on ruptured aneurysms (Table 7). Within this group, two studies each reported on ruptured ACoA aneurysms and ruptured saccular aneurysms, and one study reported on ruptured basilar tip aneurysms. Allocation to treatment within this group of studies was consecutive in eleven studies, with five of these reporting that consultation with surgical staff also affected patient allocation. Three studies reported matching patients in treatment groups by age, sex, Hunt and Hess grades, and preoperative IQ. One study was retrospective and one study was a subset of the randomised ISAT cohort.

Eight studies failed to report any exclusion criteria. Non-confirmation of aneurysm by angiography, CT or lumbar puncture excluded patients in four studies and periods varying from 72 hours to eight days post SAH excluded patients in six studies. Multiple or giant aneurysms excluded patients in three studies and the World Federation of Neurological Societies (WFNS) and Hunt and Hess grades of IV or V were also used to exclude patients. The patient's condition on admission including brain stem reflexes, severity of other systemic complications, vasoconstriction, cardiac complications and pregnancy were used to exclude patients from one study. Mycotic and traumatic aneurysms, or treatment with both endovascular and surgical methods, excluded patients from one study; while death before 12-month follow-up removed patients from the analysis of another study.

Four studies reported follow-up in the immediate postoperative period only, nine studies reported medium term follow-up (between 3-12 months) and one study reported follow-up from 3-79 months. Two studies did not report follow-up times and five reported follow-up separately for clipping (range of 0-72 months) and coiling (0-120 months).

Losses to follow-up were not reported in 15 studies. Four studies reported the losses to follow-up in the coiling patients only, and two studies reported losses to follow-up for both coiling and clipping, while one study did not complete follow-up due to the poor grade of patients at discharge. One study did not report any losses to follow-up, however 19 patients died in hospital and 7 died during the follow-up period.

Table 7: Allocation and follow-up in non-randomised comparative studies of ruptured aneurysms

Study	Aneurysm type	Allocation	Treatment decision	Exclusion criteria	Follow-up (months)	Losses to follow-up
Asgari <i>et al.</i> 2003	Ruptured	Consecutive	NR	NR	12	NR
Bellebaum <i>et al.</i> 2004	Ruptured	Matched for age, sex, Hunt and Hess grade and psychological status	Technical issues	NR	Coiling 22.7 [14.6] [†] Clipping 28.4 [11.2] [†]	NR
Chan <i>et al.</i> 2002	Ruptured ACoA	Matched for Hunt and Hess grade and aneurysm size	NR	NR	12	Coiling 1/14 (died) Clipping 1/6 (died)
Charpentier <i>et al.</i> 1999	Ruptured	Retrospective identification of 432 patients during study period	Technical issues	Angiographic confirmation of vascular abnormality, treatment >8 days post SAH, intracranial vasoconstriction on admission, endovascular + surgical treatment	6	NR
Corsten <i>et al.</i> 2001	Ruptured	NR	Endovascular preferred for specific aneurysms	NR	6	NR
Dehdashti <i>et al.</i> 2004	Ruptured	Consecutive/decision of surgical or interventional neuroradiology team	Technical and accessibility issues	WFNS grade IV or V, death < 5 days post treatment (except vasospasm), > 72hrs post SAH, mycotic or traumatic aneurysms, no brain stem function	6	NR
Fontanella <i>et al.</i> 2003	Ruptured ACoA	Consecutive/decision of surgical or interventional neuroradiology team/patient choice	Technical issues, patient choice, availability of surgical team	WFNS grade III-V, multiple or giant aneurysms	6	NR
Fukui <i>et al.</i> 2004	Ruptured	NR	Technical and anatomical issues	NR	Coiling 14-58 (33.5) [#] Clipping 3-57 (21) [#]	Coiling 11/38 (28.9%) Clipping 28/142 (19.7%)
Goddard, Raju & Gholkar 2004	Ruptured	Random – part of ISAT	Technical issues and clinical grade	Rupture not confirmed by CT or lumbar puncture, incomplete follow-up	4-8	19 patients died in hospital and 7 during follow-up
Gruber <i>et al.</i> 1999b*	Ruptured, treated within 3 - 7 days	Consecutive/decision of team	NR	>72 hrs post SAH, no brainstem reflex	NR	NR
Hadjivassilou <i>et al.</i> 2001**	Ruptured	By treatment centre, age, WFNS, IQ	Patient choice or random (ISAT) criteria	Death before 12 month follow-up	12	NR
Hirohata <i>et al.</i> 2004	Ruptured treated within 72 hours	Consecutive/decision of treatment team	Technical issues, set criteria	Cerebral haematoma	Coiling 7-47 (47) [#] Clipping NR	Coiling 16 died, 20/163 were not followed up due to poor discharge grade. Clipping NR

***Subset of Asgari database; *Clipping preferred for ACoA and coiling for PCA; **some overlap with ISAT – clipping Royal Hallamshire Hospital and coiling Radcliffe Infirmary; [#]Median; [†]Standard deviation.

Table: 7 Allocation and follow-up in non-randomised comparative studies of ruptured aneurysms continued

Study	Aneurysm type	Allocation	Treatment decision	Exclusion criteria	Follow-up (months)	Losses to follow-up
Hoh <i>et al.</i> 2004a	Ruptured	Consecutive	Neurosurgical team	Treatment not coiling or clipping, > 14 days post SAH, death <4 days post SAH, infectious or dissecting aneurysm	Immediate postoperative	None
Hoh <i>et al.</i> 2004b	Ruptured	Consecutive prospective	NR, although larger aneurysms were coiled and smaller or anterior aneurysms were clipped	NR	Immediate postoperative	NR
Kobayashi <i>et al.</i> 2001	Ruptured saccular aneurysm treated within 4 days of SAH	NR	Set criteria on the basis of aneurysm type	>4 days post SAH	NR	NR
Lusseveld <i>et al.</i> 2002	Ruptured basilar tip	NR	NR	NR	Coiling 2-19 (4) [#] Clipping 1.5-18 (3.5) [#]	Coiling only reported: 6 months 2/44, 12 months 18/44
Miss <i>et al.</i> 2004	Ruptured	Neurosurgeons and interventional neuroradiologists	Surgical team, generally anterior aneurysms were clipped and posterior aneurysms were coiled	<21 yrs old, SAH not confirmed by CT or lumbar puncture, not eligible for coil or clip, cardiovascular complications, pregnancy, multiple aneurysms	Immediate postoperative (3 days) [#]	NR
Rabinstein <i>et al.</i> 2003	Ruptured	Consecutive	Surgical team	No angiography, > 7 days post SAH, fusiform aneurysm, previous aneurysm treatment, mycotic, traumatic or multiple aneurysms	Coiling 0-72 (7) [#] Clipping 0-120 (6) [#]	NR
Richling <i>et al.</i> 2000 ^{***}	Ruptured	Consecutive/surgical team decision	Set criteria	Multiple or unruptured aneurysms, parent artery occlusion	3-79 (43.5) [#]	Coiling only 62/175 (35%)
Ross <i>et al.</i> 2002	Ruptured in Hunt and Hess grade IV or V	Consecutive	Set criteria - angioanatomy	NR	3	NR
Yalamanchili <i>et al.</i> 1998	Ruptured saccular	Consecutive	Endovascular treatment was offered to poor surgical candidates, surgical treatment was offered if the aneurysm was contraindicated for endovascular treatment	Endovascular + surgical treatment, Hunt and Hess grade IV or V	Immediate postoperative	NR

***Subset of Asgari database; *Clipping preferred for ACoA and coiling for PCA; **some overlap with ISAT – clipping Royal Hallamshire Hospital and coiling Radcliffe Infirmary; [#]Median; [†]Standard deviation.

Unruptured aneurysms

Seven studies reported on unruptured aneurysms (Table 8). Two studies reported on saccular aneurysms, with single studies reporting on ICS/ophthalmic aneurysms, intradural and non-giant saccular aneurysms and ACoA and MCA aneurysms. One study reported only on patients with multiple aneurysms. Allocation in six studies was consecutive; however five of these studies also reported that surgical teams were involved in patient allocation. Patient age and history, in addition to clinical and radiographic presentation, were used to allocate patients in one study.

One study did not report follow-up and three studies reported follow-up periods of between 6 and 13 months. Immediate postoperative follow-up was reported in one study with another stating that follow-up ranged from 1 week postoperatively to 84 months. Treatment follow-up periods were reported in one study, with a follow-up period of 37 months for coiling patients and 54 months for clipping patients.

Losses to follow-up were not reported in four studies, and single deaths for each treatment were reported in two studies. One study restricted follow-up to patients with a preoperative Rankin score of one.

Table 8: Allocation and follow-up in non-randomised comparative studies of unruptured aneurysms

Study	Aneurysm type	Allocation	Treatment decision	Exclusion criteria	Follow-up (months)	Losses to follow-up
Boet <i>et al.</i> 2005	Unruptured ICA/OphthA	Combined endovascular/surgical team	NR	NR	1 week-84 months	Coiling 1/14 (died) Clipping 1/6 (died)
Bilistra <i>et al.</i> 2004	Unruptured intradural saccular	Doctor selected	NR	Mycotic, bacterial or traumatic aneurysms, ruptured/unruptured treated concurrently, EC-IC bypass	12	Coiling 13/19 (1 died) Clipping 27/32 (1 died)
Manabe <i>et al.</i> 2004	Unruptured non giant saccular	Review by at least 2 neurosurgeons	NR	NR	Immediate postoperative	NR
Porter <i>et al.</i> 2001	Multiple	Consecutive/surgeon and interventional neuroradiology teams	Surgical team	Giant, dissecting, inflammatory, multiple or extradural aneurysms, AVM cavernous. Insufficient clinical or angiographic information	13 (mean)	NR
Proust <i>et al.</i> 2003	ACoA	Consecutive/ surgeon and interventional radiology teams/patient	Surgical team initially, then set technical criteria	NR	6-12	NR
Regli <i>et al.</i> 2002	Unruptured MCA	Consecutive	Endovascular unless technical/set criteria not met	Treatment of other lesion concurrently, refused treatment, cerebral ischaemia from ruptured aneurysm	NR	NR
Singh <i>et al.</i> 2002	Unruptured	Patient age, history symptoms and radiographic presentation	Technical/set criteria	<18yrs, ruptured aneurysm, SAH <6 months, other aneurysm with different treatment <2months, AVM	Coiling 37 Clipping 54	Limited to Rankin score of 1 preoperatively (98 patients) 5/98 lost, 2/98 died, 8/98 refused follow-up

Ruptured and unruptured aneurysms

Four studies reported on the treatment of both ruptured and unruptured aneurysms (Table 9), three of which used consecutive patient allocation. The fourth study, which reported on the treatment of basilar tip aneurysms, required the potential to either coil or clip the aneurysm for allocation in the program. Follow-up in these studies ranged from 1 to 48 months.

Exclusion criteria included aneurysms that were not suitable for endovascular and surgical treatment, poor patient condition, cerebral haematoma, or aneurysms that were to be treated conservatively.

Losses to follow-up were reported only in one study, which involved the loss of nine patients from the coiling group.

Table 9: Allocation and follow-up in non-randomised comparative studies of ruptured and unruptured aneurysms

Study	Aneurysm type	Allocation	Treatment decision	Exclusion criteria	Follow-up (months)	Losses to follow-up
Collice <i>et al.</i> 1998	Ruptured/unruptured	Consecutive	Set criteria including age, clinical condition	Cerebral haematoma, Hunt and Hess grade V	6-36	None
Gruber <i>et al.</i> 1999c	Ruptured/unruptured (11R/10U) basilar tip	Endovascular or surgical potential	Endovascular preferred for poor grade patients	When only endovascular or surgical treatment is appropriate	12-48 (mean 26)	NR
Sano <i>et al.</i> 2000	Ruptured/unruptured (37R/33U coiling, 307R/95U clipping)	Consecutive	NR	Untreated aneurysm due to severity of systemic complications	6	NR
Vindlacheruvu <i>et al.</i> 2003	Ruptured/unruptured (48R/38U coiling, 155R/65U clipping)	Consecutive	NR	Giant aneurysms or those not receiving definitive treatment	1-24 (mean 12)	Coiling 9 patients

Endovascular versus surgical treatments

Seven studies reported on endovascular versus surgical treatments (Table 10). A variety of endovascular techniques were employed in these studies, including coiling and parent artery occlusion using balloons, as well as coiling in combination with balloons or stents. Four studies reported on ruptured aneurysms and one study reported on unruptured aneurysms. One study each reported on intracavernous carotid artery aneurysms and dissecting vertebral artery aneurysms. Two studies targeted patients with specific Hunt and Hess or Rankin grades associated with their ruptured aneurysms. The method of patient allocation was reported in only two studies, both of which allocated patients consecutively, however Sugiu *et al.* (2004) reported that allocation occurred in time blocks where all patients received the same treatment type within a certain time span.

Exclusion criteria were not reported in three studies, and the remaining studies excluded patients on the basis of fusiform or infectious aneurysms, a previous history of intracranial haemorrhage, and a survival of greater than 24 days post treatment. In this latter exclusion

criterion, the patients had been transferred from another facility and were excluded in order to prevent any bias due to their sound prognosis.

Table 10: Allocation and follow-up in non-randomised comparative studies of endovascular versus surgical treatments

Study	Aneurysm type	Allocation	Treatment allocation	Exclusion criteria	Follow-up (months)	Losses to follow-up
Groden <i>et al.</i> 2000	Ruptured vertebral artery SAH	NR	Surgical until 1995, then endovascular	Patients not treated	Endovascular 8-49 (19) Surgical 17-183 (101)	Coiling 4/12 (1 death, 3 non-compliance)
Groden <i>et al.</i> 2001	Ruptured, Hunt and Hess grade IV-V	NR	NR	Survival >24 days, not evaluable	6	Coiling 30/42 (17 died, 6 poor condition, 5 non-compliant, 2 recent treatment). Clipping, no postoperative angiography except for surgeon request (6 died)
Lihara <i>et al.</i> 2003a	Unruptured non giant paraclinoid	NR	NR	Large or giant aneurysms requiring PAO	6	NR
Kai <i>et al.</i> 2001	Dissecting vertebral artery	NR	NR	NR	29	NR
Linskey <i>et al.</i> 1991	Intracavernous carotid artery	NR	NR	NR	25	NR
Sugiu <i>et al.</i> 2004	Ruptured vertebral artery dissecting	Consecutive	1992-1997 all patients were surgical, 1998 onwards endovascular, 2000 onwards endovascular techniques were treatment of choice for all patient conditions	NR	Immediate postoperative	NR
Wiebers <i>et al.</i> 2003	At least one unruptured aneurysm and a Rankin score of 1 or 2	Consecutive and prospective	Clinical grounds	Fusiform, mycotic, or traumatic aneurysms, <2mm, SAH, prior unruptured aneurysm, history of cerebral haemorrhage, malignant tumour, incommunicable	Endovascular mean [SD] 44.4 [22.2] Surgical mean 48.0 [23.9]	Endovascular NR Surgical 6/1917

Endovascular versus conservative treatments

Comparisons between endovascular and conservative treatments were reported in five studies (Table 11). A variety of endovascular techniques were employed in these studies, including coiling alone, or in combination with balloons or stents. Four studies reported on ruptured aneurysms, where patient allocation was consecutive in two studies (one reported that patients in poor clinical condition were always treated conservatively) and one study reported retrospective allocation. The exclusion criteria, which were reported in two studies, included patients with SAH for the unruptured study and patients with massive cerebral haemorrhage, poor Glasgow Coma Scores (GCS), or those who were greater than 85 years of age. Follow-up periods were generally medium term (at least 12 months); however two studies reported longer term follow-up ranging from 53 to 88 months. Losses to follow-up were not reported in any of the studies.

Table 11: Allocation and follow-up in non-randomised comparative studies of endovascular versus conservative treatments

Study	Aneurysm type	Allocation	Treatment allocation	Exclusion criteria	Follow-up (months)	Losses to follow-up
Anxionnat <i>et al.</i> 2003	Ruptured, mixed aneurysm and patient factors	Consecutive, conservative in poor clinical condition	Endovascular techniques were the treatment of choice, except for poor grade patients and specific aneurysms	NR	12	NR
Chung & Han 2002	Ruptured, dissecting vertebralbasilar	Retrospective	NR	NR	10-92 (mean 53)	NR
Inamasu <i>et al.</i> 2002	Ruptured, Hunt and Hess grade V	Consecutive	Hunt and Hess grade V for endovascular, and recovery <12hrs for surgical, all other patients were treated conservatively	Massive cerebral haemorrhage, recovery within 12hrs, GCS 3, >85 yrs	12	NR
Naito <i>et al.</i> 2002	Unruptured, dissecting VA	NR	NR	Patients with SAH	4 days – 88 months (mean 14.2 months)	NR
Ramgren <i>et al.</i> 2005	Ruptured, dissecting vertebralbasilar	NR	NR	NR	3-46 (mean 15)	NR

Neuropsychological outcomes

Five studies, one RCT and four non-randomised comparative studies reported on neuropsychological outcomes (Table 12). Reporting covered five parameters including affective measures, premorbid intelligence, memory, attention, and executive function. Koivisto *et al.* (2002) did not report on affective measures, and the testing of other parameters in this study occurred 3 and 12 months after treatment. The remaining studies tested patients at either 6 or 12 months post treatment.

Table 12: Neuropsychological tests employed in randomised and non-randomised comparative studies

Study	Assessment time	Affective measures	Premorbid intelligence	Memory	Attention	Executive function
Bellebaum <i>et al.</i> 2004	At least 6 months after treatment	VAS for current mood Beck depression inventory (German)	Multiple vocab choice test (German)	Digit span and logical memory subtest of Wechsler memory scale, Benton visual retention test	Computer based test battery for assessment of attention (TAP), Reaction time for alertness/divided attention	Verbal fluency, Cognitive estimates task, BADS test, key search for BADS for planning, BADS questionnaire of patient reported executive outcomes
Chan, Ho & Poon 2002	12 months after treatment	<i>Motor ability and psychomotor speed</i> Grooved pegboard test, digital symbol subtest, WAIS-R	<i>Language function</i> Boston naming test, information and comprehension subtests of WAIS-R	Hong Kong list learning test, visual reproduction subtest of Wechsler memory scale and Brief visual memory scale	Colour trail making, Visual search task, Visual reproduction of Wechsler memory scale, Block design subtest of WAIS, Facial recognition test (short form)	Verbal fluency, five point test, alternative drawing test WAIS-R, semantic knowledge test
Fontanella <i>et al.</i> 2003	6 months after treatment	Beck depression inventory Stait-trait anxiety-episodic and disposition	Raven coloured matrices, Italian verbal judgement test	WMS story recall, Bi-syllabic word repetition, Corsi's block tapping test, Verbal and spatial learning	Visual search task	Verbal fluency test- phonic, semantic, alternating, Eilthom's test of special planning, WAIS picture arrangement
Hadjivassiliou <i>et al.</i> 2001	12 months after treatment	Beck depression inventory	WAIS-R vocabulary, Similarities, Block design <i>Language function</i> Boston naming test - modified	WMS story recall (immediate, delayed), WMS digit span, face, word recognition, Corsi's tapping test	Trail making B-A	Verbal fluency test (phonic, semantic), WAIS picture arrangement, digit ordering, CANTAB ID/ED shift test (shift stage, stages complete), CANTAB working memory strategy count, between errors. CANTAB Tower of London moves above minimum
Koivisto <i>et al.</i> 2002	3 and 12 months after treatment	Beck depression inventory, VAS (12 month only)	WAIS-R verbal, performance IQ, German verbal IQ	WAIS-R memory quotient, WMS story recall (immediate and delayed), WMS Visual reproduction (immediate and delayed), Benton visual retention test (correct and errors), Rey complex figure reproduction (delayed), WMS digit span (forwards and backwards)	Stroop test A,B,C, Trail making A,B,	Verbal fluency test, Boston naming test

Registry studies

Four registry studies were included in this review (Table 13). Two studies each reported on ruptured and unruptured aneurysms with patient information drawn from three databases in the USA and one in Japan.

The main endpoints reported in all studies were hospital mortality and discharge to a facility other than home. Follow-up was only reported in two studies and ranged from three to 3.3 years. Additionally, PAO, AVM and fistula were identified as conditions excluded from the study cohort. Losses to follow-up were not reported in any of the studies.

Table 13: Allocation and follow-up in included registry studies

Study	Dates	Intervention	No. of patients	Exclusion criteria	Endpoints/adverse outcomes	Follow-up (months)	Losses to follow-up
Barker <i>et al.</i> 2004 USA	1996 – 2000	UNRUPTURED endovascular surgical	3919 421 3498	SAH	In hospital mortality, discharge other than home, length of hospital stay	NR	NR
Hamada <i>et al.</i> 2004 JAPAN	Jan 96 – Dec 00	RUPTURED coiling clipping conservative	2115 178 1456 481	Recurrent SAH	GOS	3	NR
Johnston 2000a, Johnston 2000b, Johnston, Gress & Kahn 1999 USA	Jan 94 – Dec 97	RUPTURED coiling clipping not treated UNRUPTURED coiling clipping	9543 248 5174 4112 2623 264 2359	AVM, fistula	In hospital mortality, discharge other than home	NR	NR
Johnston <i>et al.</i> 2001 USA	Jan 90 – Dec 98	UNRUPTURED coiling clipping	2069 370 1699	PAO, prior SAH, AVM	In hospital mortality, discharge other than home	3.3 years	NR

Ruptured aneurysms

Comparison 1: Endovascular coiling versus surgical clipping

Randomised controlled trials

Due to study design, clinical and technical variability, it was not possible for a meaningful meta-analysis to be carried out on any of the outcomes in the two included RCTs.

Safety

Perioperative mortality

There was no significant difference in early mortality between endovascular coiling and surgical clipping in the two RCTs (Table 14). In Koivisto *et al.* (2002), 1/52 coiling patients died within 30 days of the procedure compared with 2/57 clipping patients. In Molyneux *et al.* (2005), 7% (75/1065) of coiling patients died within two months compared with 7.9% (84/1063) in the clipping group.

Table 14: Safety outcomes in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	coiling	clipping	RR (95% CI)
Mortality within 30 days			
Koivisto <i>et al.</i> (2002)	1/52 (1.9%)	2/57 (3.5%)	NR
Mortality at 2 months			
Molyneux <i>et al.</i> (2005)	75/1065 (7.0%)	84/1063 (7.9%)	NR
Rebleeding after first procedure and before 30 days			
Molyneux <i>et al.</i> (2005)	20/1073 (1.9%)	8/1070 (0.8%)	2.46 (1.09 to 5.57)
Rebleeding 30 days to 1 year			
Molyneux <i>et al.</i> (2005)	8/1073 (0.8%)	3/1070 (0.3%)	2.64 (0.70 to 9.93)
Rebleeding after 1 year			
Koivisto <i>et al.</i> (2002)	0/45 (0.0%)	0/48 (0.0%)	NR
Molyneux <i>et al.</i> (2005)	7/1073 (0.7%)	2/1070 (0.2%)	NR
Seizures after procedure			
Molyneux <i>et al.</i> (2005)	57/1073 (5.3%)	101/1070 (9.4%)	0.52 (0.37 to 0.74)

Rebleeding (due to target aneurysm)

In Molyneux *et al.* (2005), more coiling patients rebled after the first procedure and before 30 days, 1.9% (20/1073) compared with 0.8% (8/1070) in the clipping group (Table 14). After 30 days and up to one year, 8 coiling patients and 3 clipping patients rebled. Of these 8 coiling patients, 3 were independent at follow-up and 5 were dead or dependent. After one year, there were 7 rebleeds in the coiling group and 2 in the clipping group. No difference was seen in cumulative rebleeding risk between the coiling and clipping groups ($p=0.22$).

Koivisto *et al.* (2002) reported that one patient rebled after failed coiling, and subsequently died. There were no cases of rebleeding after one year in either group.

Seizures

Significantly fewer patients in the coiling group (5.3%, 57/1073) had seizures after the procedure compared with the clipping group (9.4%, 101/1070) (Table 14).

Other complications

Koivisto *et al.* (2002) reported three cases of perforation and 1 each of coil protrusion, coil migration, parent vessel obstruction by coils, haematoma and TIA, in the coiling group. In the clipping group, three patients suffered an intraoperative rupture of the aneurysm (2 died) and 1 patient had an abscess on the frontal lobe. Six percent (3/52) of the coiling group required a permanent shunt for hydrocephalus compared with 19% (11/57) in the clipping group ($p=0.045$). Koivisto *et al.* (2002) reported that there was no significant difference between the coiling and clipping groups with regards to the incidence of vasospasm, but no figures were given.

Neuropsychological outcomes

Neuropsychological outcomes were reported in one study (Koivisto *et al.* 2000), in which patients underwent a number of neuropsychological tests, 3 and 12 months after treatment (Table 15). This study showed no significant difference in any of the neuropsychological outcomes measured at either the 3 month or 12 month assessment, after coiling and clipping.

Table 15: Neuropsychological outcomes in patients undergoing coiling or clipping for ruptured aneurysms in Koivisto *et al.* (2000)

Neuropsychological outcome	Koivisto <i>et al.</i> (2000)					
	3 months			12 months		
	coiling	clipping	p value	coiling	clipping	p value
Intelligence						
WAIS-R verbal IQ	97.0 [15.8]	97.3 [14.4]	0.937	99.0 [16.5]	97.0 [16.7]	0.198
WAIS-R performance IQ	102.7 [17.9]	105.2 [16.3]	0.560	106.3 [16.6]	106.4 [20.2]	0.998
Memory						
WAIS-R memory quotient	107.8 [16.8]	109.8 [16.9]	0.626	112.2 [18.2]	110.0 [17.3]	0.526
WMS story recall – immediate	9.0 [3.2]	8.4 [3.7]	0.674	9.3 [3.3]	8.6 [3.9]	0.429
WMS story recall – delayed	7.6 [3.1]	6.7 [3.5]	0.274	8.1 [3.2]	7.5 [3.8]	0.501
WMS visual reproduction – immediate	10.9 [2.4]	11.0 [2.7]	0.855	10.9 [2.9]	10.6 [3.0]	0.620
WMS visual reproduction – delayed	8.3 [3.3]	7.7 [3.6]	0.500	8.3 [4.3]	7.0 [4.2]	0.178
Rey Complex Figure reproduction - delayed	14.4 [4.6]	12.7 [6.9]	0.458	12.4 [5.4]	12.5 [6.8]	0.948
WMS digit span - forwards	12.6 [3.6]	12.8 [3.1]	0.986	12.8 [4.0]	12.5 [3.4]	0.750
Psychomotor function						
Finger tapping test – dominant hand	50.5 [9.4]	50.2 [10.4]	0.918	49.6 [9.8]	48.5 [9.1]	0.627
Finger tapping test – nondominant hand	45.8 [8.6]	44.9 [8.4]	0.903	44.6 [8.9]	44.3 [8.3]	0.881
Attention						
Stroop test A	26.5 [8.7]	26.5 [6.2]	0.995	31.1 [26.5]	27.8 [6.8]	0.462
Stroop test B	34.5 [13.1]	33.2 [7.9]	0.625	38.3 [26.2]	34.8 [10.4]	0.449
Stroop test C	68.0 [26.0]	66.4 [23.3]	0.798	69.1 [37.0]	67.3 [23.4]	0.802
Trail making A	45.8 [27.7]	48.4 [29.7]	0.720	46.8 [34.7]	45.8 [24.9]	0.892
Trail making B	121.2 [76.7]	122.3 [68.4]	0.952	132.6 [83.8]	128.5 [73.6]	0.824
Executive function						
Verbal Fluency Test	35.7 [14.0]	33.4 [12.6]	0.498	38.3 [16.1]	36.1 [12.5]	0.510
Boston Naming Test – Modified	23.9 [3.8]	23.3 [4.4]	0.552	23.7 [3.8]	22.4 [4.4]	0.180

NOTE: WAIS-R Wechsler Adult Intelligence Scale – Revised; WMS – Wechsler Memory Scale

Effectiveness

Crossover to other procedure

Koivisto *et al.* (2002) reported crossover from coiling to clipping in twelve patients. The reasons for crossover included coil perforation (n=2), rebleeding (n=1), haematoma (n=1), parent vessel occlusion (n=1), coil collapse (n=4) and the fact that the neck of the aneurysm was too wide (n=3). Residual aneurysms in four cases resulted in the crossover from clipping to coiling.

Molyneux *et al.* (2005) reported nine crossovers from clipping to coiling due to clinical decision (n=1), patient decision (n=4) and equipment malfunction (n=4). Conversely, crossover from coiling to clipping occurred in 39 patients, due to clinical decision (n=15), and patient preference (n=18). The reason for crossover was not reported in 6 cases.

Retreatment

In Molyneux *et al.* (2005) 7.5% (81/1073) of the coiling group required retreatment within 30 days, with 67 patients undergoing clipping, while 14 patients were recoiled. In the clipping group, 2.6% (28/1070) required retreatment within 30 days, with 4 patients undergoing coiling, while 4 patients were reclipped (Table 16).

In Koivisto *et al.* (2002), 27% (12/45) of the coiling group required retreatment within a year, with 3 patients undergoing recoiling, while 9 patients were clipped. In the clipping group, 6.3% (3/48) required retreatment and all 3 patients were coiled (Table 16).

Table 16: Crossover and retreatment for patients undergoing coiling or clipping for ruptured aneurysms

Outcome	coiling	clipping	p value
Crossover to other procedure			
Koivisto <i>et al.</i> (2002)	12/52 (23.0%)	4/57 (7.0%)	0.028
Molyneux <i>et al.</i> (2005)	9/1073 (0.8%)	39/1070 (3.6%)	<0.0001
Retreatment within 30 days			
Molyneux <i>et al.</i> (2005)	81/1073 (7.5%)	28/1070 (2.6%)	NR
Retreatment within 12 months			
Koivisto <i>et al.</i> (2002)	12/45 (27%)	3/48 (6.3%)	NR

Functional outcomes (including 12-month mortality)

Koivisto *et al.* (2002) reported no overall differences between coiling and clipping in terms of functional outcomes, measured by the Glasgow Outcome Scale (GOS) score at 3 months (p=0.36) or 12 months (p=0.319) (Table 17).

Molyneux *et al.* (2005) used the Modified Rankin Scale (MRS) to measure functional outcomes at 2 and 12 months posttreatment (Table 17). Functional outcome were reported as a composite score (MRS 3-6) of death or dependency for coiling (23.5%) versus clipping (30.9%) at 12 months, which corresponded to a relative risk reduction of 23.9% (95% CI: 12.4 to 33.9). When calculated as differences in individual grades, there were significant differences in favour of coiling for MRS 0 (no symptoms) and MRS 3 (significant restriction in lifestyle) at 2 and at 12 months, however none of the other grades showed significant differences between coiling and clipping at either time point.

Table 17: Functional outcomes in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	coiling	clipping	RR reduction or p value
GOS score at 3 months (Koivisto <i>et al.</i> 2002) at 3 months			
Good outcome (GOS 4-5)	42/52 (80.8%)	45/57 (78.9%)	0.36 overall
Poor outcome (GOS 2-3)	4/52 (7.7%)	6/57 (10.5%)	
Dead (GOS 1)	6/52 (11.5%)	6/57 (10.5%)	
GOS score at 12 months (Koivisto <i>et al.</i> 2002)			
5 (good recovery)	40/52 (76.9%)	38/57 (66.7%)	0.319 overall
4 (moderate disability)	1/52 (1.9%)	5/57 (8.8%)	
3 (severe disability)	3/52 (5.8%)	4/57 (7.0%)	
2 (unresponsive)	1/52 (1.9%)	1/57 (1.8%)	
1 (dead)	7/52 (13.5%)	9/57 (15.8%)	
MRS score at 2 months (Molyneux <i>et al.</i> 2005)			
0 (no symptoms)	203/1065 (19.1%)	144/1063 (13.6%)	NR
1 (minor symptoms)	310/1065 (29.1%)	273/1063 (25.7%)	
2 (some restrictions)	274/1065 (25.7%)	254/1063 (23.8%)	
3 (significant restrictions)	107/1065 (10.1%)	189/1063 (17.8%)	
4 (partly dependent)	34/1065 (3.2%)	46/1063 (4.3%)	
5 (fully dependent)	62/1065 (5.8%)	73/1063 (6.9%)	
6 (dead)	75/1065 (7.0%)	84/1063 (7.9%)	
MRS score at 12 months (Molyneux <i>et al.</i> 2005)			
0 (no symptoms)	260/1063 (24.5%)	187/1055 (17.7%)	NR
1 (minor symptoms)	301/1063 (28.3%)	292/1055 (27.7%)	
2 (some restrictions)	252/1063 (23.7%)	250/1055 (23.7%)	
3 (significant restrictions)	107/1063 (10.1%)	141/1055 (13.4%)	
4 (partly dependent)	30/1063 (2.8%)	42/1055 (4.0%)	
5 (fully dependent)	28/1063 (2.6%)	38/1055 (3.6%)	
6 (dead)	85/1063 (8.0%)	105/1055 (9.9%)	
3-6 (dead or dependent)	250/1063 (23.5%)	326/1055 (30.9%)	23.9% (95% CI 12.4 to 33.9)

Mortality at 12 months

Neither Koivisto *et al.* (2002) nor Molyneux *et al.* (2005) reported significant differences in mortality at 12 months. Molyneux *et al.* (2005) did report that the Kaplan-Meier cumulative mortality to 7 years was significantly less for coiling ($p=0.03$).

In Koivisto *et al.* (2002), 13.5% (7/52) of the coiling patients were dead at 12 months compared with 15.8% (9/57) of the clipping patients. The corresponding figures for Molyneux *et al.* (2005) were 8.0% (85/1063) for coiling and 7.9% (84/1063) for clipping. Note that Molyneux *et al.* (2005) counted all deaths, whereas Koivisto *et al.* (2002) did not count 5 deaths, which were considered to be unrelated to SAH (2 coiling, 3 clipping).

Koivisto *et al.* (2002) reported that 9 patients died as a result of SAH/vasospasm (5 coiling, 4 clipping), 1 died from early rebleeding (coiling), 2 died as a result of the primary surgery (both clipping) and 2 died from late clipping of a residual aneurysm (1 each from the coiling and clipping groups). In Molyneux *et al.* (2005), after 2 months (and up to 8 years) there were 43 deaths in the coiling group and 66 deaths in the clipping group (Table 18).

Table 18: Causes of death at follow-up in Molyneux *et al.* (2005)

Cause of death	coiling	clipping
Complications of severe dependent survival	8	20
Treated aneurysm rebleeding	3	3
Bleed from another aneurysm	3	0
Other intracranial haemorrhage	1	0
Ischaemic stroke	2	3
Cardiac	5	10
Cancer	9	13
Suicide	2	2
Renal failure	1	2
Infections not related to dependent survival	5	6
Other causes	2	4
Unknown	2	3
TOTAL	43	66

Subgroup analyses for death and dependency

In Molyneux *et al.* (2005) there was no consistent correlation between age or clinical grade and death or dependency. Results for aneurysm location were also difficult to interpret, although aneurysms located in the internal carotid artery showed the most favourable outcomes with coiling for death and dependency: 20.1% (69/344) for coiling compared with 35.9% (125/348) for clipping, which corresponded to a significant relative risk reduction of 44% (95% CI: 38 to 47). Corresponding death and dependency results for anterior intracranial and anterior communicating aneurysms were 24.6% (131/533) for coiling and 27.5% (147/534) for clipping, a non-significant relative risk reduction of 11% (95% CI: -9 to 27).

Angiographic outcomes

In Koivisto *et al.* (2002) there was a significant overall difference in the degree of aneurysm occlusion during the immediate postoperative period, in favour of clipping ($p=0.0015$) (Table 19). During this period, coiling was significantly better than clipping for posterior circulation aneurysms ($p=0.045$), while clipping was significantly better than coiling for anterior circulation aneurysms ($p=0.005$), however no significant difference was seen for middle intracranial artery aneurysms or internal carotid artery aneurysms. At 12 months, there was no significant difference between the groups overall ($p=0.41$) and this was regardless of aneurysm location.

Molyneux *et al.* (2005) reported that angiograms were not routinely performed for patients who were clipped and so the results may reflect a group of clipping patients where there has been some concern about satisfactory occlusion. Nonetheless, a higher percentage of clipping patients (82.2%, 370/450) showed complete occlusion compared with the coiling patients (66.2%, 584/881), which is consistent with the results from Koivisto *et al.* (2002).

Table 19: Angiographic outcomes in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	coiling	clipping	p value
Degree of occlusion immediate postoperative (Koivisto <i>et al.</i> 2002)			
Total obliteration	26/52 (50%)	42/57 (74%)	Significant difference overall between groups (p=0.0015)
Neck remnant	18/52 (35%)	9/57 (16%)	
Filling of fundus	3/52 (6%)	5/57 (9%)	
No occlusion	5/52 (10%)	1/57 (2%)	
Degree of occlusion at 12 months (Koivisto <i>et al.</i> 2002)			
Total obliteration	40/52 (77%)	49/57 (86%)	No significant difference between groups overall (p=0.41)
Neck remnant	10/52 (19%)	7/57 (12%)	
Filling of fundus	2/52 (4%)	0/57 (0%)	
No occlusion	0/52 (0%)	1/57 (2%)	
Degree of occlusion at 12 months (Molyneux <i>et al.</i> 2005)			
Complete occlusion	584/881 (66%)	370/450 (82%)	NR
Neck remnant or incomplete	228/881 (26%)	55/450 (12%)	NR
Incomplete occlusion	69/881 (8%)	25/450 (6%)	NR

Technical failures

Molyneux *et al.* (2005) reported technical outcomes by procedure and not by treatment assignment. In patients who underwent coiling, 2.6% (29/1095) failed to have their target aneurysm catheterised, 3.4% (37/1095) had their target aneurysm catheterised but their anatomy was unsuitable, and coiling was not attempted in 1.4% (15/1095) of cases. In patients who were clipped, 1.3% (13/1012) were wrapped rather than clipped, while 1.4% (14/1012) of clipping procedures were not completed (partial clipping or wrapping) and in 0.8% (8/1012) of cases clipping was not attempted.

Non-randomised comparative studies

Safety

Perioperative mortality

Perioperative mortality rates were reported in fifteen studies (Table 20). The median rate of perioperative mortality was 11% (range 0 to 38%) in patients undergoing coiling, compared with 9% (range 0 to 28%) in patients undergoing clipping. Of the five studies which reported statistical data, four studies (Charpentier *et al.* 1999; Fukui *et al.* 2004; Hirohata *et al.* 2004; Miss *et al.* 2004) showed no discernible difference in the rate of perioperative mortality after coiling and clipping, while one study (Hoh *et al.* 2004a) reported a significantly higher (p=0.008) rate of perioperative mortality after coiling (27%) compared to clipping (9%), odds ratio (OR) = 0.29 (95% CI: 0.16 to 0.61).

In Proust *et al.* (2003) all patients had ACoA aneurysms, and of the five perioperative deaths in the coiling group, two were procedure-related and the remaining three were related to the initial SAH, while in the clipping group, all 6 perioperative deaths were related to the initial SAH.

Table 20: Perioperative mortality rates in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Charpentier <i>et al.</i> 1999	III-2	47/145	32%	28/99	28%	0.62
Corsten <i>et al.</i> 2001	III-2	17/139	12%	17/185	9%	NR
Fukui <i>et al.</i> 2004	III-2	1/38	3%	12/142	9%	0.29
Goddard <i>et al.</i> 2004	III-2	6/80	8%	13/212	6%	NR
Gruber <i>et al.</i> 1999b	III-2	15/77	19%	40/165	24%	NR
Hirohata <i>et al.</i> 2004	III-2	16/179	9%	5/101	5%	0.22
Hoh <i>et al.</i> 2004a	III-2	20/76	27%	38/406	9%	OR 0.29 (95% CI 0.16 to 0.61, p=0.008)
Miss <i>et al.</i> 2004	III-2	10/63	16%	15/109	14%	0.71
Sano <i>et al.</i> 2000	III-2	14/37	38%	36/307	12%	NR
Yalamanchili <i>et al.</i> 1998	III-2	0/18	0%	2/19	11%	NR
Gruber <i>et al.</i> 1999c	III-2	0/11	0%	1/15	7%	NR
Porter <i>et al.</i> 2001	III-2	1/33	3%	0/48	0%	NR
Proust <i>et al.</i> 2003	III-2	5/37	14%	6/103	6%	NR
Ross <i>et al.</i> 2002	III-2	10/40	25%	NR	NR	NA
Lusseveld <i>et al.</i> 2002	III-2/3	2/44	4%	5/44	11%	NR
Range of rates		0% to 38%		0% to 28%		15 studies
Median of rates		11%		9%		

NOTE: specific subgroups: Proust *et al.* 2003 – patients with anterior communicating artery aneurysms; Ross *et al.* 2002 – patients in Hunt and Hess grade IV or V; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms; Gruber *et al.* 1999c – patients with basilar tip aneurysms; Porter *et al.* 2001 – patients with multiple aneurysms.

Vasospasm

The incidence of symptomatic vasospasm was reported in eight studies (Table 21). The median rate of symptomatic vasospasm was 20% (range 6 to 48%) in patients undergoing coiling, compared with 29% (range 12 to 74%) in patients undergoing clipping. Of the five studies which reported statistical data on the two interventional groups, three studies (Charpentier *et al.* 1999; Dehdashti *et al.* 2004; Hoh *et al.* 2004a) showed no discernible difference in the incidence of symptomatic vasospasm after coiling and clipping, while two studies (Yalamanchili *et al.* 1998; Hirohata *et al.* 2004,) reported a significantly higher incidence of symptomatic vasospasm after clipping compared to coiling.

One study reported on the incidence of non-symptomatic vasospasm (Collice *et al.* 1998) (Table 21). This study reported that 3% of patients who underwent coiling suffered from non-symptomatic vasospasm, but did not provide comparable data for patients who underwent clipping.

Table 21: Vasospasm in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Symptomatic vasospasm						
Charpentier <i>et al.</i> 1999	III-2	25/145	17%	22/99	22%	0.37*
Dehdashti <i>et al.</i> 2004	III-2	4/26	15%	18/72	25%	0.42
Goddard <i>et al.</i> 2004	III-2	38/80	48%	103/212	49%	NR
Hirohata <i>et al.</i> 2004	III-2	8/166	9%	29/101	29%	p<0.0001
Hoh <i>et al.</i> 2004a	III-2	26/79	33%	117/413	28%	0.33
Kobayashi <i>et al.</i> 2001	III-2	3/49	6%	9/74	12%	NR
Rabinstein <i>et al.</i> 2003	III-2	23/76	30%	129/339	38%	NR
Yalamanchili <i>et al.</i> 1998	III-2	4/18	22%	14/19	74%	p<0.05
Range of rates		6% to 48%		12% to 74%		8 studies
Median of rates		20%		29%		
Non-symptomatic vasospasm		n/N	%	n/N	%	
Collice <i>et al.</i> 1998	III-2	1/37	3%	NR	NR	NR
Range of rates		NA		NA		1 study
Median of rates		NA		NA		

NOTE: *Cox proportional hazards model showed no difference between coiling and clipping in risk of symptomatic vasospasm p=0.93.

Intraoperative rupture

The incidence of intraoperative rupture was reported in five studies (Table 22). The median rate of intraoperative rupture was 3% (range 2 to 7%) in patients undergoing coiling, however only two studies reported comparable data for patients who underwent clipping, with one study reporting a 2% incidence of intraoperative rupture (Goddard *et al.* 2004) and the other study reporting a 14% incidence of intraoperative rupture (Lusseveld *et al.* 2002). Asgari *et al.* (2003) reported that the five cases of intraoperative rupture, which occurred in patients undergoing coiling, were due to guidewire perforation of the aneurysm wall (1), microcatheter perforation of the aneurysm (2) and coil placement (2).

Table 22: Intraoperative rupture in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Intraoperative rupture						
Asgari <i>et al.</i> 2003	III-2	5/164	3%	NR	NR	NA
Fukui <i>et al.</i> 2004	III-2	3/45	7%	NR	NR	NA
Goddard <i>et al.</i> 2004	III-2	2/80	3%	4/212	2%	NR
Hirohata <i>et al.</i> 2004	III-2	4/179	2%	NR	NR	NA
Lusseveld <i>et al.</i> 2002	III-2/3	3/44	7%	6/44	14%	NR
Range of rates		2% to 7%		NA		5 studies
Median of rates		3%		NA		

Delayed ischaemic neurological deficit

The incidence of delayed ischaemic neurological deficit was reported in six studies (Table 23). The median rate of delayed ischaemic neurological deficit was 15% (range 5 to 25%) in patients undergoing coiling, and also in patients undergoing clipping (range 7 to 41%). Of the three studies that reported statistical data on the two interventional groups (Goddard *et al.* 2004; Vindlacheruvu *et al.* 2003; Dehdashti *et al.* 2004), none showed a statistically significant difference in the incidence of delayed ischaemic neurological deficit after coiling and clipping.

Table 23: Delayed ischaemic neurological deficit in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
Delayed ischaemic neurological deficit		n/N	%	n/N	%	
Dehdashti <i>et al.</i> 2004	III-2	2/26	7%	7/72	9%	0.64
Goddard <i>et al.</i> 2004	III-2	11/80	14%	35/212	17%	0.69
Gruber <i>et al.</i> 1999b	III-2	7/45	16%	13/111	12%	NR
Vindlacheruvu <i>et al.</i> 2003	III-2/3	12/48	25%	63/155	41%	<0.1
Ross <i>et al.</i> 2002	III-2	9/40	23%	4/16	25%	NR
Lusseveld <i>et al.</i> 2002	III-2/3	2/44	5%	3/44	7%	NR
Range of rates		5% to 25%		7% to 41%		6 studies
Median of rates		15%		15%		

NOTE: Ross *et al.* 2002 – patients in Hunt and Hess grade IV or V; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms.

Intracranial infarction

The incidence of intracranial infarction was reported in seven studies (Table 24). The median rate of intracranial infarction was 5% (range 0 to 38%) in patients undergoing coiling, and 17% (range 7 to 27%) in patients undergoing clipping.

Table 24: Intracranial infarction in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
Intracranial infarction		n/N	%	n/N	%	
Gruber <i>et al.</i> 1999b	III-2	17/45	38%	24/111	22%	NR†
Hirohata <i>et al.</i> 2004	III-2	4/179	2%	7/101	7%	NR
Hoh <i>et al.</i> 2004b	III-2	17/114	15%	59/505	12%	NR
Sano <i>et al.</i> 2000	III-2	2/37	5%	NR	NR	NA
Porter <i>et al.</i> 2001	III-2	1/33	3%	NR	NR	NA
Proust <i>et al.</i> 2003	III-2	4/37	11%	NR	NR	NA
Lusseveld <i>et al.</i> 2002	III-2/3	0/44	0%	12/44	27%	NR
Range of rates		0% to 38%		7% to 27%		7 studies
Median of rates		5%		17%		

NOTE: specific subgroups: Proust *et al.* 2003 – patients with anterior communicating artery aneurysms; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms; Porter *et al.* 2001 – patients with multiple aneurysms.

† - trend toward higher rate for coiling but only statistically significant for HH grade V (p=0.01) but coiling preoperatively had significantly higher mean HH grade.

Thromboembolic complications

The incidence of thromboembolic complications was reported in five studies (Table 25). The median rate of thromboembolic complications was 3% (range 0 to 10%) in patients undergoing coiling; however, only two studies reported comparable data for patients who underwent clipping, with one study reporting a 0% incidence of thromboembolic complications (Hoh *et al.* 2004b) and the other study reporting a <1% incidence of thromboembolic complications (Vindlacheruvu *et al.* 2003).

Table 25: Thromboembolic complications in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Thromboembolic complications						
Fukui <i>et al.</i> 2004	III-2	3/45	7%	NR	NR	NA
Hoh <i>et al.</i> 2004b	III-2	12/114	10%	2/505	<1%	NR
Vindlacheruvu <i>et al.</i> 2003	III-2/3	1/48	2%	2/155	1%	NR
Yalamanchili <i>et al.</i> 1998	III-2	0/18	0%	NR	NR	NA
Porter <i>et al.</i> 2001	III-2	1/33	3%	NR	NR	NA
Range of rates		0% to 10%		NA		5 studies
Median of rates		3%		1%		

NOTE: Porter *et al.* 2001 – patients with multiple aneurysms.

Procedure-related complications

The incidence of procedure-related complications, including aneurysm perforation and rebleeding, coil fracture, ischaemic complications, incomplete occlusion, and parent artery or perforating artery occlusion, was reported in six studies (Table 26). The median rate of procedure-related complications was 9.5% (range 3 to 21%) in patients undergoing coiling, and 5.5% (range <1 to 25%) for patients who underwent clipping. The single study which reported statistical data on the two interventional groups, showed no discernible difference in the rate of procedure-related complications after coiling and clipping (Charpentier *et al.* 1999).

Table 26: Procedure-related complications in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Procedure-related complications						
Charpentier <i>et al.</i> 1999	III-2	28/145	19%	25/99	25%	0.27
Collice <i>et al.</i> 1998	III-2	1/37	3%	1/120	<1%	NR
Sano <i>et al.</i> 2000	III-2	6/37	16%	NR	NR	NA
Vindlacheruvu <i>et al.</i> 2003	III-2/3	10/48	21%	5/155	3%	NR
Ross <i>et al.</i> 2002	III-2	1/40	3%	NR	NR	NA
Proust <i>et al.</i> 2003	III-2	1/37*	3%	8/103†	8%	NR
Range of rates		3% to 21%		<1% to 25%		6 studies
Median of rates		9.5%		5.5%		

NOTE: Sano *et al.* 2000 – minor leakage, 1 leading to rebleeding; Charpentier *et al.* 1999 – aneurysm perforation, ischaemic complications, incomplete occlusion; Vindlacheruvu *et al.* 2003 – 3 coil fracture, 7 coil failure, clip malposition; Ross *et al.* 2002 – fatal vessel rupture during angiography; Proust *et al.* 2003 – *rebleeding (temporary), †parent artery or perforating artery occlusion.

Neurological complications

The incidence of neurological complications, including cranial nerve palsy, hemiparesis, hemiplegia and focal and global neurological deficits, was reported in four studies (Table 27). The median rate of neurological complications was 9.5% (range 3 to 21%) in patients undergoing coiling, and 5.5% (range <1 to 25%) for patients who underwent clipping. The single study which reported statistical data on the two interventional groups showed no discernible difference in the rate of procedure-related complications after coiling and clipping (Charpentier *et al.* 1999).

Table 27: Neurological complications in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
Neurological complications		n/N	%	n/N	%	
Hirohata <i>et al.</i> 2004	III-2	NR	NR	3/101	3%	NA
Yalamanchili <i>et al.</i> 1998	III-2	NR	NR	1/19	5%	NA
Porter <i>et al.</i> 2001	III-2	1/33	3%	2/48	4%	NR
Rabinstein <i>et al.</i> 2003	III-2	18/76	24%	109/339	32%	NR
Range of rates		NA		3% to 32%		4 studies
Median of rates		NA		4.5%		

NOTE: Porter *et al.* 2001 – patients with multiple intracranial aneurysms.

Effectiveness

Conversions to surgery

The rate of conversion to surgery was reported in five studies (Table 28). The median rate of conversion to surgery was 8% (range 0 to 26%). Fukui *et al.* (2004) reported that the seven conversions to surgery were due to thromboembolic complications, including the aneurysms being too small for coiling, incomplete packing, coil penetration, and difficulty with catheterisation.

Table 28: Conversions to surgery in patients undergoing coiling for ruptured aneurysms

Outcome	L of E	endovascular		
Conversion to surgery		n/N	%	
Fukui <i>et al.</i> 2004	III-2	7/45	16%	
Lusseveld <i>et al.</i> 2002	III-2	0/44	0%	
Porter <i>et al.</i> 2001	III-2	1/33	3%	
Collice <i>et al.</i> 1998	III-2	7/27	26%	
Ross <i>et al.</i> 2002	III-2	3/40	8%	
Range of rates		0% to 26%		5 studies
Median of rates		8%		

NOTE: specific subgroups: Ross *et al.* 2002 – patients in Hunt and Hess grade IV or V; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms; Porter *et al.* 2001 – patients with multiple aneurysms.

Length of hospital stay

The mean length of hospital stay was reported in two studies (Vindlacheruvu *et al.* 2003; Hoh *et al.* 2004). Hoh *et al.* (2004) reported that the mean length of hospital stay was 20.7 [SD=13.7] days in patients undergoing coiling ($n=79$), and 20.8 [SD=11.2] days in patients undergoing clipping ($n=413$), which included a mean length of stay in the ICU of 13.3 [SD=9.6] days and 12.9 [SD=5.8] days respectively. Vindlacheruvu *et al.* (2003) reported that in patients of good clinical grade, the mean length of hospital stay was 11.3 days in patients who underwent coiling ($n=48$), and 11.9 days in patients who underwent clipping ($n=155$). For those in poor clinical grade, the mean length of hospital stay was 11.5 days in patients who underwent coiling, and 14.4 days in patients who underwent clipping. This study showed no discernible difference in the mean length of hospital stay after coiling and clipping. Patients of good clinical grade were more likely to be discharged to home than patients of poor clinical grade ($p<0.05$), however there was no discernible difference between the treatment groups (coiling 48% versus clipping 36%, $p=0.83$).

Degree of aneurysm occlusion

The degree of aneurysm occlusion was reported in six studies (Table 29). Of the patients who underwent coiling, 66% (range 33-94%) of patients had totally occluded aneurysms and 27% (range 6 to 67%) of patients had partially occluded aneurysms. In patients who underwent clipping, 92% (range 91 to 98%) of patients had totally occluded aneurysms, and 8% (range 2 to 9%) of patients had partially occluded aneurysms. The single study which reported statistical data on the two interventional groups (Proust *et al.* 2003) showed significantly greater occlusion with clipping ($p=0.01$). Rabinstein *et al.* (2003) reported that of the patients who underwent coiling, subtotal occlusion of aneurysms in 56 patients was due to dog-ear remnants, residual necks and residual aneurysms. Lusseveld *et al.* (2002) reported that at 6 months follow-up, of the patients who underwent coiling, 64% (25/39 patients) had totally occluded aneurysms, and 36% (14/39 patients) had partially occluded aneurysms.

Table 29: Degree of aneurysm occlusion in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		total	partial	total	partial	
Charpentier <i>et al.</i> 1999	III-2	136/145(94%)	9/145 (6%)	97/99 (98%)	2/99 (2%)	NR
Hirohata <i>et al.</i> 2004	III-2	106/179 (59%)	66/179 (37%)	NR	NR	NR
Rabinstein <i>et al.</i> 2003	III-2	27/83 (33%)	56/83 (67%)	NR	NR	NR
Richling <i>et al.</i> 2000	III-2	66/175 (38%)	47/175 (27%)	NR	NR	NR
Proust <i>et al.</i> 2003	III-2	29/37 (78%)	8/37 (22%)	95/103 (92%)	8/103 (8%)	0.01
Lusseveld <i>et al.</i> 2002	III-2/3	32/44 (73%)	12/44 (27%)	40/44 (91%)	4/44 (9%)	NR
Range of rates		33% to 94%	6% to 67%	91% to 98%	2% to 9%	6 studies
Median of rates		66%	27%	92%	8%	

NOTE: specific subgroups: Proust *et al.* 2003 – patients with anterior communicating artery aneurysms; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms.

Impairment and disability at discharge

The GOS score at discharge was reported in seven studies (Table 30). Of the patients who underwent coiling, a median of 53% (range 22 to 70%) made a good recovery (GOS score at discharge of 5) compared to 49% (range 20 to 71%) in patients undergoing clipping. Of the three studies which reported statistical data (Charpentier *et al.* 1999; Fukui *et al.* 2004; Hirohata *et al.* 2004) two studies showed no discernible difference in the GOS score at discharge after coiling and clipping (Charpentier *et al.* 1999; Fukui *et al.* 2004), while one study reported that a higher proportion of patients made a good recovery (GOS score at discharge of 5, $p=0.0004$), and fewer patients suffered severe disability (GOS score at discharge of 3, $p<0.001$) after coiling compared to clipping.

Dehdashti *et al.* (2004) reported on the GOS score at discharge of patients with vasospasm, and showed that of the patients who underwent coiling, 25% (1/4 patients) did not survive the procedure (GOS score of 1), and 75% (3/4 patients) made a good recovery from the procedure with only moderate disability (GOS score of 4-5), compared with 22% (4/18 of patients) and 78% (14/18 patients) respectively in patients who underwent clipping. Gruber *et al.* (1999b) reported that in patients with basilar tip aneurysms, of the patients who underwent coiling, 91% (10/11 patients) made a good recovery from the procedure with only moderate disability (GOS score of 4-5), compared to 73% (11/15 patients) of patients who underwent clipping. Hoh *et al.* (2004b) reported on the GOS score at discharge of patients with intracranial infarcts on CT. Of the patients who underwent coiling, 10% (5/49 patients) made a good recovery (GOS score of 5), 16% (8/49 patients) suffered moderate disability (GOS score of 4),

18% (9/49 patients) suffered severe disability (GOS score of 3), 10 % (5/49 patients) were in a persistent vegetative state (GOS score of 2) and 46% (22/49 patients) did not survive the procedure (GOS score of 1). This compared with 21% (29/140 patients), 21% (30/140 patients), 21% (29/140 patients), 10% (14/140 patients), and 27% (38/140 patients) respectively in patients undergoing clipping. Kobayashi *et al.* (2001) reported on the GOS score at discharge of patients with moderate brain injury (GCS score <9). Of the patients who underwent coiling (mean GOS of 6.1), 33% (5/15 patients) made a good recovery (GOS score of 5), 0% (0/15 patients) suffered moderate disability (GOS score of 4), 67% (10/15 patients) suffered severe disability (GOS score of 3), and 0% (0/15 patients) did not survive the procedure (GOS of 1). This compared with 17% (5/30 patients), 13% (4/30 patients), 50% (15/30 patients) and 20% (6/30 patients) respectively in patients undergoing clipping (mean GOS score of 7.5).

The Modified Rankin Score at discharge was reported in one study (Hoh *et al.* 2004a). This study reported that of the patients who underwent coiling, 21% (16/76 patients) of patients had no symptoms (MRS of 0), 9% (7/76 patients) of patients had no significant disability despite symptoms (MRS of 1), 5% (4/76 patients) had a slight disability (MRS of 2), 5% (4/76 patients) of patients had a moderate disability (MRS of 3), 11% (8/76 patients) of patients had a moderately severe disability (MRS of 4), 22% (17/76 patients) of patients had a severe disability and 27% (20/76 patients) of patients died following the procedure. This was compared with 38% (154/406 patients), 10% (40/406 patients), 8% (33/406 patients), 8% (31/406 patients), 12% (49/406 patients), 15% (61/406 patients) and 9% (38/406 patients) respectively in patients who underwent clipping.

Table 30: Impairment and disability at discharge in patients undergoing coiling or clipping for ruptured aneurysms

GOS at discharge	L of E					coiling					clipping					p value
	5	4	3	2	1	5	4	3	2	1	5	4	3	2	1	
Charpentier et al. 1999	41/145 (29%)	NR	NR	NR	NR	20/99 (20%)	NR	NR	NR	NR	20/99 (20%)	NR	NR	NR	NR	0.62
Corsten et al. 2001*	64%	12%	3%	3%	12%	35%	38%	13%	2%	9%	35%	38%	13%	2%	9%	NR
Fukui et al. 2004	20/38 (53%)	7/38 (18%)	8/38 (21%)	2/38 (5%)	1/38 (3%)	88/142 (62%)	23/142 (16%)	18/142 (13%)	1/142 (<1%)	12/142 (9%)	88/142 (62%)	23/142 (16%)	18/142 (13%)	1/142 (<1%)	12/142 (9%)	0.3
Goddard et al. 2004	32/80 (40%)	22/80 (28%)	14/80 (18%)	6/80 (8%)	6/80 (8%)	82/212 (39%)	85/212 (40%)	23/212 (11%)	9/212 (4%)	13/212 (6%)	82/212 (39%)	85/212 (40%)	23/212 (11%)	9/212 (4%)	13/212 (6%)	NR
Gruber et al. 1999b	42/77 (55%)	8/77 (11%)	7/77 (9%)	5/77 (6%)	15/77 (19%)	80/165 (49%)	29/165 (17%)	11/165 (7%)	5/165 (3%)	40/165 (24%)	80/165 (49%)	29/165 (17%)	11/165 (7%)	5/165 (3%)	40/165 (24%)	ns
Hirohata et al. 2004	127/179 (70%)	16/179 (9%)	10/179 (6%)	10/179 (6%)	16/179 (9%)	50/101 (50%)	12/101 (12%)	27/101 (27%)	6/101 (6%)	5/101 (5%)	50/101 (50%)	12/101 (12%)	27/101 (27%)	6/101 (6%)	5/101 (5%)	p<0.001 GOS 3 p=0.0004 GOS 5
Sano et al. 2000	8/37 (22%)	6/37 (16%)	2/37 (5%)	7/37 (19%)	14/37 (38%)	219/307 (71%)	24/307 (8%)	24/307 (8%)	4/307 (1%)	36/307 (12%)	219/307 (71%)	24/307 (8%)	24/307 (8%)	4/307 (1%)	36/307 (12%)	NR
Range of rates	22% to 70	9% to 28%	3% to 21%	3% to 19%	3% to 38%	20% to 71%	8% to 40%	7% to 27%	<1% to 6%	5% to 24%	20% to 71%	8% to 40%	7% to 27%	<1% to 6%	5% to 24%	7 studies
Median of rates	53%	14%	8%	6%	11%	49%	17%	12%	3%	9%	49%	17%	12%	3%	9%	

NOTE: * n/N not reported and could not be calculated.

Impairment and disability at follow-up

The GOS score at follow-up was reported in seven studies, with follow-up periods ranging from 3 to 43 months (Table 31). Of the patients who underwent coiling, 66% (range 62 to 67%) made a good recovery (GOS score at discharge of 5) compared to 64% (range 58 to 81%) in patients undergoing clipping. Of the three studies which reported statistical data (Rabinstein *et al.* 2003; Dehdashti *et al.* 2004; Fukui *et al.* 2004), none showed any discernible difference in the GOS at follow-up after coiling and clipping.

Two studies reported the GOS score at 3 months follow-up (Lusseveld *et al.* 2002; Ross *et al.* 2002). Ross *et al.* (2002) reported that in poor grade patients of Hunt and Hess grade IV-V, of those who underwent coiling, 52% (21/40 patients) made a good recovery with only moderate disability (GOS score 4-5), compared with 87% (14/16 patients) in patients undergoing clipping. Lusseveld *et al.* (2002) reported that in patients with basilar tip aneurysms, 11.4% (5/44 patients, 95% CI: 3.8% to 24.6%) of patients who underwent endovascular treatment had a poor outcome (GOS score 1-3), compared with 29.5% (13/44 patients) of patients who underwent clipping (95% CI: 16.8% to 34.9%). The unadjusted odds ratio for poor outcome (GOS score 1-3) after coiling versus clipping was 0.31 (95% CI: 0.10 to 0.95), while the odds ratio after adjustment for age, clinical condition before treatment, and aneurysm size was 0.28 (95% CI: 0.08 to 0.99).

Table 31: Impairment and disability at follow-up in patients undergoing coiling or clipping for ruptured aneurysms

GOS at follow-up	L of E	coiling					clipping					p value
		5	4	3	2	1	5	4	3	2	1	
Collice <i>et al.</i> 1998† FU = 6 months	III-2	15/20 (75%)		3/20 (15%)	2/20 (10%)	2/20 (10%)	100/111 (90%)	4/111 (4%)	7/111 (6%)		NR	
Dehdashti <i>et al.</i> 2004 FU = 6 months	III-2	17/26 (65%)	5/26 (19%)	3/26 (12%)	0/26 (0%)	1/26 (4%)	46/72 (64%)	15/72 (21%)	5/72 (5%)	1/72 (1%)	5/72 (5%)	0.87
Goddard <i>et al.</i> 2004 FU = 4 - 8 months	III-2	53/80 (66%)	9/80 (11%)	6/80 (8%)	3/80 (4%)	9/80 (11%)	134/212 (63%)	50/212 (24%)	7/212 (3%)	4/212 (2%)	17/212 (8%)	NR
Fukui <i>et al.</i> 2004 FU=21-34 months†	III-2	18/27 (67%)	3/27 (11%)	2/27 (7%)	2/27 (7%)	2/27 (7%)	92/114 (81%)	8/114 (7%)	12/114 (11%)	1/114 (<1%)	1/114 (<1%)	0.17 GOS 4-5
Rabinstein <i>et al.</i> 2003 FU = 6 months	III-2	48/76 (62%)	8/76 (11%)	8/76 (11%)	0/76 (0%)	12/76 (16%)	196/339 (58%)	51/339 (15%)	63/339 (18%)	3/339 (1%)	26/339 (8%)	OR 0.58 (95% CI: 0.28 to 1.21)
Richling <i>et al.</i> 2000 FU = 43.5 months	III-2	119/175 (68%)		29/175 (17%)	27/175 (15%)	27/175 (15%)	168/248 (68%)		30/248 (12%)	50/248 (20%)		NR
Lusseveld <i>et al.</i> 2002 FU = 3 months	III-2/3	39/44 (89%)		3/44 (7%)	2/44 (4%)	2/44 (4%)	31/44 (71%)	8/44 (18%)		5/44 (11%)		NR
Range of rates		62% to 67%	11% to 19%	7% to 17%	0% to 7%	4% to 16%	58% to 81%	15% to 24%	3% to 18%	<1% to 2%	<1% to 11%	7 studies FU 3-43 months
Median of rates		66%	11%	11%	2%	7%	64%	18%	8%	1%	8%	

NOTE: specific subgroups: Lusseveld *et al.* 2002 – patients with basilar tip aneurysms.

† - as treated (exclude 7 patients converted to surgical).

† - coiling mean 34 months, clipping mean 21 months.

Two studies reported on measures of disability and impairment at 6 months follow-up (Corsten *et al.* 2001; Vindlacheruvu *et al.* 2003). Corsten *et al.* (2002) reported that of the patients who underwent coiling, 75% (104/139 patients) had intact preoperative activities, 12.5% (17/139 patients) had permanent cognitive, motor or sensory deficits limiting normal activities, 12.5% (17/139 patients) had a cranial nerve deficit which limited their ability to work or drive, and 0% (0/139 patients) died, compared with 51% (94/185 patients), 15% (28/185 patients), 10% (19/185 patients) and 2% (4/185 patients) respectively in patients who underwent clipping. Vindlacheruvu *et al.* (2003) reported that in good grade patients (WFNS 1-2), of those that underwent coiling, 86.5% had a favourable outcome (GOS score 4-5) compared with 89.5% of patients who underwent clipping.

Aneurysm recurrence or enlargement

Aneurysm recurrence or enlargement was reported in seven studies, with follow-up periods of between 12 and 47 months (Table 32). Of the patients who underwent coiling, 18% (range 0-53%) experienced aneurysm recurrence or enlargement; however, only one study (Boet *et al.* 2005) reported comparable data for patients who underwent clipping, reporting that none of the six patients who were clipped experienced aneurysm recurrence or enlargement during the 35 month follow-up period.

Table 32: Aneurysm recurrence or enlargement in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	FU (months)	coiling		clipping		p value
			n/N	%	n/N	%	
Recurrence or enlargement							
Asgari <i>et al.</i> 2003	III-2	12	21/130	16%	NR	NR	NA
Fukui <i>et al.</i> 2004	III-2	34	6/27	22%	NR	NR	NA
Hirohata <i>et al.</i> 2004	III-2	47	26/143	18%	NR	NR	NA
Richling <i>et al.</i> 2000	III-2	19	20/113	18%	NR	NR	NA
Boet <i>et al.</i> 2005	III-2	32 - 34†	8/15	53%	0/6	0%	NR
Porter <i>et al.</i> 2001	III-2	13	5/88	6%	NR	NR	NA
Lusseveld <i>et al.</i> 2002	III-2/3	23	0/26	0%	NR	NR	NA
Range of rates			0 to 53%		NA	NA	7 studies
Median of rates			18%		NA	NA	FU 12 – 47 months

NOTE: specific subgroups: Boet *et al.* 2005 – patients with paraclinoid/ophthalmic segment ICA aneurysms; Porter *et al.* 2001 – patients with multiple aneurysms; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms.

† mean follow-up coiling – 30.4 months, clipping – 34.8 months.

Aneurysm retreatment

Aneurysm retreatment was reported in six studies, with follow-up periods of between 7 and 47 months (Table 33). Of the patients who underwent coiling, 25% (range 6-83%) required aneurysm retreatment, however only two studies (Asgari *et al.* 2003; Boet *et al.* 2005) reported comparable data for patients who underwent clipping, with both studies reporting that no patient required aneurysm retreatment.

Table 33: Aneurysm retreatment in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	FU (months)	coiling		clipping		p value
			n/N	%	n/N	%	
Retreatment							
Asgari <i>et al.</i> 2003	III-2	12	21/130	16%	0/171	0%	NR
Fukui <i>et al.</i> 2004	III-2	34	5/6	83%	NR	NR	NA
Hirohata <i>et al.</i> 2004	III-2	47	10/179	6%	NR	NR	NA
Rabinstein <i>et al.</i> 2003	III-2	19	31/83	37%	NR	NR	NA
Richling <i>et al.</i> 2000	III-2	44	19/113	17%	NR	NR	NA
Boet <i>et al.</i> 2005	III-2	32 - 34†	5/15	33%	0/6	0%	NR
Range of rates			6% to 83%		NA		6 studies FU 7 – 47 months
Median of rates			25%		0%		

NOTE: specific subgroups: Boet *et al.* 2005 – patients with paraclinoid/ophthalmic segment ICA aneurysms.

† Mean follow-up coiling – 30.4 months, clipping – 34.8 months.

Aneurysm rebleeding

Aneurysm rebleeding was reported in eight studies, with follow-up periods of between 12 and 47 months (Table 34). Of the patients who underwent coiling, 2% (range 0 to 7%) experienced aneurysm rebleeding, compared with less than 1% (range 0 to 2%) of patients who underwent clipping.

Table 34: Aneurysm rebleeding in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	FU (months)	coiling		clipping		p value
			n/N	%	n/N	%	
Rebleeding							
Asgari <i>et al.</i> 2003	III-2	12	6/443	1%	5/727	<1%	NR
Fukui <i>et al.</i> 2004	III-2	34	2/27	7%	NR	NR	NA
Gruber <i>et al.</i> 1999b	III-2	NR	3/77	4%	3/165	2%	NA
Hirohata <i>et al.</i> 2004	III-2	47	1/179	<1%	NR	NR	NA
Rabinstein <i>et al.</i> 2003	III-2	7	0/83	0%	NR	NR	NA
Boet <i>et al.</i> 2005	III-2	32 - 34†	0/15	0%	0/6	0%	NR
Porter <i>et al.</i> 2001	III-2	13	0/33	0%	0/48	0%	NR
Lusseveld <i>et al.</i> 2002	III-2/3	23	1/44	2%	1/44	2%	NR
Range of rates			0% to 7%		0% to 2%		8 studies FU 12 – 47 months
Median of rates			2%		<1%		

NOTE: specific subgroups: Boet *et al.* 2005 – patients with paraclinoid/ophthalmic segment ICA aneurysms; Porter *et al.* 2001 – patients with multiple aneurysms; Lusseveld *et al.* 2002 – patients with basilar tip aneurysms.

† Mean follow-up coiling – 30.4 months, clipping – 34.8 months.

Mortality at follow-up

Mortality at follow-up was reported in seven studies, with follow-up periods of between 4 and 34 months (Table 35). Of the patients who underwent coiling, 8% (range 0 to 19%) were dead at follow-up, compared with 5% (range 0 to 2%) of patients who underwent clipping.

Table 35: Mortality at follow-up in patients undergoing coiling or clipping for ruptured aneurysms

Outcome	L of E	FU (months)	coiling		clipping		p value
			n/N	%	n/N	%	
Mortality at follow-up							
Collice <i>et al.</i> 1998	III-2	6	3/37	8%	6/120	5%	NR
Charpentier <i>et al.</i> 1999	III-2	6	19/98	19%	14/71	19%	NR
Corsten <i>et al.</i> 2001	III-2	6	0/122	0%	2/168	1%	NR
Dehdashti <i>et al.</i> 2004	III-2	6	1/26	4%	5/72	5%	NR
Fukui <i>et al.</i> 2004	III-2	21 – 34*	2/27	7%	1/114	<1%	NR
Goddard <i>et al.</i> 2004	III-2	4 – 8	9/80	11%	17/212	8%	NR
Rabinstein <i>et al.</i> 2003	III-2	7	12/76	16%	26/339	8%	NR
Range of rates			0% to 19%		<1% to 19%		7 studies FU 4 – 34 months
Median of rates			8%		5%		

NOTE: * mean follow-up coiling = 34 months, clipping = 21 months.

Neuropsychological outcomes

Neuropsychological outcomes were reported in four studies (Hadjivassilou *et al.* 2001;, Chan *et al.* 2002; Fontanella *et al.* 2003; Bellebaum 2004) in which patients underwent a number of neuropsychological tests, from between 6 to 12 months after successful treatment. Bellebaum *et al.* (2004) (Table 36) examined neuropsychological outcomes in patients at least 6 months after treatment. This study demonstrated that patients who underwent clipping exhibited more depressive symptoms ($p=0.039$), scored higher on affect arousal ($p=0.012$) and reported more dysexecutive problems ($p=0.05$) than patients who underwent coiling.

Table 36: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Bellebaum *et al.* (2004)

Neuropsychological outcome	Bellebaum <i>et al.</i> 2004 (III-2)			p value	p value
	coiling	clipping	control	coil vs clip	all 3 gps
Affective measures					
Beck Depression Inventory	5.5	10.5	3.8	0.039	0.012
VAS	25.0	37.0	17.5	0.012	0.002
Intelligence					
German verbal IQ	28.0 [5.6]	27.8 [4.6]	30.4 [2.9]	0.696	ns
Memory					
WMS story recall–immediate	23.5	24.0	31.5	ns	0.005
WMS story recall–delayed	18.5	18.0	26.0	ns	0.005
Benton Visual Retention Test–correct	6.0	6.0	7.2	ns	0.02
Benton Visual Retention Test–errors	5.6	6.6	3.2	ns	0.014
WMS digit span–forwards	7.1 [1.9]	7.1 [2.0]	7.8 [1.8]	0.780	ns
WMS digit span–backwards	6.0 [2.0]	6.4 [2.1]	6.7 [1.7]	0.515	ns
Attention					
TAP alertness task–with tone	0.29	0.30	0.24	ns	0.093
TAP alertness task–without tone	0.25	0.27	0.24	ns	0.093
TAP divided attention task–reaction time	0.7 [0.1]	0.7 [0.1]	0.7 [0.1]	0.590	ns
TAP divided attention task–missed items	2.6 [2.7]	3.7 [4.4]	1.6 [1.9]	0.669	ns
TAP divided attention task–false alarms	1.0 [1.5]	1.6 [2.9]	1.1 [1.2]	0.423	ns
TAP selective attention task–reaction time	0.6 [0.1]	0.6 [0.2]	0.6 [0.1]	0.270	ns
TAP selective attention task–missed items	2.7 [1.6]	4.4 [2.6]	1.9 [2.6]	0.138	ns
TAP selective attention task–false alarms	1.5 [1.1]	2.9 [1.0]	1.2 [1.2]	0.956	ns
Executive function					
German Verbal Fluency Test–Semantic	20.7 [6.4]	19.1 [9.3]	25.0 [9.6]	0.341	ns
German Verbal Fluency Test–Phonemic	9.7 [4.1]	10.2 [3.1]	11.0 [3.3]	0.642	ns
German Verbal Fluency Test–Alternating	14.3 [4.3]	15.1 [4.8]	16.3 [2.9]	0.838	ns
BADS key search test	11.8 [3.6]	10.7 [4.5]	11.9 [3.6]	0.642	ns
BADS temporal judgement test	2.5 [0.8]	2.4 [1.1]	2.5 [1.1]	0.867	ns
Cognitive Estimates Test	5.4 [3.4]	6.3 [4.1]	4.4 [3.3]	0.590	ns
BADS dysexecutive questionnaire	16.5	24.0	17.5	0.05	0.05

NOTE: WMS–Wechsler Memory Scale; TAP–German computer-based test battery for assessment of attention; BADS–Behavioural Assessment of Dysexecutive Syndrome.

Chan *et al.* (2002) examined neuropsychological outcomes in patients at least 12 months after treatment (Table 37). This study reported that the performance of patients with clipping was significantly poorer than that of the patients treated with coiling on verbal memory and executive function. Patients’ cognitive domains were classified as impaired if the scores were below 1 SD from the mean scores of the normal control subjects. 67% of patients treated with clipping demonstrated executive function impairment compared with 22% of patients treated with coiling. In addition, 43% of patients who underwent clipping demonstrated memory impairment compared with 14% of patients who underwent coiling. Patients who underwent clipping were more impaired in terms of flexible thinking and sensitivity to interference, demonstrated a higher rate of forgetting, and had a significantly reduced ability to recognise newly learned materials compared to patients treated with coiling.

Table 37: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Chan *et al.* (2002)

Neuropsychological outcome	Chan <i>et al.</i> 2002 (III-2) Assessment at 12 months			p value all groups
	coiling n=9	clipping n=9	control n=19	
Attention				
Trail making B	164.0 [100.3]	206.2 [110.8]	114.4 [61.6]	0.04
Executive function				
Verbal Fluency Test	20.0 [9.3]	18.6 [6.6]	26.4 [5.6]	0.01
Verbal Fluency Test–errors	0.4 [0.5]	0.1 [0.3]	0.0 [0.0]	0.01
Five-Point Test	13.9 [7.2]	12.2 [8.6]	20.4 [8.0]	0.03
Alternative Drawing Test	39.1 [15.7]	67.7 [54.2]	29.1 [9.4]	0.01
WAIS-R Similarities	11.0 [5.8]	7.7 [8.9]	12.3 [5.6]	0.28
WAIS-R Comprehension	14.9 [6.9]	11.7 [6.4]	15.7 [6.0]	0.30
HKLLT–intrusion	1.1 [1.2]	0.4 [0.5]	2.6 [0.5]	0.02
HKLLT–false alarm	1.6 [2.4]	2.9 [3.0]	0.3 [0.5]	0.01
Z-scores on cognitive domains				
verbal memory	-0.33 [0.55]	-1.00 [1.01]	-0.10 [0.64]	0.02
visual memory	-0.18 [1.04]	-0.86 [1.63]	0.01 [0.80]	0.22
executive function	-1.11 [0.62]	-1.68 [2.00]	-0.09 [0.65]	0.02
motor ability	-2.88 [4.74]	-3.04 [2.34]	0.00 [0.85]	0.01
language	-0.41 [1.18]	-0.70 [1.16]	-0.40 [0.88]	0.34
visual perception	0.05 [0.79]	-0.11 [1.40]	0.00 [0.62]	0.94

NOTE: WAIS-R Wechsler Adult Intelligence Scale–Revised; HKLLT–Hong Kong List Learning Test.

Fontanella *et al.* (2003) examined neuropsychological outcomes in patients 6 months after treatment (Table 38). This study reported that no significant differences were seen in the performance outcomes of patients who underwent clipping and coiling, however there were trends towards a worse performance on a number of tests in patients who underwent clipping.

Table 38: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Fontanella *et al.* (2003)

Neuropsychological outcome	Fontanella <i>et al.</i> 2003 (III-2) Assessment at 6 months				p value		
	coiling n=17	clipping n=20	SAH n=16	control n=18	all groups	clip vs control	coil vs control
Affective measures							
Beck Depression Inventory	13.1 [9.7]	14.4 [7.6]	11.1 [7.7]	8.9 [5.7]	ns	ns	ns
Stait-Trait Anxiety–episodic	42.0 [7.7]	44.0 [7.5]	39.0 [9.4]	36.5 [5.3]	ns	ns	ns
Stait-Trait Anxiety–disposition	43.1 [11.4]	44.0 [7.5]	41.7 [12.4]	37.6 [6.9]	ns	ns	ns
Intelligence							
Raven Coloured Matrices	28.9 [6.0]	28.9 [5.7]	28.9 [6.0]	31.0 [2.1]	ns	ns	ns
Italian verbal judgement test	51.7 [8.1]	47.1 [9.7]	50.2 [8.4]	51.1 [9.4]	ns	ns	ns
Memory							
WMS story recall	15.3 [2.2]	13.9 [9.5]	16.2 [7.7]	22.7 [8.7]	<0.05	0.019	ns
Bi-syllabic word repetition	4.4 [1.0]	4.3 [0.8]	4.3 [1.0]	4.1 [0.8]	ns	ns	ns
Corsi's Block Tapping test	4.4 [0.5]	4.6 [0.6]	5.1 [1.2]	4.6 [0.7]	ns	ns	ns
Verbal learning	10.4 [5.3]	12.3 [3.5]	9.6 [4.6]	8.1 [4.6]	ns	ns	ns
Spatial learning	16.9 [7.9]	16.5 [8.1]	19.5 [8.6]	21.7 [2.9]	ns	ns	ns
Attention							
Visual search task	50.0 [6.1]	49.9 [8.6]	51.4 [9.9]	52.6 [6.4]	ns	ns	ns
Executive function							
Verbal Fluency Test–Semantic	13.7 [2.6]	15.8 [10.5]	17.3 [7.7]	27.3 [11.2]	<0.05	0.003	0.013
Verbal Fluency Test–Phonemic	11.5 [2.3]	8.9 [5.1]	11.0 [5.1]	12.3 [3.4]	0.001	ns	ns
Verbal Fluency Test–Alternating	21.5 [3.4]	16.6 [5.6]	18.4 [5.7]	21.2 [3.4]	0.020	0.031	ns
Elithorn's Test of spatial planning	27.2 [3.3]	23.3 [5.8]	25.8 [5.2]	28.9 [1.6]	0.004	0.002	ns
WAIS Picture Arrangement	18.3 [3.7]	17.1 [6.7]	20.8 [6.4]	23.1 [4.1]	0.045	0.046	ns
Language function							
Sentence construction test	15.1 [2.5]	13.5 [2.5]	14.3 [2.5]	15.6 [1.8]	ns	0.034	ns

NOTE: WMS–Wechsler Memory Scale.

Hadjivassilou *et al.* (2001) examined neuropsychological outcomes in patients 12 months after treatment (Table 39). This study reported that patients who underwent clipping performed significantly poorer than patients who underwent coiling in the semantic fluency test ($p=0.05$), vocabulary subtest of the WAIS-R ($p=0.02$), complex-figure recall test ($p=0.04$), and the extradimensional stage of the ID/ED shift test from the CANTAB ($p=0.01$).

Table 39: Neuropsychological outcomes in control patients and patients undergoing coiling or clipping for ruptured aneurysms in Hadjivassilou *et al.* (2001)

Neuropsychological outcome	Hadjivassilou <i>et al.</i> 2001 (III-2) Assessment at 12 months			p value		
	coiling n=40	clipping n=40	control n=31	coil vs clip	clip vs control	coil vs control
Affective measures						
Beck Depression Inventory	9.1 [7.9]	11.3 [9.0]	4.9 [3.4]	0.30	0.008	0.08
Intelligence						
WAIS-R Vocabulary	10.3 [3.0]	8.8 [2.6]	11.3 [1.9]	0.02	0.0002	0.09
WAIS-R Similarities	10.6 [3.6]	10.2 [2.7]	11.5 [2.1]	0.59	0.08	0.19
WAIS-R Block design	10.2 [3.6]	9.2 [2.8]	12.4 [2.5]	0.15	0.0001	0.005
Memory						
WMS story recall–immediate	8.6 [4.4]	8.7 [3.5]	11.6 [2.6]	0.9	0.0002	0.001
WMS story recall–delayed	7.3 [4.0]	6.3 [3.8]	10.5 [2.6]	0.26	0.0001	0.0004
WMS digit span	9.0 [3.3]	9.6 [2.6]	10.9 [2.2]	0.37	0.03	0.01
Face recognition	41.3 [6.0]	40.8 [6.0]	45.6 [3.5]	0.80	0.0006	0.002
Word recognition	46.1 [5.4]	45.1 [6.0]	48.5 [3.0]	0.33	0.0007	0.009
Corsi's Block Tapping test	4.9 [1.0]	4.9 [1.2]	5.2 [0.4]	0.89	0.12	0.06
Visual perceptual function						
Form discrimination–correct	3.5 [1.7]	3.5 [2.0]	2.3 [0.7]	0.9	0.001	0.0001
Form discrimination–errors	5.2 [6.0]	4.9 [4.0]	2.9 [1.0]	0.7	0.001	0.02
Attention						
Trail making B-A	93.0 [90.0]	57.0 [36.0]	25.0 [12.0]	0.15	0.0008	0.0001
Executive function						
Verbal Fluency Test–Semantic	33.2 [13.3]	27.9 [9.0]	44.7 [6.5]	0.05	0.0001	0.0001
Verbal Fluency Test–Phonemic	28.3 [11.2]	27.2 [9.7]	42.0 [9.4]	0.67	0.0001	0.0001
WAIS Picture Arrangement	9.2 [2.8]	9.5 [3.2]	11.8 [1.7]	0.65	0.0008	0.0004
Digit ordering	63.8 [21.0]	65.3 [18.9]	85.1 [12.4]	0.75	0.0001	0.0001
CANTAB ID/ED shift test–shift stage	14.4 [8.0]	23.5 [13.0]	11.0 [3.8]	0.01	0.0003	0.33
CANTAB ID/ED shift test–stages complete	8.0 [2.0]	7.8 [1.3]	8.7 [1.0]	0.09	0.005	0.33
CANTAB working memory strategy count	36.6 [3.9]	36.4 [3.8]	33.2 [3.9]	0.82	0.001	0.001
CANTAB working memory between errors	43.4 [20.0]	41.7 [20.0]	23.9 [15.3]	0.7	0.001	0.0001
CANTAB Tower of London moves above min	17.3 [7.9]	15.2 [5.3]	14.7 [9.4]	0.16	0.70	0.22
Language function						
Boston Naming Test – Modified	35.2 [5.4]	35.1 [4.4]	37.1 [2.1]	0.42	0.13	0.50

NOTE: WAIS-R–Wechsler Adult Intelligence Scale–Revised; WMS–Wechsler Memory Scale; CANTAB–Cambridge Automated Neuropsychological Test Battery; ID/ED–interdimensional/extradimensional.

Comparison 2: Endovascular versus surgical treatment

Non-randomised comparative studies

A variety of endovascular devices were employed in these studies, including coiling (4 studies), balloons (2 studies), as well as coiling in combination with balloons (1 study) or stents (1 study).

Safety

Perioperative mortality

Perioperative mortality rates were reported in four studies (Table 40). The median rate of perioperative mortality was 20% (range 10 to 40%) in patients undergoing endovascular treatment, compared with 12% (range 0 to 29%) in patients undergoing surgical treatment.

Groden *et al.* (2000) reported that in patients with VA aneurysms, both deaths in the endovascular group were due to vasospasm, while the six deaths in the surgical group were due to vasospasm (1), temporary occlusion leading to infarct (1), cardiac or pulmonary failure (3) and an unknown cause (1).

Table 40: Perioperative mortality in patients undergoing endovascular or surgical treatments for ruptured aneurysms

Outcome	L of E	endovascular		surgical		p value
		n/N	%	n/N	%	
Perioperative mortality						
Groden <i>et al.</i> 2001	III-2	10/20	50%	6/21	29%	NR
Sugiu <i>et al.</i> 2005	III-2	4/20	20%	0/5	0%	NR
Kai <i>et al.</i> 2001	III-2/3	1/5	20%	0/3	0%	NR
Groden <i>et al.</i> 2000	III-3	2/20	10%	6/26	23%	NR
Range of rates		10% to 50%		0% to 29%		4 studies
Median of rates		20%		12%		

NOTE: Groden *et al.* 2001 – patients in Hunt and Hess grade IV-V; Sugiu *et al.* 2005 – dissecting VA aneurysms; Kai *et al.* 2001 – dissecting VA aneurysms; Groden *et al.* 2000 – VA aneurysms.

Vasospasm

The incidence of vasospasm was reported in 2 studies (Groden *et al.* 2000; Groden *et al.* 2001). Groden *et al.* (2001) reported that in patients of Hunt and Hess grade IV-V, the incidence of vasospasm was 40% (17/43 patients) in patients undergoing endovascular treatment compared with 29% (6/21 patients) in patients undergoing surgical treatment. Groden *et al.* (2000) reported that in patients with VA aneurysms, the incidence of vasospasm was 15% (3/20 patients) in patients undergoing endovascular treatment compared with 8% (2/26 patients) in patients undergoing surgical treatment.

Intraoperative rupture

The incidence of intraoperative rupture was reported in three studies (Table 41). The median rate of intraoperative rupture was 5% (range 5 to 15%) in patients undergoing endovascular treatment. Only two studies reported comparable data for patients who underwent surgical treatment, with one study reporting no incidence of intraoperative ruptures (Sugiu *et al.* 2005) and the other study reporting a 27% incidence of intraoperative rupture (Groden *et al.* 2000).

Table 41: Intraoperative rupture in patients undergoing endovascular or surgical treatments for ruptured aneurysms

Outcome	L of E	endovascular		surgical		p value
		n/N	%	n/N	%	
Groden <i>et al.</i> 2001	III-2	2/43	5%	NR	NR	NA
Sugiu <i>et al.</i> 2005	III-2	1/20	5%	0/5	0%	NR
Groden <i>et al.</i> 2000	III-3	3/20	15%	7/26	27%	NR
Range of rates		5% to 15%		NA		3 studies
Median of rates		5%		NA		

NOTE: Groden *et al.* 2001 – patients in Hunt and Hess grade IV-V; Sugiu *et al.* 2005 – dissecting VA aneurysms; Groden *et al.* 2000 – VA aneurysms.

Delayed ischaemic neurological deficit

The incidence of delayed ischaemic neurological deficit was reported in two studies (Groden *et al.* 2000; Groden *et al.* 2001). Groden *et al.* (2001) reported that the rate of delayed ischaemic neurological deficit was 30% (13/43 patients) in patients undergoing endovascular treatment, and 19% (4/21 patients) in patients undergoing surgical treatment. Groden *et al.* (2000) reported that the rate of delayed ischaemic neurological deficit was 5% (1/20 patients) in patients undergoing endovascular treatment and 8% (2/26 patients) in patients undergoing surgical treatment.

Intracranial or ischaemic infarction

The incidence of intracranial or ischaemic infarction was reported in two studies (Groden *et al.* 2000; Groden *et al.* 2001). Groden *et al.* (2001) reported that in patients of Hunt and Hess grade IV-V, the incidence of intracranial or ischaemic infarction was 37% (16/43 patients) in patients undergoing endovascular treatment, and 29% (6/21 patients) in patients undergoing surgical treatment. Groden *et al.* (2000) reported that in patients with VA aneurysms, the incidence of intracranial or ischaemic infarction was 13% (1/8 patients) in patients undergoing endovascular treatment and 4% (1/24 patients) in patients undergoing surgical treatment.

Thromboembolic complications

The incidence of thromboembolic complications was reported in two studies (Groden *et al.* 2000; Groden *et al.* 2001). Groden *et al.* (2001) reported that the rate of thromboembolic complications was 5% (2/43 patients) in patients undergoing endovascular treatment, but did not provide comparable data for patients who underwent surgical treatment. Groden *et al.* (2000) reported that the rate of thromboembolic complications was 13% (3/24 patients) in patients undergoing surgical treatment, but did not provide comparable data for patients who underwent endovascular treatment.

Procedure-related complications

The incidence of procedure-related complications, including coil breakage and coil interruption, was reported in two studies (Groden *et al.* 2000; Groden *et al.* 2001). The rate of procedure-related complications in patients undergoing endovascular treatment was 2% (1/43 patients) in one study (Groden *et al.* 2001) and 8% (1/12 patients) in the other study, however neither study reported comparable data for patients who underwent surgical treatment.

Effectiveness

Conversions to surgery

The rate of conversion to surgery was reported in one study (Grodén *et al.* 2001). The rate of conversion to surgery in this study was 2.4% (1/42 patients).

Degree of aneurysm occlusion

The degree of aneurysm occlusion was reported in two studies (Grodén *et al.* 2000, Kai *et al.* 2001). Kai *et al.* (2001) reported that in patients with dissecting VA aneurysms, 80% (4/5 patients) of the patients who underwent endovascular treatment had a total occlusion of their aneurysm, and 20% (1/5 patients) of patients had a subtotal occlusion of their aneurysm. This compared with 67% (2/3 patients) and 33% (1/3 patients) of patients respectively who underwent surgery. Grodén *et al.* (2000) reported that in patients with VA aneurysms, 100% (20/20 patients) of the patients who underwent endovascular treatment had a total occlusion of their aneurysm; however, no comparable data was reported for patients who underwent surgery.

Impairment and disability at discharge

The GOS score at discharge was reported in two studies (Grodén *et al.* 2000; Sugiu *et al.* 2005). Sugiu *et al.* (2005) reported on the GOS score at discharge of patients with dissecting VA aneurysms, and showed that of the patients who underwent endovascular treatment, 60% (12/20 patients) made a good recovery (GOS score of 5) compared to patients that underwent surgical treatment, where 100% (5/5 patients) made a good recovery. Grodén *et al.* (2000) reported on the GOS score at discharge of patients with VA aneurysms, and showed that of the patients who underwent endovascular treatment, 65% (13/20 patients) made a good recovery (GOS score of 5), compared to 46% (12/26 patients) of patients who underwent surgical treatment.

Impairment and disability at follow-up

The GOS score at follow-up was reported in one study, with a follow-up period of 6 months (Grodén *et al.* 2001). This study reported that in poor grade patients, Hunt and Hess grade IV-V, of the patients who underwent endovascular treatment, 26% (11/43 patients) made a good recovery (GOS score of 5) compared to 14% (3/21 patients) of patients who underwent surgical treatment.

Aneurysm recurrence or enlargement

Aneurysm recurrence or enlargement was reported in one study (Grodén *et al.* 2000). This study reported that of the patients who received endovascular treatment, 22% (8/36 patients) were stable 12 months after treatment; however, comparable data was not reported for patients who received surgical treatment.

Aneurysm retreatment

Aneurysm retreatment was reported in one study (Grodén *et al.* 2000). Of the patients who underwent endovascular treatment, none (0/20 patients) required aneurysm retreatment; however, no comparable data was reported for patients who underwent surgical treatment.

Aneurysm rebleeding

Aneurysm rebleeding was reported in one study (Groden *et al.* 2000). This study reported that of the patients who received endovascular treatment, 0% (0/20 patients) experienced rebleeding, compared to 8% (2/26 patients) of patients who received surgical treatment. Of the 2 surgically treated patients who experienced rebleeding, one patient rebled 9 years after surgery, while the other patient rebled 12 days after surgery, with both patients subsequently undergoing coiling.

Registry studies

Both registry studies employed endovascular coiling. These studies utilised databases covering a total of 74 hospitals (Johnston 2000; Hamada *et al.* 2004). Specifically, Hamada *et al.* (2004) utilised the Kumamoto Data Bank for Cerebral Aneurysms; a Japanese database covering 14 hospitals. Johnston (2000) utilised the University Healthsystems Consortium database, which covered 60 US hospitals. Hamada *et al.* (2004) reported that 8% (178/2115), 69% (1456/2115) and 23% (477/2115) of patients received endovascular, surgical and conservative treatment respectively. Johnston (2000) reported that 3% (248/9534), 54% (5175/9534) and 43% (4111/9534) of patients received endovascular, surgical and conservative treatment respectively.

Safety

Perioperative mortality

Johnston (2000a) reported that perioperative mortality was 13% (32/248 patients), 12% (626/5175 patients) and 38% (1560/4111 patients) following endovascular, surgical and conservative treatment respectively. In hospitals with a higher volume of endovascular cases the relative risk reduction of in-hospital mortality was 9% (95% CI: 0.86 to 0.96, $p=0.001$) for every 10% of cases treated using endovascular techniques (Johnston 2000). Perioperative mortality was 24% in hospitals with no previous endovascular cases, 23% in hospitals that had between 1 and 10 endovascular cases and 14% in hospitals that had more than 10 endovascular cases (Johnston 2000).

Effectiveness

Impairment and disability at discharge

Hamada *et al.* (2004) reported that of the patients who underwent endovascular treatment, 55% (98/178 patients) made a good recovery (GOS score of 5), 20% (36/178 patients) suffered moderate disability (GOS score of 4), 11% (19/178 patients) suffered severe disability (GOS score of 3), 10% (17/178 patients) were in a persistent vegetative state (GOS score of 2) and 4% (8/178 patients) did not survive the procedure (GOS score of 1). This compared with 56% (813/1456 patients), 14% (206/1456 patients), 13% (194/1456 patients), 5% (71/1456 patients), and 12% (172/1456 patients) respectively in patients who underwent surgical treatment. Overall, whilst the baseline characteristics between the endovascular and surgical groups were not comparable, patients treated with endovascular coiling demonstrated better outcomes when compared with patients treated surgically, although this was not statistically significant ($p=0.14$).

Table 42: Impairment and disability in patients undergoing endovascular, surgical or conservative treatment for ruptured aneurysms

Outcome	endovascular	surgical	conservative
GOS score			
5	98/178 (55%)	813/1456 (56%)	12/477 (2%)
4	36/178 (20%)	206/1456 (14%)	8/477 (2%)
3	19/178 (11%)	194/1456 (13%)	42/477 (9%)
2	17/178 (10%)	71/1456 (5%)	5/477 (16%)
1	8/178 (4%)	172/1456 (12%)	340/477 (71%)

Comparison 3: Endovascular versus conservative treatment

Non-randomised comparative studies

A variety of endovascular devices were employed in these studies, including coiling (1 study), balloons (2 studies), as well as coiling in combination with balloons (2 studies) or stents (1 study).

Safety

Perioperative mortality

Perioperative mortality rates were reported in three studies (Table 43). The median rate of perioperative mortality was 41% (range 8 to 43%) in patients undergoing endovascular treatment, compared with 40% (range 19 to 94%) in patients undergoing conservative treatment. Anxionnat *et al.* (2003) reported that in three patients with dissecting aneurysms, perioperative mortality in patients undergoing conservative treatment was due to a poor initial patient grade (2), and aneurysmal rerupture (1), while a single cause of death in the endovascular group was not reported. Chung & Han (2002) reported that in patients with dissecting VA aneurysms, all 3 deaths in patients undergoing endovascular treatment were due to recurrent haemorrhage, while both deaths in patients undergoing conservative treatment were due to initial SAH. Inamasu *et al.* (2002) reported that in patients of Hunt and Hess grade V, perioperative mortality was due to uncontrollable intracranial pressure (endovascular 4/22, conservative 6/18, ns), delayed ischaemic neurological deficit (endovascular 2/22, conservative 2/18), rebleeding (endovascular 1/22, conservative 9/18, $p < 0.005$), and cardiac complications (endovascular 2/22, conservative NR).

Table 43: Perioperative mortality in patients undergoing endovascular or conservative treatment for ruptured aneurysms

Outcome	L of E	endovascular		conservative		p value
		n/N	%	n/N	%	
Perioperative mortality						
Anxionnat <i>et al.</i> 2003	III-2	1/12	-	3/16	-	NR
Chung & Han 2002	III-2	3/7	-	2/5	-	NR
Inamasu <i>et al.</i> 2002	III-3	9/22	41%	17/18	94%	NR
Range of rates		NA		NA		4 studies
Median of rates		NA		NA		

NOTE: Anxionnat *et al.* 2003 – dissecting aneurysms; Chung & Han 2002 – dissecting VA aneurysms; Inamasu *et al.* 2002 – patients in Hunt and Hess grade V.

Intraoperative rupture

The incidence of intraoperative rupture was reported in one study (Ramgren *et al.* 2005). The rate of intraoperative rupture was 20% (3/15 patients) in patients undergoing endovascular treatment.

Delayed ischaemic neurological deficit

The incidence of delayed ischaemic neurological deficit was reported in one study (Inamasu *et al.* 2002). This study reported that the rate of delayed ischaemic neurological deficit was 9% (2/22 patients) in patients undergoing endovascular treatment, compared with 11% (2/18 patients) in patients receiving conservative treatment.

Intracranial or ischaemic infarction

The incidence of intracranial or ischaemic infarction was reported in one study (Anxionnat *et al.* 2003). This study reported that in patients with dissecting aneurysms, the incidence of intracranial or ischaemic infarction was 17% (2/12 patients) in patients undergoing endovascular treatment, but did not provide comparable data for patients who received conservative treatment.

Unruptured aneurysms

Comparison 1: Endovascular coiling versus surgical clipping

Non-randomised comparative studies

Safety

Perioperative mortality

Six studies reported on perioperative mortality rates (Table 44). There was no discernible difference in the rate of perioperative mortality after coiling and clipping (one study: Singh *et al.* 2002) with a median rate of 0% mortality in patients undergoing coiling (range 0 to 3%) and in patients undergoing clipping (range 0 to 4%).

Table 44: Perioperative mortality in patients undergoing coiling or clipping for unruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Perioperative mortality						
Sano <i>et al.</i> 2000	III-2	1/33	3%	1/95	1%	NR
Singh <i>et al.</i> 2002	III-2	1/62	2%	3/68	4%	ns
Manabe <i>et al.</i> 2004	III-2	0/15	0%	0/75	0%	NR
Regli <i>et al.</i> 2002	III-2	0/14	0%	0/60	0%	NR
Porter <i>et al.</i> 2001	III-2	0/55	0%	1/122	<1%	
Gruber <i>et al.</i> 1999c	III-2	0/10	0%	1/5	-	NR
Range of rates		0% to 3%		0% to 4%		6 studies
Median of rates		0%		0%		

NOTE: specific subgroups: Manabe *et al.* 2004 – patients with non-giant saccular aneurysms; Regli *et al.* 2002 – patients with MCA aneurysms; Gruber *et al.* 1999c – patients with MCA aneurysms; Porter *et al.* 2001 – patients with multiple intracranial aneurysms.

Intraoperative rupture

The incidence of intraoperative rupture was reported in four studies (Table 45). The median rate of intraoperative rupture was 4.5% (range 2 to 7%) in patients undergoing coiling. Only one study reported comparable data for patients who underwent clipping, reporting a 4% incidence of intraoperative rupture, which was not significantly different from the coiling group (Singh *et al.* 2002).

Table 45: Intraoperative rupture in patients undergoing coiling or clipping for unruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Intraoperative rupture						
Sano <i>et al.</i> 2000	III-2	1/33*	3%	NR	NR	NA
Singh <i>et al.</i> 2002	III-2	4/62	6%	4/68	4%	ns
Manabe <i>et al.</i> 2004	III-2	1/15	7%	NR	NR	NR
Porter <i>et al.</i> 2001	III-2	1/55	2%	NR	NR	NR
Range of rates		2% to 7%		NA		4 studies
Median of rates		4.5%		NA		

NOTE: specific subgroups: Manabe *et al.* 2004 – patients with non-giant saccular aneurysms; Porter *et al.* 2001 – patients with multiple intracranial aneurysms.

* fatal.

Intracranial or ischaemic infarction

The incidence of intracranial or ischaemic infarction was reported in four studies (Table 46). The median rate of intracranial or ischaemic infarction was 9% (range 1 to 17%) in patients undergoing clipping. Only two studies reported comparable data for patients who underwent coiling. One study (Vindlacheruvu *et al.* 2003) reported a 4% incidence of intracranial or ischaemic infarction and the other study (Brilstra *et al.* 2004) reported a 5% incidence of intracranial or ischaemic infarction.

Table 46: Intracranial or ischaemic infarction in patients undergoing coiling or clipping for unruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Intracranial or ischaemic infarction						
Brilstra <i>et al.</i> 2004	III-2	1/19	5%	5/32	16%	NR
Vindlacheruvu <i>et al.</i> 2003	III-2/3	1/26	4%	5/29	17%	NR
Regli <i>et al.</i> 2002	III-2	NR	NR	1/60	2%	NR
Porter <i>et al.</i> 2001	III-2	NR	NR	1/74*	1%	NR
Range of rates		NA		1% to 17%		4 studies
Median of rates		5%		9%		

NOTE: specific subgroups: Regli *et al.* 2002 – patients with MCA aneurysms; Porter *et al.* 2001 – patients with multiple intracranial aneurysms.

* fatal

Procedure-related complications

The incidence of procedure-related complications, including failed coiling, coil compaction, coil fragmentation, and clots during coiling, was reported in four studies (Table 47). The median rate of procedure-related complications was 17.5% (range 2 to 24%) in patients undergoing coiling; however only two studies reported comparable data for patients who underwent clipping, with one study reporting a 46% incidence of procedure-related complications (Singh *et al.* 2002), and the other study reporting a 7% incidence of procedure-related complications (Vindlacheruvu *et al.* 2003). The single study which reported statistical data on the two interventional groups, reported a significantly higher ($p=0.009$) incidence of procedure-related complications after clipping (46%) compared to coiling (23%).

Table 47: Procedure-related complications in patients undergoing coiling or clipping for unruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		n/N	%	n/N	%	
Procedure related complications						
Sano <i>et al.</i> 2000	III-2	8/33	24%	NR	NR	NA
Singh <i>et al.</i> 2002	III-2	14/62	23%	31/68	46%	$p=0.009$
Vindlacheruvu <i>et al.</i> 2003	III-2/3	3/26	12%	2/29	7%	NR
Porter <i>et al.</i> 2001	III-2	1/55*	2%	NR	NR	NR
Range of rates		2% to 24%		NA		4 studies
Median of rates		17.5%		NA		

NOTE: Porter *et al.* 2001 – patients with multiple intracranial aneurysms, *clot during coiling; Sano *et al.* 2000 – failed coiling 5, coil compaction 2, coil fragmentation 1; Vindlacheruvu *et al.* 2003 – failed procedure.

Neurological complications

The incidence of neurological complications, including cortical deficit and seizures, was reported in one study (Singh *et al.* 2002). This study reported that 9% (6/62 patients) of patients that underwent coiling suffered a cortical deficit compared with 31% (21/68

patients) who underwent clipping ($p=0.004$), while none of the patients that underwent coiling suffered seizures compared with 3% (2/68 patients) who underwent clipping.

Effectiveness

Conversions to surgery

The rate of conversion to surgery was reported in four studies (Table 48). The median rate of conversion to surgery was 14.5% (range 0 to 79%). Regli *et al.* (2002) reported that the 11 conversions to surgery were due to a wide aneurysm neck, incorporated arterial branches, and catheterisation failure; while Porter *et al.* (2001) reported that their 11 conversions to surgery were due to a wide aneurysm neck, difficult access, proximal vessels, and a clot in the parent vessel.

Table 48: Conversions to surgery in patients undergoing endovascular treatment for unruptured aneurysms

Outcome	L of E	endovascular		
		n/N	%	
Brilstra <i>et al.</i> 2004	III-2	3/19	16%	
Collice <i>et al.</i> 1998	III-2	0/10	0%	
Regli <i>et al.</i> 2002	III-2	11/14	79%	
Porter <i>et al.</i> 2001	III-2	7/55	13%	
Range of rates		0% to 79%		4 studies
Median of rates		14.5%		

NOTE: Regli *et al.* 2002 – patients with MCA aneurysms; Porter *et al.* 2001 – patients with multiple intracranial aneurysms.

Length of hospital stay

The mean length of hospital stay was reported in four studies (Table 49). The mean length of hospital stay was 4.8 days (range 4 to 6.3) in patients who underwent coiling, and 12.7 days (range 10.3 to 17.1) in patients who underwent clipping. Of the two studies which reported statistical data (Singh *et al.* 2002; Vindlacheruvu *et al.* 2003), both reported a significantly longer stay after clipping compared to coiling.

Table 49: Length of hospital stay in patients undergoing coiling or clipping for unruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		mean days	N	mean days	N	
Brilstra <i>et al.</i> 2004	III-2	4 (1 – 9)	19	15 (9 – 60)	32	NR
Singh <i>et al.</i> 2002	III-2	5.0	62	7.7	68	$p<0.0001$
Vindlacheruvu <i>et al.</i> 2003	III-2/3	4.8	38	10.3	65	p significant (value NR)
Manabe <i>et al.</i> 2004	III-2	6.3 (2 – 32)	12	17.1 (9 – 80)	38	NR
Range of means		4 to 6.3 days		10.3 to 17.1 days		4 studies
Median of means		4.8 days		12.7 days		

NOTE: specific subgroups: Manabe *et al.* 2004 – patients with non-giant saccular aneurysms.

Degree of aneurysm occlusion

The degree of aneurysm occlusion was reported in three studies (Table 50). Of the patients who underwent coiling, 50% (range 21 to 84%) of patients had totally occluded aneurysms and 50% (range 16 to 79%) of patients had partially occluded aneurysms. In patients who underwent clipping, 97% (range 92 to 100%) of patients had totally occluded aneurysms, and 3% (range 0 to 8%) of patients had partially occluded aneurysms. The one study which reported statistical data (Manabe *et al.* 2004) reported a significantly greater ($p=0.015$) degree of aneurysm occlusion in patients after clipping

compared to coiling. Manabe *et al.* (2004) reported that of the patients who underwent coiling, subtotal occlusion of aneurysms in eight patients was due to neck remnants, body filling, and a failed coiling procedure.

Table 50: Degree of aneurysm occlusion in patients undergoing coiling or clipping for unruptured aneurysms

Outcome	L of E	coiling		clipping		p value
		total	partial	total	partial	
Brilstra <i>et al.</i> 2004	III-2	16/19 (84%)	3/19 (16%)	36/37 (97%)	1/37 (3%)	NR
Manabe <i>et al.</i> 2004	III-2	8/16 (50%)	8/16 (50%)	82/93 (92%)	11/93 (8%)	0.015
Regli <i>et al.</i> 2002	III-2	3/14 (21%)	11/14 (79%)*	60/60 (100%)	0/60 (0%)	NR
Range of rates		21% to 84%	16% to 79%	92% to 100%	0% to 8%	3 studies
Median of rates		50%	50%	97%	3%	

NOTE: specific subgroups: Manabe *et al.* 2004 – patients with non-giant saccular aneurysms; Regli *et al.* 2002 – patients with MCA aneurysms.

*11 patients had a failed coiling procedure.

Measures of impairment and disability at discharge

The GOS score at discharge was reported in three studies (Gruber *et al.* 1999c; Sano *et al.* 2000; Singh *et al.* 2002). Sano *et al.* (2000) reported that of the patients who underwent clipping, 99% (94/95 patients) made a good recovery (GOS score at discharge of 5) and 1% (1/95 patients) did not survive the procedure (GOS at discharge of 1); however this study did not provide comparable data for patients who underwent coiling. Gruber *et al.* (1999c) reported that in patients with basilar tip aneurysms, of the patients who underwent coiling, 90% (9/10 patients) made a good recovery with only moderate disability (GOS score of 4-5) compared with 80% (4/5 patients) of patients who underwent clipping. Singh *et al.* (2000) reported that of the patients who underwent coiling, 87% (54/62 patients) made a good recovery, compared with 62% (42/68 patients) in patients who underwent clipping.

The Rankin Score (RS) at discharge was reported in one study (Singh *et al.* 2002). This study reported that of the patients who underwent coiling, 69% (43/62 patients) had no significant disability despite symptoms (RS of 1) compared with 38% (154/406 patients) of patients who underwent clipping. This study also reported that of the patients who underwent coiling, 92% (57/62 patients) had a change in RS score at discharge of 0, compared with 59% of patients who underwent clipping. Overall, changes in RS at discharge were significantly greater after clipping compared to coiling ($p < 0.0001$). Poor outcomes (change in RS score at discharge of ≥ 2) were reported in 8% (5/62 patients) of patients who underwent coiling compared with 25% (17/68 patients) who underwent clipping ($p = 0.01$). Clipping was associated with poor outcomes (change in RS score at discharge of ≥ 2) more frequently than coiling in all aneurysm locations, except for OpthA aneurysms, where a poor outcome occurred once with each intervention. There was a significantly greater risk of poor outcome (change in RS score at discharge of ≥ 2) in patients who underwent clipping versus patients who underwent coiling (OR 9.0, 95% CI: 2.5 to 32.9, $p = 0.001$), in posterior circulation versus anterior circulation aneurysms (OR 3.8, 95% CI: 1.0 to 13.9, $p = 0.04$), in symptomatic versus incidental presentation (OR 5.3, 95% CI: 1.6 to 16.7, $p = 0.006$) and in older versus younger patients (OR 1.7, 95% CI: 1.1 to 2.6, $p = 0.02$).

Measures of impairment and disability at follow-up

The RS at 3 months was reported in one study (Brilstra *et al.* 2004). This study reported that of the patients who underwent coiling, 5% (1/19 patients) had no symptoms (RS of 0), compared with 9% (3/32 patients) in patients who underwent clipping. This study also reported that of the patients who underwent coiling, 26% (5/19 patients) had a worsening of their functional health (a higher RS), 42% (8/19 patients) exhibited no change in their functional health (no change in RS) and 32% (6/19 patients) had an improvement in their functional health (a lower RS) compared with 44% (14/32 patients), 47% (15/32 patients) and 9% (3/32 patients) respectively in patients who underwent clipping. Of the patients who underwent coiling, 5% (1/19 patients) were dependent compared to 16% (5/32 patients) of patients who underwent clipping.

Two studies reported the GOS score at 6 months follow-up (Collice *et al.* 1998; Vindlacheruvu *et al.* 2003). Collice *et al.* (1998) reported that of those patients who underwent coiling, 70% (7/10 patients) made a good recovery with only moderate disability (GOS score 4-5) and 30% (3/10 patients) suffered severe disability (GOS score 3) compared with 100% (16/16 patients) and 0% (0/16 patients) respectively in patients who underwent clipping. Vindlacheruvu *et al.* (2003) reported that 88% (23/26 patients) of patients who underwent coiling made a good recovery (GOS score of 5) following the procedure compared with 76% (22/29 patients) who underwent clipping.

Comparison 2: Endovascular versus surgical treatment

Non-randomised comparative studies

Several endovascular devices were employed in these studies, including coiling (1 study), balloons (1 study), and coiling in combination with balloons (1 study).

Safety

Perioperative mortality

Two studies reported on perioperative mortality rates (Kai *et al.* 2001; Wiebers *et al.* 2003). Wiebers *et al.* (2003) reported that the rate of perioperative mortality 30 days after treatment was 2% in patients undergoing endovascular treatment (8/451 patients) and in patients undergoing surgical treatment (29/1917 patients). Kai *et al.* (2001) reported that in patients with dissecting VA aneurysms, there were no deaths during the perioperative period in either treatment group.

Intraoperative rupture

The incidence of intraoperative rupture was reported in one study (Wiebers *et al.* 2003). The rate of intraoperative rupture was 6% (116/1917 patients) in patients undergoing surgical treatment, however no comparable data was reported for patients who underwent endovascular treatment.

Intracranial or ischaemic infarction

The incidence of intracranial or ischaemic infarction was reported in two studies (Linskey *et al.* 1991; Wiebers *et al.* 2003). Wiebers *et al.* (2003) reported that the incidence

of intracranial or ischaemic infarction was 5% (26/451 patients) in patients undergoing endovascular treatment, and 11% (208/1917 patients) in patients undergoing surgical treatment. Linskey *et al.* (1991) reported that in patients with intracavernous ICA aneurysms, the incidence of intracranial or ischaemic infarction was 18% (2/11 patients) in patients undergoing endovascular treatment, and 17% (1/6 patients) in patients undergoing surgical treatment.

Neurological complications

The incidence of neurological complications was reported in one study (Lihara *et al.* 2003a). In this study of patients with non-giant paraclinoid aneurysms, 9% (3/35 patients) of surgical patients suffered from cranial nerve palsy and 3% (1/35 patients) suffered from seizures.

Effectiveness

Degree of aneurysm occlusion

The degree of aneurysm occlusion was reported in four studies (Table 51). Of the patients who underwent endovascular treatment, 74% (range 51 to 100%) of patients had totally occluded aneurysms and 26% (range 0 to 44%) of patients had partially occluded aneurysms. In patients who underwent surgery, 100% (range 71 to 100%) of patients had totally occluded aneurysms, and 0% (range 0 to 29%) of patients had partially occluded aneurysms.

Table 51: Degree of aneurysm occlusion in patients undergoing endovascular or surgical treatment for unruptured aneurysms

Outcome	L of E	endovascular		surgery		p value
		total	partial	total	partial	
lihara <i>et al.</i> 2003a	III-2	51/77 (66%)	26/77 (34%)	25/35 (71%)	10/35 (29%)	NR
Weibers <i>et al.</i> 2003	III-2	231/451 (51%)	199/451 (44%)*	NR	NR	NR
Kai <i>et al.</i> 2001	III-2/3	4/4 (100%)	0/4 (0%)	5/5 (100%)	0/5 (0%)	NR
Linskey <i>et al.</i> 1991	III-2/3	9/11 (82%)	2/11 (18%)	6/6 (100%)	0/6 (0%)	NR
Range of rates		51% to 100%	0% to 44%	71% to 100%	0% to 29%	4 studies
Median of rates		74%	26%	100%	0%	

NOTE: lihara *et al.* 2003a – non-giant paraclinoid aneurysms; Kai *et al.* 2001 – dissecting VA aneurysms; Linskey *et al.* 1991 – intracavernous ICA aneurysms.

* 21 of the 451 patients had an unknown degree of aneurysm occlusion.

Impairment and disability at follow-up

One study reported on measures of disability and impairment at 1 and 12 months follow-up (Wiebers *et al.* 2003). At 1 month follow-up, of the patients who underwent endovascular treatment, 2.2% (10/451 patients) had a moderate to severe disability (RS of 3-5), 3.3% (15/451 patients) had an impaired cognitive status, and 1.7% (8/451 patients) had both a moderate to severe disability (RS of 3-5) and impaired cognition. This compared with 2.9% (55/1917 patients), 4.6% (89/1917 patients) and 4.2% (81/1917 patients) respectively in patients who underwent surgical treatment. At 12 months follow-up, of the patients who underwent endovascular treatment, <1% (10/451 patients) had a moderate to severe disability (RS of 3-5), 3.5% (15/451 patients) had an impaired cognitive status, and 2% (9/451 patients) had both a moderate to severe disability (RS of 3-5) and impaired cognition, compared with 1.3% (25/1917 patients),

5.7% (110/1917 patients) and 2.8% (53/1917 patients) respectively of patients who underwent surgical treatment.

Aneurysm recurrence or enlargement

Aneurysm recurrence was reported in one study (Iihara *et al.* 2003a). This study reported that in patients with non-giant paraclinoid aneurysms, aneurysm recurrence occurred in 4% (3/77 patients) of patients who received endovascular treatment, however comparable data was not reported for patients who received surgical treatment.

Aneurysm retreatment

Aneurysm retreatment was reported in one study (Iihara *et al.* 2003a). This study reported that in patients with non-giant paraclinoid aneurysms, of those who underwent endovascular treatment, 4% (3/77 patients) required aneurysm retreatment, compared to 0% (0/35 patients) of patients who underwent surgical treatment.

Aneurysm rebleeding

Aneurysm rebleeding was reported in one study (Iihara *et al.* 2003a). This study reported that in patients with non-giant paraclinoid aneurysms, aneurysm rebleeding occurred in 0% of patients who received endovascular treatment (0/77 patients) and surgical treatment (0/35 patients).

Mortality at follow-up

Mortality at follow-up was reported in one study (Weibers *et al.* 2003). Of the patients who underwent endovascular treatment, 3% (14/451 patients) were dead within the follow-up period of 12 months, compared with 2% (45/1917 patients) of patients who underwent surgical treatment.

Registry studies

Endovascular coiling was used in all three registry studies. These studies utilised databases covering a total of 696 hospitals (Johnston 2000; Johnston *et al.* 2001; Barker *et al.* 2004). Specifically, Barker *et al.* (2004) utilised the Nationwide Inpatient Sample hospital discharge database which covered 469 hospitals; Johnston (2000) utilised the University Healthsystems Consortium database, which covered 60 US hospitals; and Johnston *et al.* (2001) utilised the Office of Statewide Planning California database which covered 167 US hospitals. Barker *et al.* (2004) reported that 11% (421/3919) of patients received endovascular treatment, while 89% (3498/3919) of patients received surgical treatment. Johnston (2000) reported that 10% (255/2623) of patients received endovascular treatment, while 89% (2357/2623) of patients received surgical treatment. Johnston *et al.* (2001) reported that 18% (370/2069) of patients received endovascular treatment, while 82% (1699/2069) of patients received surgical treatment.

Safety

Perioperative mortality

Barker *et al.* (2004) reported that the rate of perioperative mortality was 1.7% (7/421 patients) following endovascular treatment and 2.1% (73/3498 patients) following surgical treatment; unadjusted OR 1.3 (95% CI: 0.6 to 2.8, p=0.6) and adjusted OR 1.2

(95% CI: 0.9 to 2.9, $p=0.7$). Johnston (2000) reported that the rate of perioperative mortality was 0.4% (10/255 patients) following endovascular treatment and 2.3% (119/5174 patients) following surgical treatment; unadjusted OR 6.1 (95% CI: 1.3 to 44.0, $p=0.039$) and adjusted OR 6.3 (95% CI: 0.9 to 46.1, $p=0.07$). Johnston *et al.* (2001) reported that the rate of perioperative mortality was 0.5% (2/370 patients) following endovascular treatment and 3.5% (72/2069 patients) following surgical treatment; adjusted OR 6.3 (95% CI: 3.5 to 11.4, $p<0.001$). In hospitals with a higher volume of endovascular cases the relative risk reduction of in-hospital mortality was 16% (95% CI: 0.78 to 0.91, $p<0.0001$) for every 10% of cases treated using endovascular techniques (Johnston 2000). The rate of perioperative mortality was 1.2% in hospitals treating more than 10% of endovascular cases compared with 4% in hospitals treating less than 10% of endovascular cases ($p<0.001$) (Johnston *et al.* 2001).

Table 52: Perioperative mortality in patients undergoing endovascular or surgical treatment for unruptured aneurysms

Outcome	endovascular		surgical		unadjusted OR (95%CI)	p value	adjusted OR (95%CI)	p value
	n/N	%	n/N	%				
Perioperative mortality								
Barker <i>et al.</i> 2004	7/421	1.7	73/3498	2.1	1.3 (0.6 – 2.8)	0.6	1.2 (0.9 – 2.9)	0.7
Johnston 2000	10/25	0.4	119/517	2.3	6.1 (1.3 – 44.0)	0.039	6.3 (0.9 – 46.1)	0.07
Johnston <i>et al.</i> 2001	2/370	0.5	72/2069	3.5	NR	0.003	6.3 (3.5 – 11.4)	<0.001

Barker *et al.* 2004 adjusted for age, sex, race, primary payer, hospital geographic region, medical comorbidity score, presenting symptoms, hospital volume, year of treatment, clustering by hospital; Johnston 2000 adjusted for age, sex, race, transfer admission, emergency admission, year of treatment; Johnston *et al.* 2001 adjusted for age, sex, ethnicity, source of admission, year of treatment.

Complications

Barker *et al.* (2004) reported several complications which were observed in patients following endovascular and surgical treatment (Table 53). In multivariate analysis significantly more neurological complications ($p=0.002$), hemiparesis/hemiplegia ($p=0.008$) and transfusions ($p=0.03$) were observed following surgical treatment compared with endovascular treatment (Table 53). The complication rate was 14% in hospitals treating more than 10% of endovascular cases compared with 28% in hospitals treating less than 10% of endovascular cases ($p<0.001$) (Johnston *et al.* 2001).

Table 53: Complications in patients undergoing endovascular or surgical treatment for unruptured aneurysms in Barker *et al.* (2004)

Outcome	endovascular	surgical	OR (95% CI)	p value
Complications				
neurological	21/421 (5%)	274/3498 (8%)	2.0 (1.3 – 3.2)	0.002
aphasia	7/421 (2%)	102/3498 (3%)	2.0 (0.95 – 4.2)	0.07
hemiparesis or hemiplegia	8/421 (2%)	184/3498 (5%)	2.8 (1.3 – 5.9)	0.008
occlusion of cerebral artery	37/421 (9%)	223/3498 (6%)	0.8 (0.5 – 1.2)	0.3
mechanical ventilation	14/421 (3%)	180/3498 (5%)	1.8 (0.9 – 3.6)	0.07
tracheotomy	4/421 (1%)	29/3498 (1%)	0.96 (0.2 – 4.2)	1.0
gastrotomy	3/421 (1%)	65/3498 (2%)	4.3 (0.98 – 19)	0.05
hydrocephalus	11/421 (3%)	68/3498 (2%)	0.9 (0.5 – 1.4)	0.6
haematoma	16/421 (4%)	78/3498 (2%)	0.8 (0.3 – 1.9)	0.6
cardiac	2/421 (1%)	60/3498 (2%)	3.8 (0.7 – 20)	0.11
thrombotic	4/421 (1%)	28/3498 (1%)	0.7 (0.2 – 2.1)	0.5
transfusion	3/421 (1%)	129/3498 (4%)	5.6 (1.2 – 26)	0.03
physical therapy consultation	2/421 (1%)	95/3498 (3%)	3.8 (0.9 – 16)	0.07

Effectiveness

Length of hospital stay

Barker *et al.* (2004) reported that the median length of hospital stay was 2 days following endovascular treatment and 5 days following surgical treatment (Table 54). Johnston (2000) reported that the mean length of hospital stay was 4.6 days (95% CI: 4.0 to 5.1) following endovascular treatment and 9.6 days (95% CI: 9.1 to 10) following surgical treatment; unadjusted OR 5 (95% CI: 3.6 to 6.3, $p < 0.001$) and adjusted OR 4.5 (95% CI: 3.2 to 5.9, $p < 0.001$) (Table 54). Johnston *et al.* (2001) reported that the mean length of hospital stay was 7.1 days (95% CI: 6.2 to 8.0) following endovascular treatment and 11.8 days (95% CI: 11.4 to 12.4) following surgical treatment; adjusted OR 1.4 (95% CI: 1.3 to 1.6, $p < 0.001$) (Table 54). The length of hospital stay was 8.6 days in hospitals treating more than 10% of endovascular cases compared with 12.4 days in hospitals treating less than 10% of endovascular cases ($p < 0.001$) (Johnston *et al.* 2001).

Table 54: Length of hospital stay in patients undergoing endovascular or surgical treatment for unruptured aneurysms

Outcome	endovascular	surgical	unadjusted OR (95% CI)	p value	adjusted OR (95% CI)	p value
	mean (95% CI)	mean (95% CI)				
LOS (days)						
Barker <i>et al.</i> 2004	median 2 days	median 5 days	NR	<0.001	NR	<0.001
Johnston 2000	4.6 (4.0 – 5.1)	9.6 (9.1 – 10.0)	5 (3.6 – 6.3)*	<0.001	4.5 (3.2 – 5.9)*	<0.001
Johnston <i>et al.</i> 2001	7.1 (6.2 – 8.0)	11.8 (11.4 – 12.4)	NR	<0.000	1.4 (1.3 – 1.6)†	<0.001

Barker *et al.* 2004 adjusted for age, sex, race, primary payer, hospital geographic region, medical comorbidity score, presenting symptoms, hospital volume, year of treatment, clustering by hospital; Johnston 2000 adjusted for age, sex, race, transfer admission, emergency admission, year of treatment; Johnston *et al.* 2001 adjusted for age, sex, ethnicity, source of admission, year of treatment.

* difference between endovascular and surgical; † - ratio of endovascular to surgical.

Death or discharge to nursing home

Barker *et al.* (2004) reported that 91% of patients were discharged home following endovascular treatment compared with 82% of patients following surgical treatment. Johnston (2000) reported that following endovascular treatment 10.6% (27/255) of patients died or were discharged to a nursing home compared with 18.5% (957/5174) of patients following surgical treatment; unadjusted OR 1.9 (95% CI: 1.3 to 2.9, $p = 0.002$) and adjusted OR 2.1 (95% CI: 1.4 to 3.3, $p = 0.001$) (Table 55). Johnston *et al.* (2001) reported that following endovascular treatment 9.7% (36/370) of patients died or were discharged to a nursing home compared with 25.4% (427/2069) of patients following surgical treatment; adjusted OR 3.1 (95% CI: 2.5 to 4.0, $p < 0.001$) (Table 55).

Table 55: Death or discharge to nursing home in patients undergoing endovascular or surgical treatment for unruptured aneurysms

Outcome	endovascular		surgical		unadjusted OR (95% CI)	p value	adjusted OR (95% CI)	p value
	n/N	%	n/N	%				
Death or discharge to nursing home								
Barker <i>et al.</i> 2004	NR	NR	NR	NR	1.4 (0.8 – 2.3)	0.2	1.6 (0.9 – 2.9)	0.15
Johnston 2000	27/255	10.6	957/5174	18.5	1.9 (1.3 – 2.9)	0.002	2.1 (1.4 – 3.3)	0.001
Johnston <i>et al.</i> 2001	36/370	9.7	427/2069	25.4	NR	<0.001	3.1 (2.5 – 4.0)	<0.001

Barker *et al.* 2004 adjusted for age, sex, race, primary payer, hospital geographic region, medical comorbidity score, presenting symptoms, hospital volume, year of treatment, clustering by hospital; Johnston 2000 adjusted for age, sex, race, transfer admission, emergency admission, year of treatment; Johnston *et al.* 2001 adjusted for age, sex, ethnicity, source of admission, year of treatment.

Comparison 3: Endovascular versus conservative treatment

Non-randomised comparative studies

Endovascular coiling was employed in the single study.

Effectiveness

Impairment and disability at follow-up

The GOS score at follow-up was reported in one study (Naito *et al.* 2002). This study reported that in patients with dissecting VA aneurysms, of those who underwent endovascular treatment, 78% (7/9 patients) made a good recovery (GOS score of 5) and 22% (2/9 patients) suffered moderate disability (GOS score of 4), compared to 92% (11/12 patients) and 8% (1/12 patients) respectively in patients who underwent conservative treatment.

Economic considerations

Literature review of comparative costing studies and economic models

Ruptured aneurysms

Bairstow *et al.* (2002) examined the costs incurred by 22 patients with ruptured aneurysms recruited to ISAT at the Royal Perth and Sir Charles Gairdner Hospitals, Australia. The authors concluded that while coiling was more expensive than clipping in terms of consumables; staffing costs were lower and hospital stays (and therefore costs) were lower for coiling. Total costs for staffing, consumables and hospital stay were about A\$18 000 for coiling and about A\$22 000 for clipping.

Koguchi *et al.* (2004) found no significant differences in coiling and clipping costs for ruptured aneurysm (477 890 points versus 456 084 points where 1 point equates to 10 yen).

Niskanen *et al.* (2004) found that coiling and clipping required similar amounts of resources in the first year, although they only measured length of ICU stay or overall hospital stay.

Unruptured aneurysms

In Hoh *et al.* (2003), median total hospital charges for endovascular treatment of unruptured aneurysms were US\$26 069 for hospitals with fewer than eight annual endovascular procedures and US\$17 274 for hospitals with eight or more annual procedures.

Barker *et al.* (2004) reported that median hospital charges were lower for coiling than for clipping in 421 coiling patients and 3 498 clipping patients (US\$13 200 versus US\$21 800, $p=0.007$).

Another study (Johnston *et al.* 2001) also reported lower mean charges for coiling but both coiling and clipping charges were much higher than those presented in Barker *et al.* (2004) (US\$37 000 for 370 patients treated endovascularly versus US\$64 000 for 1699 patients treated surgically).

A third study (Johnston, Gress & Kahn 1999) also reported lower charges for coiling (mean US\$30 000 for 255 coiling procedures and mean US\$43 000 for 2357 clipping procedures).

Kallmes *et al.* (1998) performed a cost-utility analysis comparing coiling with no treatment for patients with unruptured aneurysms not considered to be suitable for surgical clipping. For patients refused surgery on the basis of the size, location or morphology of the aneurysm the incremental cost-utility ratio was \$23 000/QALY. For patients whose pre-existing medical condition precluded surgery this was \$19 000/QALY.

Mixed ruptured and unruptured aneurysms

Le Feuvre & Taylor (2004) selected 17 patients with posterior communicating artery aneurysms, since these aneurysms were considered to be equally suitable for either clipping or coiling. They found that the average cost of coiling was 37 041 rands and 44 104 rands for clipping (i.e. clipping 16% more expensive than coiling).

Yentur *et al.* (2004) found coiling costs to be greater than clipping costs and this was driven largely by the high cost of consumables required for coiling.

Economic model

The economic analysis has been done from a health system perspective, with sensitivity analyses examining longer term need for nursing home care.

Assumptions

- Since much of the treatment and management of ruptured aneurysms is due to the underlying disease process which leads to subarachnoid haemorrhage, resource requirements such as length and type of hospital stay have been assumed to be similar.
- The aneurysm can be treated by either coiling or clipping.
- There are no apparent important differences in outcome for different locations of ruptured aneurysms, which could be treated by either coiling or clipping.
- A second, separate digital subtraction angiography will be required in 20% of cases of ruptured aneurysms and 50% of cases of unruptured aneurysms.
- Coiling is at least as effective as clipping for treating unruptured aneurysms.
- Length and pattern of hospital stay is similar for coiling and clipping in the base case for ruptured aneurysms.
- Length of hospital stay is longer for clipping than for coiling for unruptured aneurysms.

Sources

Table 56: Sources for the costs associated with the treatment of ruptured and unruptured aneurysms

Item	Source	Comment
Imaging	Based on MBS item numbers for digital subtraction angiography (10 or more runs)	
Procedure costs for clipping	MBS item number 39800	
Procedure costs for coiling	Notional amount modelled on a range which includes the 39800 amount	
Theatre band 6 for clipping	Assumed to be of similar complexity as carotid endarterectomy (see MSAC assessment of carotid stenting)	
Theatre band 12 for clipping	Assumed to be of similar complexity as carotid stenting (see MSAC assessment of carotid stenting)	
Anaesthetist costs	Provided by Anaesthetics Department, The Queen Elizabeth Hospital, SA, in 2004	
Clipping consumables	Bairstow <i>et al.</i> 2002	Cost study based on ISAT participants from Australia
Coiling consumables	Bairstow <i>et al.</i> 2002	Cost study based on ISAT participants from Australia
Costs per day of hospital stay	Bairstow <i>et al.</i> 2002	Cost study based on ISAT participants from Australia
Hospital stay (ruptured aneurysms)	Advisory panel for this review; Royal North Shore and Dalgross Hospitals, website (www.avmsurgeon.com)	
Effectiveness (measured by Modified Rankin Score)	Absolute risk difference of 7% fewer patients with MRS 3-6 derived from ISAT	
Nursing home care for first 12 months	Deduced from ISAT	
Hospital stay (unruptured aneurysms)	This review	
Conversions	The two RCTs (ruptured) and non-randomised studies (unruptured) in this review	
Need for retreatment	The two RCTs (ruptured) and non-randomised studies (unruptured) in this review	

Ruptured aneurysms

Table 57: Unit costs for the base case for treatment of ruptured aneurysms

Clipping		Coiling	
Procedure	A\$	Procedure	A\$
Imaging as part of procedure	NA	Digital subtraction angiography, 10 or more runs (MBS item 60005) – estimated to be required in addition to the diagnostic DSA on 20% procedures	275.26
ANEURYSM, clipping or reinforcement of sac (MBS item 39800)	2 473.10	'notional' reimbursement (modelled)	1 500 to 2 500
Theatre band 6	920	Catheter lab/Theatre band 12	1 200
Anaesthetist costs	478.50	Anaesthetist costs	412.50
SUBTOTAL	3 872	SUBTOTAL	3 388 to 4 388
Consumables			
Clips and associated consumables	1 034	Coils and associated consumables	4 351
SUBTOTAL	1 034	SUBTOTAL	4 351
Length of hospital stay			
Intensive care (4 days @ \$2517)	10 068	Intensive care (4 days @ \$2517)	10 068
General ward (8 days @ \$373)	2 984	General ward (8 days @ \$373)	2 984
Rehabilitation ward (7 days @ \$349/day)	2 443	Rehabilitation ward (7 days @ \$349/day)	2 443
SUBTOTAL (19 days)	15 495	SUBTOTAL (19 days)	15 495
After care			
Included in MBS fee	NA	3 consultations at \$68.70	206.10
SUBTOTAL	NA	SUBTOTAL	206
OVERALL TOTAL	20 401	OVERALL TOTAL	23 440 to 24 440

The most robust effectiveness figures are available from the ISAT study (Molyneux *et al.* 2005). At 12 months, 250/1063 (24%) of coiling patients were dead or dependent compared with 326/1055 (31%) of clipping patients. This equates to a risk difference of –0.07 (95% CI: –0.11 to –0.04).

The incremental cost effectiveness ratio (ICER) calculation (difference in costs divided by differences in effectiveness) for the base case is:

$$\frac{20\,401 - (23\,440 \text{ to } 24\,440)}{-0.07}$$

$$= \$43\,414 \text{ to } \$57\,770$$

This means that for each additional death or dependency avoided, an additional \$43 414 to \$57 770 (95% CI: 27 627 to 100 975) must be spent.

Sensitivity analyses

1. Changing length of hospital stay

If hospital stay of clipping patients is increased from seven days to 10 days in the rehabilitation ward, the ICER calculation becomes:

$$\frac{21\,448 - (23\,440 \text{ to } 24\,440)}{-0.07}$$
$$= \$28\,457 \text{ to } \$42\,743$$

This means that for each additional death or dependency avoided, an additional \$28 457 to \$42 743 (95% CI: 18 109 to 74 800) must be spent.

2. Threshold analysis based on hospital stay (two-way)

The threshold for ICU stay at which costs become comparable for coiling and clipping is 1.5 days (either an increase from 4 days to 5.5 days for coiling or a decrease from 4 days to 2.5 days for clipping). The threshold for general and rehabilitation ward stay at which costs become comparable for coiling and clipping is about 10 days (either an increase from 15 days to 25 days for coiling or a decrease from 15 days to 5 days for clipping).

3. Threshold analysis based on cost of consumables (one-way)

All other things being equal, the costs of coils and associated consumables would need to decrease by about \$3 000 to \$4 000 for coiling and clipping to have comparable costs.

4. Using MRS 4-6 instead of MRS 3-6

When MRS 3 patients are omitted from the effectiveness analysis, the comparison of dead or dependent becomes statistically non-significant. Using the base case costs and this effectiveness measure, coiling and clipping have similar effectiveness with coiling being modestly more expensive (see Table 57).

5. Including conversion to clipping in coiling costs

Assuming a need to convert 2% of coiling patients to clipping and 4% of clipping patients to coiling at the time of operation would incur additional costs. These extra costs would add \$21 to the unit base case costs for coiling and \$229 for clipping.

6. Including need for retreatment

Assuming that 10% of coiling patients will need to be re-coiled and 4% of clipping patients would need to be re-treated in the first 12 months would add \$2 344 to \$2 444 to the unit base case costs for coiling and \$816 to the unit base costs for clipping.

7. Recalculation of ICER including conversions and re-coiling

This incremental cost effectiveness ratio calculation is:

$$\frac{21\,446 - (25\,805 \text{ to } 26\,901)}{-0.07}$$

$$= \$62\,271 \text{ to } \$77\,929$$

This means that for each additional death or dependency avoided, an additional \$62 271 to \$77 929 (95% CI: 39 627 to 136 375) must be spent.

8. Rehabilitation costs over one year

The main economic analysis has been done from a health system perspective, using the number of patients who were dead or dependent at 12 months as the measure of effectiveness. However, nursing home costs for patients who survive but who are dependent have not been included in the base case. We have assumed that MRS 4 (partly dependent) and MRS 5 (fully dependent) patients would need fulltime nursing home care but that MRS 3 (significant restrictions) patients could remain in their homes (with family/community assistance).

Using the ISAT results of 5.4% coiling patients being MRS 4-5 compared with 7.6% of clipping patients, the costs of nursing home care (at \$300 a day) in the first year would amount to an additional average cost per patient of \$5 913 for coiling patients and \$8 322 for clipping patients.

Overall economic impact

Of the order of 850 patients with ruptured aneurysms are likely to present for treatment each year in Australia (extrapolation of WA figures provided by Mark Khangure, December 2005). If the vast majority of these patients were now to be treated with coiling rather than clipping, the Australian health system would need to contribute an additional \$3 million to \$4 million a year (taking into account the need for conversions and recoiling/other retreatment within that year).

Unruptured aneurysms

Table 58: Unit costs for the base case for the treatment of unruptured aneurysms

Clipping		Coiling	
Procedure	A\$	Procedure	A\$
Imaging as part of procedure	NA	Digital subtraction angiography, 10 or more runs (MBS item 60005) – estimated to be required in addition to the diagnostic DSA on 50% procedures	688.15
ANEURYSM, clipping or reinforcement of sac (MBS item 39800) or ANEURYSM or arteriovenous malformation, intracranial proximal artery clipping (MBS item 39806)	1112.85 to 2473.10	'Notional' reimbursement (modelled)	1 500 to 2 500
Theatre band 6	920	Catheter lab/Theatre band 12	1 200
Anaesthetist costs	478.50	Anaesthetist costs	412.50
SUBTOTAL	2 511 to 3 872	SUBTOTAL	3 801 to 4 801
Consumables			
Clips and associated consumables	1 034	Coils and associated consumables	4 351
SUBTOTAL	1 034	SUBTOTAL	4 351
Length of hospital stay			
Intensive care (1 day @ \$2517)	2 517	Intensive care (1 day @ \$2517)	2 517
General ward (10 days @ \$373)	3 730	General ward (4 days @ \$373)	1 492
SUBTOTAL	6 247	SUBTOTAL	4 009
OVERALL TOTAL	9 792 to 11 153	OVERALL TOTAL	12 161 to 13 161

Thus coiling for unruptured aneurysms is about 20% more expensive than clipping, with a likely, but unproven, similar level of effectiveness.

If conversions from clipping to coiling (14.5%) and re-coiling (11% over four years) are included, the costs for coiling rise by \$1 987 from \$12 161 - \$13 161 to \$14 148 - \$15 148.

For unruptured aneurysms, coiling is slightly to moderately more expensive than clipping, with unknown but probably similar effectiveness to clipping.

Overall economic impact

Of the order of 150 patients with unruptured aneurysms are likely to present for treatment each year in Australia (extrapolation of WA figures provided by Mark Khangure, December 2005). If most of these patients were now to be treated with coiling rather than clipping, the Australian health system would need to contribute an additional \$450 000 to \$600 000 a year (taking into account the need for conversions and recoiling/other retreatment within that year).

Discussion

This review included 182 studies of which only 2 were RCTs, with the remaining data obtained from lower level evidence, including non-randomised comparative studies, case series and case reports. In relation to the important criteria of method of randomisation, allocation concealment and blinding, both RCTs provided adequate detail in their reports to determine whether minimum standards had been met.

Ruptured aneurysms

Limitations of the RCT evidence

The first prospective randomised trial to compare the safety and efficacy of endovascular coiling with surgical clipping for intracranial aneurysms was published by Koivisto *et al.* (2002), and was a single centre study of 109 patients. ISAT was the first international, multi-centre, prospective randomised trial of about 2000 patients, to compare the safety and efficacy of endovascular coiling with surgical clipping for intracranial aneurysms (Molyneux *et al.* 2005). Koivisto *et al.* (2002) selected patients who were of a good (61%), average (24%) and poor (15%) clinical grade, with small, medium and large intracranial aneurysms, which were located in both the posterior and anterior circulations. In this relatively small study, of the 242 consecutive patients with angiographically proved aneurysmal SAH, 111 (46%) were randomly assigned to the study.

In ISAT, a total of 9559 patients were assessed for eligibility and 2143 (22.4%) were randomised. Although the study initially aimed to recruit 2500 patients, the steering committee stopped recruitment prematurely at 2143 patients. There was no description of the 7416 patients who were eligible but not randomised. Over the course of the study, neurovascular teams in the participating centres felt that surgery was the best option for the majority of patients with ruptured aneurysms who were not randomised. Outcomes and follow-up were not provided for the non-randomised patients. Any pre-existing bias is likely to be multifactorial, including personal experiences at the individual centres, knowledge of the results of previous retrospective reviews of treatment of aneurysms with particular characteristics, patient's preference and clinical status after SAH (Nichols, Brown & Meyer 2002). The contribution of the participant centres to the study varied between 1 to 44% of their real patient population, which seems to be due to the differences in the levels of expertise of clipping versus coiling in different centres (Debrun 2003). This raised the question of whether there was a bias towards one of the treatment modalities in those centres with higher rates of patient recruitment (Ausman 2003). It has been noted that the major contributing centres had more expertise in endovascular treatment, with Lindsay (2003) reporting that the proportion of patients referred to endovascular treatment as 49% in the major participating centres of the study as compared to the average of 34% in the UK. These major centres provided 76.7% of the patients in this study. One of the major criticisms of ISAT has been that the patients randomised to the study represented only a selected subgroup of patients with SAH in clinical practice i.e. good clinical grade (88% had WFNS 1-2), with small aneurysms (92% <1 cm in diameter, 50% <5 mm), located in the anterior circulation (97% of patients; 50.5% ACA, 32.5% ICA, 14.1% MCA). It may be difficult to extrapolate the findings from this study to other types of ruptured aneurysms, or to the entire population of unruptured aneurysms (Nichols, Brown & Meyer 2002). Others have

argued that the low (22.4%) randomisation rate does not limit the internal validity of the study data. In addition, it has also been argued that to randomly assign patients in who clinical equipoise did not exist would not be ethical or practical, and the data generated from such a study would not be useful (Derdeyn *et al.* 2003).

Koivisto *et al.* (2002) had a follow-up period of just one year. It is well accepted that one-year follow-up is not enough to evaluate the results of endovascular treatment (Harbaugh *et al.* 2003; Raabe *et al.* 2003). ISAT is following-up patients up to 7 years after initial treatment (Molyneux *et al.* 2005).

Koivisto *et al.* (2002) measured clinical outcome following endovascular coiling or surgical clipping using the Glasgow Outcome Score (GOS). In ISAT, the Modified Rankin Scale (MRS) was used to assess the functional outcomes of the study (Molyneux *et al.* 2005), where the primary outcome measure was the proportion of patients dead or disabled, as defined by an MRS of 3-6. The MRS is a simple measure with well-studied reliability and is a time efficient tool by which to categorise level of functional outcome, making it convenient for use in large centres or in large trials (Wade 1992; de Haan *et al.* 1995). However, the subjective nature of the score and the lack of clear criteria by which to assign grades may reduce the usefulness of the scale. The categories within the scale have been criticised as being broad and poorly defined, left open to interpretation of the individual (Wilson 2002). A structured interview format for the administration of the MRS is available, and its use has been associated with significant improvements in inter-observer reliability (Wilson 2002).

In ISAT, data was collected via a postal questionnaire and the ability of a postal questionnaire to differentiate Grade 2 (some restriction in lifestyle) from Grade 3 (significant restriction in lifestyle) is uncertain (Lindley, Waddell & Livingstone 1994). Harbaugh (2003) showed that the statistical significance between functional outcomes of each treatment group exists only when the groups are pooled as 0-2 and 3-6; however this statistical difference disappears if the groups are compared one by one, or are pooled as 0-1 and 2-6 or 0-3 and 4-6. Some critics of ISAT have argued that an optimum outcome assessment should include clinical outcome assessment with a universally accepted scale (Sade & Mohr 2004), which may make comparisons of morbidity data with other studies more reliable. Derdeyn *et al.* (2003) have argued that the difference observed in clinical outcome between the treatment groups in ISAT is in fact meaningful, as the primary end-point (dependency or death, MRS 3-6), was predetermined, rather than set in a post hoc data analysis. This study further argued that a trend toward better outcome with endovascular therapy was seen across all subgroups; however, the study was not powered to address these differences, particularly when enrolment was prematurely halted. In addition, it was argued that the difference between existence with a significant lifestyle restriction (MRS 2) compared with partial dependency (MRS 3) would be important to most patients after SAH, with fewer than half of the affected patients returning to their pre-haemorrhage status following treatment (Derdeyn *et al.* 2003).

Like other complex procedures, surgical clipping and coil embolisation are associated with a steep learning curve. Malisch *et al.* (1997) evaluated the learning curve for coil embolisation, comparing the first 100 cases with the second 100 treated at a single institution. The rate of procedure-related complications in this study, which included patients with both ruptured and unruptured aneurysms, decreased from 14% to 7%. Singh *et al.* (2002) sought to determine whether outcomes for endovascular coil

embolisation improved with experience of the practitioner after adjusting for the perceived risk of treatment. In this study of three practitioners at a single centre, the risk of complications with coil embolisation of unruptured aneurysms dramatically decreased with increasing physician experience, even after adjustment for case complexity (OR, 0.69 for every five cases treated; 95% CI: 0.50 to 0.96; $p=0.03$), the result corresponding to a 30% odds reduction for complication for every five cases treated.

Koivisto *et al.* (2002) noted that most surgical procedures were performed by a team of neurosurgeons with a collective experience of approximately 2000 aneurysm operations. However, because coil embolisation was a relatively new technique, neurointerventional radiologists in the study had far more limited experience, and as such, a learning curve was observed in this study, with most of the complications associated with coiling occurring at the beginning of the study.

The ISAT protocol required surgical centres participating in the study to have good vascular neurosurgical expertise with regular experience of aneurysm clipping; however, the experience of individual surgeons was not reported. Endovascular operators were required to have had wide interventional neuroradiological experience and to have treated at least 30 cases with GDC devices before randomising patients in the trial. Critics of the trial have argued that this may have contributed to an expertise bias in favour of the endovascular group, if the number of coiling cases per endovascular practitioner was significantly greater than the number of clipping cases per neurosurgical practitioner, and that this data should be published (Harbaugh 2003). However Derdeyn *et al.* (2003) has suggested that ISAT neurosurgeons clipped three aneurysms in the non-randomised group for every one surgically clipped aneurysm in the randomised group, and may actually have been more experienced when compared to endovascular operators, who would have begun coiling soon after the introduction of the technique to Europe in 1992.

Lower level evidence

The majority of non-randomised comparative studies failed to demonstrate any significant difference after coiling and clipping in the rate of perioperative mortality and complications such as intraprocedural rupture, intracranial or ischaemic infarction and thromboembolic, procedure-related and neurological complications. However, fewer patients suffered from vasospasm after coiling. Some durability outcomes were poorly reported for clipping, so comparisons with coiling were rare; however, the degree of aneurysm occlusion seen in the postoperative period was significantly greater after clipping, a difference that was not observed at follow-up. Most non-randomised comparative studies failed to demonstrate any significant difference in the degree of impairment or disability at discharge or follow-up; however, where differences were reported, a higher proportion of patients made a good recovery after coiling. Patients who received coiling performed significantly better on a number of neuropsychological tests measuring depression, executive function and memory compared with those who had been clipped.

A large number of studies reported safety and effectiveness outcomes for mixed patient and aneurysm factors; however, many studies also reported on specific subgroups of aneurysms or patients. Unfortunately, insufficient data were available to perform any subgroup analyses based on aneurysm size, location or type, or the patient's age, comorbidities or neurological status on admission. A number of studies also reported on other endovascular techniques used in the treatment of intracranial aneurysms either

alone or in combination with coiling, including stents, balloons and liquid embolic agents. However there was insufficient evidence on these other endovascular treatments to make any strong conclusions about their safety or effectiveness in treating intracranial aneurysms.

Unruptured aneurysms

No prospective, randomised controlled trials have been conducted to compare endovascular coiling and surgical clipping for unruptured aneurysms; however, the results from lower level evidence indicate that endovascular coiling appears to be as safe as surgical clipping. The evidence for efficacy was less clear, particularly with regard to durability outcomes, which were poorly reported in comparative studies. However, clipping appeared to result in a greater degree of impairment or disability at discharge, as well as a longer hospital stay. There were few studies which reported data for the comparison of safety and effectiveness outcomes for asymptomatic and symptomatic patients undergoing endovascular coiling. The single study that did report this comparison for unruptured aneurysms showed that there was a significantly greater risk of poor outcome in symptomatic versus asymptomatic patients.

Conclusions

In certain types of patients, coiling for ruptured aneurysms is more effective than surgical clipping, and for other patients clipping is the more suitable choice. Therefore it is imperative for treatment to be optimised for each patient, ideally through assessment in a multidisciplinary setting which offers 24-hour expertise in both coiling and clipping.

Most of the evidence in this review comes from a single large international randomised trial. While this trial has attracted some criticism regarding its entry criteria and outcome measurement, it was of high methodological quality and internal validity. Their findings of a clear survival advantage strengthen the case for coiling. Compared with clipping, coiling is more expensive but it has a relatively low cost per death or dependency avoided. Adverse events were not well reported in the RCTs, but complications were generally low and similar between coiling and clipping in the non-randomised comparative studies. No conclusions can be drawn about the effect of aneurysm location or size, or patient's preoperative neurological status on outcome.

The evidence for the relative benefit of coiling over clipping for unruptured aneurysms is less clear. A small number of comparative studies suggest that it may be at least as safe and effective as clipping. However, coiling of unruptured aneurysms is slightly to moderately more expensive than clipping.

The published evidence for endovascular approaches other than coiling is very scant and no conclusions can yet be drawn about relative safety, effectiveness and cost effectiveness of these approaches over surgical clipping.

Recommendation

Available evidence suggests that endovascular treatment of intracranial aneurysms using coils is as safe and effective as surgical clipping for appropriately selected patients. The procedure is also cost effective when compared to surgery. MSAC recommended public funding for this procedure.

The Minister for Health and Ageing accepted this recommendation on 6 June 2006.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Samantha Robertson	Department representative
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health

Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory Panel

Advisory panel for MSAC Reference 33

Dr Gerry Fitzgerald (Chair) Chief Health Officer Queensland Health Brisbane QLD	member of MSAC
Dr Ewa Piejko General Practitioner Melbourne VIC	member of MSAC
Dr Terri Jackson Senior Research Fellow School of Public Health LaTrobe University Melbourne VIC	member of MSAC
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Professor Mark Khangure Radiology Department Royal Perth Hospital Perth WA	Royal Australian and New Zealand College of Radiologists nominee
Professor Craig Anderson The George Institute for International Health Royal Prince Alfred Hospital Sydney NSW	Australian Association of Neurologists nominee
Ms Barbara Smith Consumer Representative Consumers' Health Forum of Australia Sydney NSW	Consumers' Health Forum of Australia nominee

Evaluators

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Ms Philippa Middleton
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Ms Brenda Campe
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Ms Christine Berry
Department of Health and Ageing

Project Manager

Appendix C Case reports

Ruptured aneurysms

Safety

Adverse events

Stenosis

Stenosis following endovascular treatment was reported in one study, which described the treatment of an anterior circulation aneurysm with coiling (Abadal Cantellas *et al.* 2005).

Aneurysm perforation

Aneurysm perforation following endovascular treatment was reported in three studies which described the treatment of anterior circulation aneurysms (Ricolfi *et al.* 1998; Willinsky & TerBrugge 2000; Mangiafico *et al.* 2002), and four studies which described the treatment of posterior circulation aneurysms (Ricolfi *et al.* 1998; Hirai *et al.* 2002; Mangiafico *et al.* 2002; Sugiu *et al.* 2004). The endovascular treatments used in these studies were coiling, balloon assisted coiling and stent assisted coiling.

Aneurysm recurrence

Aneurysm recurrence following endovascular treatment was reported in one study, which described the treatment of anterior circulation aneurysms (Makoui *et al.* 2000), and seven studies which described the treatment of posterior circulation aneurysms (Kwan *et al.* 1991; Ladouceur *et al.* 1993; Mericle *et al.* 1998; Boet *et al.* 2003; Guzman, Remonda & Barth 2003; Sauvageau *et al.* 2004; Sawada *et al.* 2005). The endovascular treatments used in these studies were coiling and balloon occlusion therapy.

De novo aneurysms

De novo aneurysms following endovascular treatment were reported in one study which described the treatment of posterior circulation aneurysms with coiling (Guzman, Remonda & Barth 2003).

Aneurysm rupture or rerupture

Aneurysm rupture or rerupture following endovascular treatment was reported in five studies, which described the treatment of posterior circulation aneurysms with coiling, stent assisted coiling, and balloon occlusion therapy (Kwan *et al.* 1991; Birchall *et al.* 2001; Fujimura *et al.* 2003; Kaku *et al.* 2003; Sugiu *et al.* 2004).

Device-related complications

Device-related complications following endovascular treatment were reported in four studies which described the treatment of anterior circulation aneurysms (Phatouros 1999b, Shin 2000; Sudhoff *et al.* 2000; Alfke *et al.* 2004), and four studies which described the treatment of posterior circulation aneurysms (Kwan *et al.* 1991; Zoarski *et al.* 1997; Lenthall, McConachie & Jaspan 2000; Boet 2003). The endovascular treatments used in these studies were coiling and balloon occlusion therapy.

Intracranial abscess or infection

Intracranial abscess or infection following endovascular treatment was reported in three studies which described the treatment of anterior circulation aneurysms with coiling and balloon assisted coiling (Kirolos *et al.* 2002; Marcoux, Roy & Bojanowski 2002; Jenkinson *et al.* 2003), and one study which described the treatment of posterior circulation aneurysms with coiling (Meyers *et al.* 2004).

Vision-related complications

Vision-related complications following endovascular treatment were reported in one study, which described the treatment of anterior circulation aneurysms (Ascaso & Cristobal 1999), and one study which described the treatment of posterior circulation aneurysms (Arita *et al.* 2003). Both studies used coiling.

Thromboembolic complications

Thromboembolic complications following endovascular treatment were reported in three studies which described the treatment of anterior circulation aneurysms with coiling (Sinson *et al.* 2001; Mangiafico *et al.* 2002; Standhardt *et al.* 2004), and one study which described the treatment of posterior circulation aneurysms with stents (Levy *et al.* 2002).

Death

Death following endovascular treatment was reported in three studies which described the treatment of anterior circulation aneurysms with coiling (Huddle & Chaloupka 1998; Sinson *et al.* 2001; Koebbe *et al.* 2002) and six studies which described the treatment of posterior circulation aneurysms with coiling, stent assisted coiling, balloon occlusion therapy and stents (Kwan *et al.* 1991; Ricolfi *et al.* 1998; Levy *et al.* 2002; Mangiafico *et al.* 2002; Fujimura *et al.* 2003; Kaku *et al.* 2003).

Other complications

A range of other complications following endovascular treatment were reported in four studies which described the treatment of anterior circulation aneurysms with coiling and balloon assisted coiling (Huddle & Chaloupka 1998; Koebbe *et al.* 2002; Mangiafico *et al.* 2002; Uchiyama *et al.* 2004), and four studies which described the treatment of posterior circulation aneurysms with coiling, stent assisted coiling and stents (Cloft *et al.* 1997; Nomura *et al.* 2000; Levy *et al.* 2002; Kaku *et al.* 2003).

Unruptured aneurysms

Safety

Adverse events

Stenosis

Stenosis following endovascular treatment was reported in one study which described the treatment of an anterior circulation aneurysm with coiling (Fiorella *et al.* 2004a).

Aneurysm perforation

Aneurysm perforation following endovascular treatment was reported in one study which described the treatment of anterior circulation aneurysms with balloon assisted coiling (Phatouros *et al.* 1999a), and another study which described the treatment of posterior circulation aneurysms with coiling (Short *et al.* 2002).

Aneurysm recurrence

Aneurysm recurrence following endovascular treatment was reported in five studies which described the treatment of anterior circulation aneurysms (Umezumi *et al.* 1993; Hodgson, Carroll & Jellinek 1998; Numagami *et al.* 1999; Horowitz *et al.* 2002a; Magoufis, Vrachliotis & Stringaris 2004), and six studies which described the treatment of posterior circulation aneurysms (Hirasawa *et al.* 1992; Ladouceur 1993; Berlis *et al.* 2003; Boet *et al.* 2003; Iihara *et al.* 2003b; Bhatti *et al.* 2004). The endovascular treatments used in these studies were coiling, stent assisted coiling, balloon occlusion therapy, and liquid embolics.

De novo aneurysms

De novo aneurysms following endovascular treatment were reported in two studies which described the treatment of anterior circulation aneurysms with coiling and balloon occlusion therapy (Timperman *et al.* 1995; Briganti *et al.* 2002).

Aneurysm rupture or rerupture

Aneurysm rupture or rerupture following endovascular treatment was reported in four studies which described the treatment of anterior circulation aneurysms (Timperman *et al.* 1995; Hodgson, Carroll & Jellinek 1998; Briganti *et al.* 2002; Horowitz *et al.* 2002a) and three studies which described the treatment of posterior circulation aneurysms (Hodes *et al.* 1990; Boet *et al.* 2003; Massimi *et al.* 2003). The endovascular treatments used in these studies were coiling and balloon occlusion therapy.

Device-related complications

Device-related complications following endovascular treatment were reported in four studies which described the treatment of anterior circulation aneurysms with stents, coiling, and balloon occlusion therapy (Umezumi 1993; Castillo *et al.* 2000; Broadbent *et al.* 2003; Schumacher & Berlis 2003) and three studies which described the treatment of posterior circulation aneurysms with coiling and balloon occlusion therapy (Hodes *et al.* 1990; Kwon *et al.* 2002b; Bhatti *et al.* 2004).

Intracranial abscess or infection

Intracranial abscess or infection following endovascular treatment was reported in one study which described the treatment of anterior circulation aneurysms (Meyers *et al.* 2004) and one study which described the treatment of posterior circulation aneurysms (Al-Okaili & Patel 2002). Both studies used coiling.

Vision-related complications

Vision-related complications following endovascular treatment were reported in four studies which described the treatment of anterior circulation aneurysms using coiling, balloon assisted coiling and stent assisted coiling (Litofsky *et al.* 1994; Castillo *et al.* 2000; Doan *et al.* 2004; Castillo *et al.* 2005).

Thromboembolic complications

Thromboembolic complications following endovascular treatment were reported in four studies which described the treatment of anterior circulation aneurysms with coiling (Litofsky *et al.* 1994; Castillo *et al.* 2000; Pierot *et al.* 2002; Studley, Robinson & Howe 2002) and two studies which described the treatment of posterior circulation aneurysms with coiling and balloon occlusion therapy (Forsting *et al.* 1991; Renowden & Molyneux 1995).

Death

Death following endovascular treatment was reported in two studies which described the treatment of anterior circulation aneurysms with coiling (Roitberg *et al.* 2000; Horowitz *et al.* 2002a) and seven studies which described the treatment of posterior circulation aneurysms with coiling, stent assisted coiling, and balloon occlusion therapy (Hodes *et al.* 1990; Forsting *et al.* 1991; Hirasawa *et al.* 1992; Ling *et al.* 1999; Berlis *et al.* 2003; Boet *et al.* 2003; Massimi *et al.* 2003).

Other complications

A range of other complications following endovascular treatment were reported in three studies which described the treatment of anterior circulation aneurysms with coiling, balloon occlusion therapy, and stent assisted coiling (Roitberg *et al.* 2000; Blanc *et al.* 2001; Doan *et al.* 2004) and two studies which described the treatment of posterior circulation aneurysms with coiling and balloon occlusion therapy (Ling *et al.* 1999; Russell, Nelson & Jafar 2002).

Appendix D Grading and outcome scales

Table D1: Hunt and Hess Classification of Subarachnoid Haemorrhage

Grade	Functional Outcome
I	Asymptomatic of minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbance
V	Deep coma, decerebrate rigidity, moribund appearance

Table D2: Glasgow Outcome Scale

Score	Rating	Definition
5	Good recovery	Resumption of normal life despite minor deficits
4	Moderate disability	Disabled but independent. Can work in sheltered setting
3	Severe disability	Conscious but disabled. Dependent for daily support
2	Persistent vegetative	Minimal responsiveness
1	Death	Non-survival

From www.trauma.org

Table D3: Modified Rankin Scale

Scale	Functional Outcome	Questionnaire Response
0	No symptoms	I have no symptoms and I cope well with life
1	Minor symptoms	I have a few symptoms but these do not interfere with my everyday life
2	Some restriction in lifestyle	I have symptoms which have changed my life but I am still able to look after myself
3	Significant restriction in lifestyle	I have symptoms which have significantly changed my life and prevent me from coping fully, and I need some help looking after myself
4	Partly dependent	I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night
5	Fully dependent	I have major symptoms which severely handicap me and I need constant attention day and night
6	Dead	

Molyneux *et al.* (2002)

Abbreviations

ACA	anterior intracranial artery
AChA	anterior choroidal artery
ACoA	anterior communicating artery
ACROSS	Australian Cooperative Research on Subarachnoid Hemorrhage Study
AICA	anterior inferior cerebellar artery
AIWH	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ASITN	American Society of Interventional and Therapeutic Neuroradiology
AVM	arterio-venous malformations
BA	basilar artery
BasTip	basilar tip
BasTrunk	basilar trunk
CA	carotid artery
CI	confidence interval
CT	computed tomography
cTi	cardiac troponin
GCS	Glasgow Coma Score
GDC	Guglielmi Detachable Coil
GOS	Glasgow Outcome Scale
HADS	Hospital Anxiety and Depression Scale
HIC	Health Insurance Commission
HIV	human immunodeficiency virus
HH	Hunt and Hess Scale
ICA	internal carotid artery
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms
LMWH	low molecular weight heparin
LT	left
LVEF	left ventricular ejection fraction
MBS	Medical Benefits Schedule
MCA	middle intracranial artery
MONICA	Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases
MR	magnetic resonance
MRS	Modified Rankin Scale
MSAC	Medical Services Advisory Committee
<i>n</i> -BCA	<i>n</i> -butylcyanoacrylate
NEMESIS	North East Melbourne Stroke Incidence Study
NHMRC	National Health and Medical Research Council
n/N	number of observations in a subset/total number of observations
NR	not reported
OphA	ophthalmic artery
OR	Odds Ratio
ParaOphA	paraophthalmic artery
PCA	posterior intracranial artery
PCoA	posterior communicating artery
PeriA	pericallosal artery
PICA	posterior inferior cerebellar artery
PTFE	polytetrafluoroethylene

QALY	quality adjusted life year
RCT	randomised controlled trial
RR	relative risk
RT	right
RWMA	regional wall motion abnormalities
SAH	subarachnoid haemorrhage
SCA	superior cerebellar artery
SF-36	Medical Outcome Study Short Form 36
SupCer	superior cerebellar artery
VA	vertebral artery
VADA	vertebral artery dissecting aneurysms
VBJ	vertebrobasilar junction
WFNS	World Federation of Neurological Societies
WHO	World Health Organisation

Units of measurement

[]	standard deviation
()	range
{ }	unit of variance not stated
mm	millimetres

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