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Coil Embolization for Intracranial Aneurysms

An Evidence-Based Analysis

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Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2N6
Email: MASinfo@moh.gov.on.ca
Telephone: 416-314-1092

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Abbreviations

CI	Confidence interval
CT	Computed tomography
GOS	Glasgow Outcome Score
H & H	Hunt and Hess
MRI	Magnetic Resonance Imaging
MRA	Magnetic resonance angiography
SAH	Subarachnoid hemorrhage
WFNS	World Federation of Neurological Surgeons

Executive Summary

Objective

To determine the effectiveness and cost-effectiveness of coil embolization compared with surgical clipping to treat intracranial aneurysms.

The Technology

Endovascular coil embolization is a percutaneous approach to treat an intracranial aneurysm from within the blood vessel without the need of a craniotomy. In this procedure, a microcatheter is inserted into the femoral artery near the groin and navigated to the site of the aneurysm. Small helical platinum coils are deployed through the microcatheter to fill the aneurysm, and prevent it from further expansion and rupture. Health Canada has approved numerous types of coils and coil delivery systems to treat intracranial aneurysms. The most favoured are controlled detachable coils. Coil embolization may be used with other adjunct endovascular devices such as stents and balloons.

Background

Intracranial Aneurysms

Intracranial aneurysms are the dilation or ballooning of part of a blood vessel in the brain. Intracranial aneurysms range in size from small (<12 mm in diameter) to large (12–25 mm), and to giant (>25 mm). There are 3 main types of aneurysms. Fusiform aneurysms involve the entire circumference of the artery; saccular aneurysms have outpouchings; and dissecting aneurysms have tears in the arterial wall. Berry aneurysms are saccular aneurysms with well-defined necks.

Intracranial aneurysms may occur in any blood vessel of the brain; however, they are most commonly found at the branch points of large arteries that form the circle of Willis at the base of the brain. In 85% to 95% of patients, they are found in the anterior circulation. Aneurysms in the posterior circulation are less frequent, and are more difficult to treat surgically due to inaccessibility.

Most intracranial aneurysms are small and asymptomatic. Large aneurysms may have a mass effect, causing compression on the brain and cranial nerves and neurological deficits. When an intracranial aneurysm ruptures and bleeds, resulting in a subarachnoid hemorrhage (SAH), the mortality rate can be 40% to 50%, with severe morbidity of 10% to 20%. The reported overall risk of rupture is 1.9% per year and is higher for women, cigarette smokers, and cocaine users, and in aneurysms that are symptomatic, greater than 10 mm in diameter, or located in the posterior circulation. If left untreated, there is a considerable risk of repeat hemorrhage in a ruptured aneurysm that results in increased mortality.

In Ontario, intracranial aneurysms occur in about 1% to 4% of the population, and the annual incidence of SAH is about 10 cases per 100,000 people. In 2004-2005, about 660 intracranial aneurysm repairs were performed in Ontario.

Treatment of Intracranial Aneurysms

Treatment of an unruptured aneurysm attempts to prevent the aneurysm from rupturing. The treatment of a ruptured intracranial aneurysm aims to prevent further hemorrhage. There are 3 approaches to treating an intracranial aneurysm.

Small, asymptomatic aneurysms less than 10 mm in diameter may be monitored without any intervention other than treatment for underlying risk factors such as hypertension.

Open surgical clipping, involves craniotomy, brain retraction, and placement of a silver clip across the neck of the aneurysm while a patient is under general anesthesia. This procedure is associated with surgical risks and neurological deficits.

Endovascular coil embolization, introduced in the 1990s, is the health technology under review.

Literature Review

Methods

The Medical Advisory Secretariat searched the International Health Technology Assessment (INAHTA) Database and the Cochrane Database of Systematic Reviews to identify relevant systematic reviews. OVID Medline, Medline In-Process and Other Non-Indexed Citations, and Embase were searched for English-language journal articles that reported primary data on the effectiveness or cost-effectiveness of treatments for intracranial aneurysms, obtained in a clinical setting or analyses of primary data maintained in registers or institutional databases. Internet searches of Medscape and manufacturers' databases were conducted to identify product information and recent reports on trials that were unpublished but that were presented at international conferences. Four systematic reviews, 3 reports on 2 randomized controlled trials comparing coil embolization with surgical clipping of ruptured aneurysms, 30 observational studies, and 3 economic analysis reports were included in this review.

Results

Safety and Effectiveness

Coil embolization appears to be a safe procedure. Complications associated with coil embolization ranged from 8.6% to 18.6% with a median of about 10.6%. Observational studies showed that coil embolization is associated with lower complication rates than surgical clipping (permanent complication 3-7% versus 10.9%; overall 23% versus 46% respectively, p=0.009). Common complications of coil embolization are thrombo-embolic events (2.5%–14.5%), perforation of aneurysm (2.3%–4.7%), parent artery obstruction (2%–3%), collapsed coils (8%), coil malposition (14.6%), and coil migration (0.5%–3%).

Randomized controlled trials showed that for ruptured intracranial aneurysms with SAH, suitable for both coil embolization and surgical clipping (mostly saccular aneurysms <10 mm in diameter located in the anterior circulation) in people with good clinical condition:Coil embolization resulted in a statistically significant 23.9% relative risk reduction and 7% absolute risk reduction in the composite rate of death and dependency compared to surgical clipping (modified Rankin score 3–6) at 1-year.

The advantage of coil embolization over surgical clipping varies widely with aneurysm location, but endovascular treatment seems beneficial for all sites.

There were less deaths in the first 7 years following coil embolization compared to surgical clipping (10.8% vs 13.7%). This survival benefit seemed to be consistent over time, and was statistically significant (log-rank p= 0.03).

Coil embolization is associated with less frequent MRI-detected superficial brain deficits and ischemic lesions at 1-year.

The 1- year rebleeding rate was 2.4% after coil embolization and 1% for surgical clipping. Confirmed rebleeding from the repaired aneurysm after the first year and up to year eight was low and not significantly different between coil embolization and surgical clipping (7 patients for coil embolization vs 2 patients for surgical clipping, log-rank p=0.22).

Observational studies showed that patients with SAH and good clinical grade had better 6-month outcomes and lower risk of symptomatic cerebral vasospasm after coil embolization compared to surgical clipping.

For <u>unruptured intracranial aneurysms</u>, there were no randomized controlled trials that compared coil embolization to surgical clipping. Large observational studies showed that:

The risk of rupture in unruptured aneurysms less than 10 mm in diameter is about 0.05% per year for patients with no pervious history of SAH from another aneurysm. The risk of rupture increases with history of SAH and as the diameter of the aneurysm reaches 10 mm or more.

Coil embolization reduced the composite rate of in hospital deaths and discharge to long-term or short-term care facilities compared to surgical clipping (Odds Ratio 2.2, 95% CI 1.6–3.1, p<0.001). The improvement in discharge disposition was highest in people older than 65 years.

In-hospital mortality rate following treatment of intracranial aneurysm ranged from 0.5% to 1.7% for coil embolization and from 2.1% to 3.5% for surgical clipping. The overall 1-year mortality rate was 3.1% for coil embolization and 2.3% for surgical clipping. One-year morbidity rate was 6.4% for coil embolization and 9.8% for surgical clipping. It is not clear whether these differences were statistically significant.

Coil embolization is associated with shorter hospital stay compared to surgical clipping.

For both ruptured and unruptured aneurysms, the outcome of coil embolization does not appear to be dependent on age, whereas surgical clipping has been shown to yield worse outcome for patients older than 64 years.

Angiographic Efficiency and Recurrences

The main drawback of coil embolization is its low angiographic efficiency. The percentage of complete aneurysm occlusion after coil embolization (27%–79%, median 55%) remains lower than that achieved with surgical clipping (82%–100%). However, about 90% of coiled aneurysms achieve near total occlusion or better. Incompletely coiled aneurysms have been shown to have higher aneurysm recurrence rates ranging from 7% to 39% for coil embolization compared to 2.9% for surgical clipping. Recurrence is defined as refilling of the neck, sac, or dome of a successfully treated aneurysm as shown on an angiogram. The long-term clinical significance of incomplete occlusion following coil embolization is unknown, but in one case series, 20% of patients had major recurrences, and 50% of these required further treatment.

Long-Term Outcomes

A large international randomized trial reported that the survival benefit from coil embolization was sustained for at least 7 years. The rebleeding rate between year 2 and year 8 following coil embolization was low and not significantly different from that of surgical clipping. However, high quality long-term angiographic evidence is lacking. Accordingly, there is uncertainty about long-term occlusion status, coil durability, and recurrence rates. While surgical clipping is associated with higher immediate procedural risks, its long-term effectiveness has been established.

Indications and Contraindications

Coil embolization offers treatment for people at increased risk for craniotomy, such as those over 65 years of age, with poor clinical status, or with comorbid conditions. The technology also makes it possible to treat surgical high-risk aneurysms.

Not all aneurysms are suitable for coil embolization. Suitability depends on the size, anatomy, and location of the aneurysm. Aneurysms more than 10 mm in diameter or with an aneurysm neck greater than or equal to 4 mm are less likely to achieve total occlusion. They are also more prone to aneurysm recurrences and to complications such as coil compaction or parent vessel occlusion. Aneurysms with a dome to neck ratio of less than 1 have been shown to have lower obliteration rates and poorer outcome following coil embolization. Furthermore, aneurysms in the middle cerebral artery bifurcation are less suitable for coil embolization. For some aneurysms, treatment may require the use of both coil embolization and surgical clipping or adjunctive technologies, such as stents and balloons, to obtain optimal results.

Diffusion

Information from 3 countries indicates that coil embolization is a rapidly diffusing technology. For example, it accounted for about 40% of aneurysm treatments in the United Kingdom.

In Ontario, coil embolization is an insured health service, with the same fee code and fee schedule as open surgical repair requiring craniotomy. Other costs associated with coil embolization are covered under hospitals' global budgets. Utilization data showed that in 2004-2005, coil embolization accounted for about 38% (251 cases) of all intracranial aneurysm repairs in the province. With the 2005 publication of the positive long-term survival data from the International Subarachnoid Aneursym Trial, the pressure for diffusion will likely increase.

Economic Analysis

Recent economic studies show that treatment of unruptured intracranial aneurysms smaller than 10 mm in diameter in people with no previous history of SAH, either by coil embolization or surgical clipping, would not be effective or cost-effective. However, in patients with aneurysms that are greater than or equal to 10 mm or symptomatic, or in patients with a history of SAH, treatment appears to be cost-effective.

In Ontario, the average device cost of coil embolization per case was estimated to be about $7,500 higher than surgical clipping. Assuming that the total number of intracranial aneurysm repairs in Ontario increases to 750 in the fiscal year of 2007, and assuming that up to 60% (450 cases) of these will be repaired by coil embolization, the difference in device costs for the 450 cases (including a 15% recurrence rate) would be approximately $3.8 million. This figure does not include capital costs (e.g. $3 million for an angiosuite), additional human resources required, or costs of follow-up. The increase in expenditures associated with coil embolization may be offset partially, by shorter operating room times and hospitalization stays for endovascular repair of unruptured aneurysms; however, the impact of these cost savings is probably not likely to be greater than 25% of the total outlay since the majority of cases involve ruptured aneurysms. Furthermore, the recent growth in aneurysm repair has predominantly been in the area of coil embolization presumably for patients for whom surgical clipping would not be advised; therefore, no offset of surgical clipping costs could be applied in such cases. For ruptured aneurysms, downstream cost savings from endovascular repair are likely to be minimal even though the savings for individual cases may be substantial due to lower perioperative complications for endovascular aneurysm repair.

Guidelines

The two Guidance documents issued by the National Institute of Clinical Excellence (UK) in 2005 support the use of coil embolization for both unruptured and ruptured (SAH) intracranial aneurysms, provided that procedures are in place for informed consent, audit, and clinical governance, and that the procedure is performed in specialist units with expertise in the endovascular treatment of intracranial aneurysms.

Conclusion

For people in good clinical condition following subarachnoid hemorrhage from an acute ruptured intracranial aneurysm suitable for either surgical clipping or endovascular repair, coil embolization results in improved independent survival in the first year and improved survival for up to seven years compared to surgical clipping. The rebleeding rate is low and not significantly different between the two procedures after the first year. However, there is uncertainty regarding the long-term occlusion status, durability of the stent graft, and long-term complications.

For people with unruptured aneurysms, level 4 evidence suggests that coil embolization may be associated with comparable or less mortality and morbidity, shorter hospital stay, and less need for discharge to short-term rehabilitation facilities. The greatest benefit was observed in people over 65 years of age. In these patients, the decision regarding treatment needs to be based on the assessment of the risk of rupture against the risk of the procedure, as well as the morphology of the aneurysm.

In people who require treatment for intracranial aneurysm, but for whom surgical clipping is too risky or not feasible, coil embolization provides survival benefits over surgical clipping, even though the outcomes may not be as favourable as in people in good clinical condition and with small aneurysms. The procedure may be considered under the following circumstances provided that the aneurysm is suitable for coil embolization:

- Patients in poor/unstable clinical or neurological state
- Patients at high risk for surgical repair (e.g. people>age 65 or with comorbidity), or
- Aneurysm(s) with poor accessibility or visibility for surgical treatment due to their location (e.g. ophthalmic or basilar tip aneurysms)

Compared to small aneurysms with a narrow neck in the anterior circulation, large aneurysms (> 10 mm in diameter), aneurysms with a wide neck (>4mm in diameter), and aneurysms in the posterior circulation have lower occlusion rates and higher rate of hemorrhage when treated with coil embolization.

The extent of aneurysm obliteration after coil embolization remains lower than that achieved with surgical clipping. Aneurysm recurrences after successful coiling may require repeat treatment with endovascular or surgical procedures. Experts caution that long-term angiographic outcomes of coil embolization are unknown at this time. Informed consent for and long-term follow-up after coil embolization are recommended.

The decision to treat an intracranial aneurysm with surgical clipping or coil embolization needs to be made jointly by the neurosurgeon and neuro-intervention specialist, based on the clinical status of the patient, the size and morphology of the aneurysm, and the preference of the patient.

The performance of endovascular coil embolization should take place in centres with expertise in both neurosurgery and endovascular neuro-interventions, with adequate treatment volumes to maintain good outcomes. Distribution of the technology should also take into account that patients with SAH should be treated as soon as possible with minimal disruption.

Objective

To determine the effectiveness and cost-effectiveness of coil embolization compared with surgical clipping to treat intracranial aneurysms.

Background

Clinical Need

Intracranial Aneurysms

An intracranial aneurysm, also known as a cerebral aneurysm, is an abnormal localized dilatation that bulges or balloons out of an artery that supplies blood to the brain.(1) It usually results from a weakness in the vessel wall.

Based on a systematic review of prospective autopsy studies and angiographic studies, Rinkel et al. (2) estimated the prevalence of intracranial aneurysm at 4.3% (95% confidence interval (CI), 4.0–4.7). For adults without risk factors for subarachnoid bleeding, the prevalence is about 2%. The risk of developing an intracranial aneurysm increases with a family history of aneurysm, certain inherited disorders (e.g., autosomal dominant polycystic kidney disease), atherosclerosis, age greater than 50 years, female gender, current cigarette smoking, and use of cocaine. [2]

When an aneurysm ruptures, it often bleeds into the subarachnoid space. This is called a subarachnoid hemorrhage (SAH), often resulting in death or disability. Rupture of an intracranial aneurysm may also result in intraparenchymal, intraventricular, or subdural hemorrhaging. (3)

Ruptured Versus Unruptured Intracranial Aneurysms

Unruptured intracranial aneurysms may be symptomatic or asymptomatic. Mortality and morbidity from an unruptured intracranial aneurysm depend on its the risks of rupture. The goal is to identify and treat these high-risk aneurysms to prevent rupture and hemorrhage.

The reported overall risk of rupture is 1.9% per year. Although females and older patients are at higher risk of aneurysm rupture, it depends more on the size, characteristics and location of the aneurysm than on the features of the patients. This risk is higher in symptomatic aneurysms, posterior circulation aneurysms, and aneurysms greater than 10 mm in diameter. (2)

For ruptured intracranial aneurysms, the risk of a second hemorrhage within the first 3 weeks is about 40% if left untreated. Rebleeding has been shown to result in death or dependence in 80% of patients. (4) For this reason, patients that have a ruptured intracranial aneurysm should be treated as soon as possible to prevent rebleeding.

Types of Intracranial Aneurysms

Intracranial aneurysms may be small (less than or equal to 10 mm in diameter) or large (11–25 mm in diameter). Aneurysms with diameters greater than 25 mm are classified as giant aneurysms and account for about 5% of all aneurysms. (5) Rinkel et al. (2) found that about 7% of the aneurysms were greater than 10 mm in diameter.

An intracranial aneurysm may also be classified according to its shape. (See Appendix 1)

Dolichoectatic, fusiform or arteriosclerotic aneurysms are elongated outpouching of proximal arteries that involves the entire circumference of the vessel. They account for 7% of all intracranial aneurysms.

Saccular aneurysms are aneurysms with a saccular outpouching. Saccular or congenital aneurysms constitute about 90% of all cerebral aneurysms. A saccular aneurysm with a well-defined neck is called a berry aneurysm. Dissecting aneurysms are the result of cystic medial necrosis or a traumatic tear of an artery.

Location of Intracranial Aneurysms

Although aneurysms may occur in any cerebral blood vessel, they are most commonly found at the branch points and branches of the large arteries that form the circle of Willis at the base of the brain or coming out of the brain (Appendix 1). About 20% of patients have multiple aneurysms, many at mirror sites bilaterally.(5)

Saccular aneurysms (including berry aneurysms) are located in the anterior circulation in 85% to 95% of cases, whereas dolichoectatic aneurysms affect mostly vertebrobasilar systems. Infectious aneurysms typically are situated in distal branches of the middle cerebral artery. (6)

Posterior circulation aneurysms are aneurysms that occur in the vertebral artery, the posterior inferior cerebellar artery, the anterior-inferior cerebellar artery, the basilar trunk, the superior cerebellar artery, the posterior cerebral artery, and the basilar apex. Treatment of these aneurysms is challenging, and presents considerable risk of morbidity and mortality. (7)

The 3 most common locations for giant aneurysms are at the terminal internal carotid artery, the middle cerebral artery bifurcation, and the top of the basilar artery.

Clinical Grading of Patients with Intracranial Aneurysms

The most important predictor of the outcome of subarachnoid hemorrhage is the patient's clinical condition on arrival at the hospital. (8) One of the most widely used systems for assessing the patient's clinical condition after an SAH is the World Federation of Neurological Surgeons (WFNS) Scale (Table 1). It is based on the Glasgow Coma scale and is used to measure the level of consciousness following SAH. (9)

Table 1: World Federation of Neurological Surgeons Scale (9)

Grade	Glasgow Coma Scale	Motor Deficit
1	15	Absent
2	15	Absent
3	13-14	Present
4	7-12	Present or absent
5	3-6	Present or absent

The Hunt and Hess Classification (9) is also frequently used to grade the clinical status of a patient with an intracranial aneurysm.

Table 2: Hunt and Hess Classification

Grade	Clinical Condition at Presentation
0	Unruptured aneurysm
1	Asymptomatic or minimal headache, slight nuchal rigidity
2	Moderately severe or severe headache, nuchal rigidity; no neurological deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis, possible early decerebrate rigidity and vegetative disturbances
5	Deep coma, decerebrate rigidity, moribund appearance

Signs and Symptoms

Most intracranial aneurysms, particularly those that are very small, do not grow, bleed, or cause any complications. Many of the signs and symptoms of intracranial aneurysms are associated with SAH following rupture of the aneurysm. These include excruciating headache, nausea, vomiting, alteration in consciousness, facial pain, seizures, weakness on one side of the body, numbness, tingling, speech disturbance, and double vision that does not go away. (3)

Subarachnoid Hemorrhage

SAH is bleeding into the fluid-filled spaces that surround the brain. Excluding head trauma, rupture of a saccular intracranial aneurysm is the most common cause of SAH. (5) It often occurs without warning.

Risk for SAH increases linearly with age. The prognosis for SAH has remained largely unaffected despite improvements in medical and neurological treatment. Overall, about 40% to 50% of SAHs result in death. Thirty percent of patients die within 24 hours of a hemorrhage, and, if not treated, a further 25% to 30% will succumb within 4 weeks from rebleeding, vasospasm, or hydrocephalus. About 10% to 20% will survive with severe disability. Only about 40% of patients with SAH recover to reach independent status.(10) If patients survive but the aneurysm is not obliterated, then the annual rebleed rate is about 3%.(5)

Complications of Subarachnoid Hemorrhage

SAH is often accompanied by a sudden loss of consciousness in about half of the patients, lasting up to several days in about 10% of patients. A brief moment of excruciating headache may precede loss of consciousness. Furthermore, vomiting is common, and focal neurological deficits may occur. Delayed ischemic neurological deficits may result from 4 main complications following SAH. (5) These complications are described below.

Rerupture and rebleeding: The risk of rerupture in untreated ruptured aneurysms is about 30%. Rerupture of aneurysms after SAH is associated with 60% mortality and poor outcome. Early treatment of aneurysms can lower rebleeding rates.

Acute hydrocephalus (accumulation of water in the brain) can cause stupor and coma. More often, subacute hydrocephalus develops over a few days or weeks, and causes progressive drowsiness or abulia (lack of will or inability to make decisions) with incontinence. Hydrocephalus may clear spontaneously, or it may require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months after SAH and manifest as gait difficulty, incontinence, or abulia.

Vasospasm: Narrowing of the artery at the base of the brain following SAH causes symptomatic ischemia and infarction in about 30% of patients with SAH. Delayed ischemic neurological deficits from cerebral vasospasm have become the major cause of morbidity and mortality in patients with SAH. (11)

Hyponatremia: This is a cerebral salt-wasting syndrome that may develop rapidly in the first 2 weeks following SAH and may be profound. It usually results from an inappropriate secretion of factors that cause excessive excretion of sodium.

Epidemiology

The population-based incidence rates of SAH vary considerably from 6 to 20 cases per 100,000 people per year. The highest rates are in Japan and Finland. (12) Rupture of an intracranial aneurysm causing SAH occurs in 6 to 8 cases per 100,000 people in most western populations. (13) An annual incidence of 10 cases per 100,000 people has been reported for Canada (expert consultant).

Diagnosis

The following technologies diagnose and monitor intracranial aneurysms.

Intra-arterial catheter angiography: This technology continues to be the gold standard in the diagnostic evaluation of intracranial aneurysms. It involves placing a catheter and injecting a contrast agent (dye) into an artery. Transcatheter studies provide the most information about small perforating vessels and produce higher-resolution images than other imaging modalities. Unfortunately, this imaging technology is invasive. It has been associated with a rate of catheter-related complications of about 5%, and a permanent neurological morbidity rate of almost 0.5%. (6)

Computed tomography (CT): A CT scan of the head will confirm the presence of blood within the brain or subarachnoid space if an aneurysm has ruptured. The Fisher system (9) commonly used to grade CT findings is shown in Table 3.

Table 3: Fisher Grade for Computed Tomography Findings

Grade	Computed Tomography Findings
1	No blood detected
2	Diffuse thin layer of subarachnoid blood
3	Localized thrombus or thick layer of subarachnoid blood
4	Intracerebral or intraventricular hemorrhage with diffuse or no subarachnoid blood

Computed tomographic angiography (CTA): This technology uses x-rays and computerized analysis of the images to visualize blood flow in arterial vessels throughout the body, including the brain. Following injection of a contrast material into a peripheral vein, beams of x-ray radiation are passed through the brain from several different angles to create cross-sectional images. A computer then assembled the images into a three-dimensional picture of the brain. CTA may show aneurysms as small as 2 to 3 mm with sensitivities of 77% to 97%, and specificity of 87% to 100%. CTA has been used as a screening tool in populations at high risk for intracranial aneurysms. (6)

Magnetic resonance angiography (MRA): This is a magnetic resonance imaging (MRI) study of blood vessels. The images produced undergo computer reformation to display several vessels in multiple projections, providing additional views that cannot be obtained with intra-arterial catheter angiography. MRA is useful as a screening modality or to detect subtle changes in aneurysm size. It has sensitivity rates of 69% to 93% and is particularly useful for aneurysms greater than 3 to 5 mm.(6)

Transcranial Doppler ultrasound: this technology may be used to diagnose vasospasm and to monitor cerebral blood flow at the patient's bedside.

Lumbar puncture: This technology may help to establish a diagnosis of SAH by showing the presence of blood in the cerebrospinal fluid if the results of the CT scan are equivocal.

Treatment of Intracranial Aneurysms

Ruptured intracranial aneurysms that may be accompanied by SAH must be repaired as soon as possible to prevent rebleeding and vasospasm. The treatment of an unruptured aneurysm depends on its size and risk of rupture. There are several ways to treat intracranial aneurysms. These are outlined below.

Observation

Small, unruptured aneurysms are sometimes managed conservatively through periodic fluoroscopic and angiographic surveillance,(14) in conjunction with treatment for underlying risk factors such as hypertension.

Surgical Clipping

Complete surgical clipping of the aneurysm's neck with preservation of the parent vessels and arterial branches has been the gold standard in the treatment of intracranial aneurysms, because it allows intensive medical care and management of SAH complications. (15) Surgical clipping involves placing a silver clip across the neck of the aneurysm (Appendix 2). This procedure requires craniotomy and brain retraction, which can be associated with neurologic deficits.(5)

Certain complex aneurysms, such as fusiform aneurysms, may require trapping (clipping of the artery at each end of the aneurysm) and a surgical bypass to obliterate the aneurysm and maintain adequate cerebral blood flow. (16)

Endovascular Treatment

Endovascular treatments of intracranial aneurysms are based on the use of a percutaneous catheter system to repair the aneurysm from inside the vessel without a craniotomy. These treatments have evolved over the last 30 years. Using a detachable balloon was the first reliable technique, but this procedure was limited by a high rate of secondary deflation and by the need to force the aneurysm to conform to the shape of the balloon. (17)

Fiber coils overcame the problems of detachable balloons; however, they cannot be removed or replaced if the size or shape of the coils is inadequate. (17) The main endovascular technology now used to treat intracranial aneurysms is embolization with controlled detachable flexible platinum coils. This technology, coil embolization, is the focus of this health technology assessment.

Tools to Evaluate Outcome of Treatment

The tools that are most often used to evaluate the outcomes of intervention of intracranial aneurysms are the Rankin Score and the Glasgow Outcome Score.

The Rankin Score (Table 4) is a 6-point scale to define the degree of a patient's functional disability and assess neurologic disability

Table 4: Rankin Score (9)

Score	Clinical Status
Rankin - 0	No symptoms at all
Rankin - 1	No significant disability despite symptoms; able to carry out all usual duties and activities
Rankin - 2	Slight disability unable to carry out all normal activities but able to look after own affairs without assistance
Rankin - 3	Moderate disability requiring some help but able to walk without assistance
Rankin - 4	Moderately severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance
Rankin - 5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

The Glasgow Outcome Score (9) is a 5-point scale originally designed to assess long-term outcome after head trauma. It is currently used to assess the outcome of many neurologic insults including SAH, and it is the only measure that has been shown to "respond" to therapeutic interventions in patients with SAH. (9) The full scale is in Appendix 3. The revised scale is shown in Table 5.

Table 5: Revised Glasgow Outcome Score

Grade		Clinical Condition at Presentation
GOS - 1	Good recovery	Capacity to resume normal occupational and social activities, although there may be minor physical or mental deficits or symptoms
GOS - 2	Moderate disability	Independent and can resume almost all activities of daily living Disabled to the extent that they cannot participate in a variety of social and work activities.
GOS - 3	Severe Disability	No longer capable of engaging in most previous persona, social or work activities Limited communication skills and have abnormal behavioral or emotional responses Typically are partially or totally dependent on assistance from others in daily living
GOS - 4	Persistent Disability	Not aware of surroundings or purposely responsive to stimuli
GOS - 5	Dead	Dead

New Technology Being Reviewed

Endovascular coil embolization (coil embolization) was introduced in 1991 as an alternative to surgical clipping. The procedure is usually performed by an interventional neuroradiologist. It involves occluding the aneurysm without a craniotomy. A microcatheter containing flexible platinum coils on a guidewire is inserted into a large blood vessel (usually the femoral artery in the groin area). The catheter is navigated to the site of the aneurysm under x-ray guidance. Multiple coils are placed inside the aneurysm through the same catheter until the aneurysm is densely packed. (18) The coils fill the aneurysm sack, promote thrombosis, and exclude the aneurysm from the arterial circulation, thus reducing the risk of rupture and rebleeding (Appendix 2).

Coil embolization is usually performed under general anesthesia, although some centres use only sedatives and analgesic agents to allow monitoring of the patients' neurological conditions during the process. (18) There is no consensus on how patients should be anticoagulated before, during, or after coil embolization. Patients with unruptured aneurysms may receive antiplatelet agents a few days before coiling to reduce the risks of thromboembolic complications. Patients with ruptured aneurysms generally do not receive antiplatelet agents before the procedure for fear of increasing the risk of hemorrhage. (18)

Many coils are designed to embolize intracranial aneurysms. They fall into 2 main categories: pushable coils and detachable coils.

Pushable coils are free coils that are pushed with a special device, a coil pusher, and are sent from the catheter tip into the aneurysm. Once delivered or even partially delivered, they cannot be withdrawn even if they are improperly positioned. (19)

Detachable coils are soft platinum helical coils that are soldered to a stainless steel delivery guidewire. The coils are detached using an energy source such as an electrical current that dissolves the connection between the coil and the guidewire. The first coil is usually a 3-dimensional coil that forms a peripheral basket inside the aneurysm into which other coils can be deposited. The diameter of the basket coil should approximate the diameter of the aneurysm dome. Angiographic images are obtained after each coil is placed to ensure proper positioning before detachment. Detachable coils can be withdrawn and repositioned before detachment if necessary. (18)

Matrix coils are detachable platinum coils that are coated with a bioabsorbable copolymer. They promote the formation of intra-aneurysmal connective tissues, thicker aneurysm neck tissue, and smaller aneurysms.

Adjunctive Technology

Endovascular balloons and stents are used with coil embolization in special cases. When treating aneurysms with a wide neck, inflating a balloon or placing a stent across the wide neck of the aneurysm can prevent the coils from falling or protruding into the parent vessel. (18)

In patients with ruptured dissecting or fusiform vertebro-posterior cerebral aneurysms, the parent artery may be purposefully occluded at the same time the aneurysm is packed with coils. The occlusion of the parent artery is performed after evaluating the presence of arterial collateral vessels to eliminate the possibility of postembolization brain infarction or ischemia. (20)

Regulatory Status of Coils in Canada

The Health Protection Branch of Health Canada has licensed numerous coils and delivery systems use in the brain. The approved coils and indications are summarized in Appendix 4. Most of the coils are approved for the embolization of high-risk intracranial aneurysms and arteriovenous malformations.

Literature Review

Objective

To determine the effectiveness and cost-effectiveness of coil embolization compared with surgical clipping to treat intracranial aneurysms.

Questions Asked

Does coil embolization provide any significant advantages over surgical clipping in improving patient survival and reducing disability and dependence?

What are the long-term safety, effectiveness, and reliability of coil embolization in the treatment of ruptured or unruptured intracranial aneurysm?

What are the complications associated with endovascular coil embolization of intracranial aneurysms?

Is coil embolization more cost-effective than surgical clipping in treating ruptured or unruptured intracranial aneurysms?

What are the indications and contraindications for endovascular coil embolization of intracranial aneurysms?

The population of interest consisted of people with ruptured or unruptured intracranial aneurysms. The Medical Advisory Secretariat compared coil embolization with open surgical clipping on the following outcomes: death, survival, disability (dependence), function, angiographic efficacy (% of total occlusion or near total occlusion), recurrence, rebleeding, long-term stability of coils, complications, other clinical outcomes, length of hospital stay, and cost-effectiveness ratios.

Methods

Inclusion Criteria

This review included English-language journal articles that reported primary data on the effectiveness or cost-effectiveness of treatments for intracranial aneurysms obtained in a clinical setting, or analyses of primary data maintained in registers or institutional databases. Studies had to meet the following criteria:

- The design and method are clearly described.
- **Belong to one of the following classifications:**
    - Systematic reviews
    - Randomized controlled trials (RCTs) regardless of sample size
    - Non-randomized studies comparing coil embolization to surgical clipping (minimum sample size of 200 and at least 50 subjects treated with coil embolization)*;

    - Cohort studies or case series of coil embolization only (a minimum sample size of more than 100 subjects),
    - Canadian studies regardless of sample size.
- Not superseded by a publication with the same purpose, by the same group or a later publication that included the data from the same study (unless the article addressed different outcomes).
- Published in the period of November 1998 to November 2003.
- Published in English

*Only RCTs and systematic reviews were included in the 2006 update, non-randomized studies were excluded from further analysis

Exclusion Criteria

Interim reports on trials that had final results reported in a more recent article
Studies relating to the treatment of arteriovenous malformation
In vitro studies and animal studies
Reports available only in a foreign language
Non systematic reviews, editorials, letters

Databases and Search Strategy

Search date: October, 2003; January 2004 update; January 2006 update

Databases searched: Cochrane Central Registry of Controlled Trials (CENTRAL) and Database of Systematic Reviews (DSR), International Agency for Health Technology Assessment (INAHTA), OVID MEDLINE; EMBASE ; and MEDLINE In-Process & Other Non-Indexed Citations (formerly PREMEDLINE)

Search terms: The detailed search strategy can be viewed in Appendices 5a (2003) and 5b (2006).

The Medical Advisory Secretariat also performed Internet searches of Medscape and manufacturers' databases to identify product information and recent reports on trials that were unpublished but that were presented at international conferences.

Results of Literature Search

Systematic Reviews

Searching health technology assessment databases yielded 2 English-language systematic reviews and 1 rapid review. One English language review is based on a case series of endovascular coiling of ruptured and unruptured intracranial aneurysms, and the other is a review of endovascular treatment of posterior circulation aneurysms. None of the English language systematic reviews compared endovascular coil embolization with surgical clipping.

Two foreign language reviews (1 Danish review and 1 French) each provided a summary in English.

The 2006 update yielded one 2005 Cochrane systematic review.

Research Reports

The initial search of MEDLINE, EMBASE, and MEDLINE In-Process yielded 418 citations. After reviewing the abstracts, 31 research reports and 3 reports on economic analysis met the selection criteria.

This review excluded 384 citations because either the sample size was too small, they were reviews or editorials, or they were studies on arterio-venous malformations.

An updated search in January 2004 yielded 1 more study, therefore 32 research reports and 3 reports on economic analysis were included in this review. Another 16 references provided background information.

An updated search conducted on January 9, 2006 yielded 169 citations, of which 4 reports met the inclusion criteria. Of the 4 reports, one was an update of an already published research report, one was a Cochrane systematic review, and 2 were guidance statements.

Quality Assessment and Data Extraction

One researcher reviewed the full-text reports and extracted data using a data extraction form. The quality of the studies was assessed using criteria based on the Jaddad scale. Levels of evidence were assigned according to a scale based on the hierarchy by Goodman (1985) (Table 6). An additional designation "g" was added for unpublished reports of studies that have been presented to international scientific meetings.

The systematic reviews and selected studies are summarized in Appendices 6 to 13.

Table 6: Quality of Evidence*

Type of Study (Design)	Level of Evidence	No. of Eligible Studies
Large RCT,	1	2
Large RCT, unpublished but reported to an international scientific meeting	1(g) †	
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3 a	
Non-RCT with historical control	3b	
Non-RCT unpublished but reported to an international scientific meeting	3(g)	
Surveillance (database or register)	4a	2
Case series, multisite	4b	7
Case series, single-site	4c	20
Case series unpublished but presented to an international scientific meeting	4(g)	1
Total		33

*does not include the 3 articles on economic analysis
† "g" designates unpublished reports of studies that have been presented to international scientific meetings

Description of Systematic Reviews

The English-language systematic reviews are summarized in Appendix 9a and 9b.

Brilstra et al (1999) (21) systematically reviewed 48 case series with 1,383 patients. The purpose of the review was to assess the short-term efficacy of endovascular embolization of ruptured or unruptured intracranial aneurysms using either controlled detachable coils or pushable coils that do not have a system for controlled detachment. They did not compare endovascular coil embolization with surgical clipping. Fourteen studies (comprising 58% of all patients) were prospective.

Overall, results showed that treatment with controlled detachable coils resulted in a lower rate of complete aneurysm occlusion (54% compared with 88% for pushable coils), but better functional outcome. Of patients treated with controlled detachable coils, 89.6% were functionally independent, compared with 76.7% of patients treated with pushable coils. Complications included perforated aneurysms and ischemic complications. Rates were 12% in the patients treated with controlled detachable coils and 19% in those treated with pushable coils. There were no statistically significant differences in the rates of permanent complications for the treatment groups (3.7% for controlled detachable coils and 7.1% for pushable coils). Patients with ruptured aneurysms had a higher rate of occlusion, but worse functional outcome compared with patients with unruptured aneurysms. The overall mortality rate was 5.3% in controlled detachable coils and 13.8% in pushable (21) coils.

Lozier (22) conducted a systematic review in 2002 of 12 reports comprising 495 patients to assess the degree and durability of aneurysm occlusion and the short-term outcome after endovascular embolization of posterior circulation aneurysms using controlled detachable coils. This review is discussed in the section on high-risk aneurysms.

Another systematic review published in Danish with an English-language summary in 2000 by the Danish Centre for Evaluation and Health Technology Assessment (12) (DACEHTA), concluded that despite the lack of long-term results, using endovascular coil embolization to treat intracranial aneurysms is an attractive alternative to surgery, and, in some cases, it is the only possible treatment.

The Agence Nationale d'Accréditation en Santé (23) in France conducted a systematic review to compare surgical clipping with coil embolization to treat ruptured intracranial aneurysms. Published in French with an English-language summary in 2000, the review was based on 368 references and included 14 comparative studies. Only 1 of these studies was an RCT. The review concluded that endovascular coil embolization is a more recent technique than microsurgical exclusion of ruptured aneurysms, one that has reached a fairly stable point in its technological development, and is feasible and safe. Rates of morbidity of endovascular coil embolization ranged from 0% to 40% (median, 9%) and rates of mortality ranged from 0% to 15% (median, 2%). The review identified several unresolved issues relating to the use of this technology, including the need for properly designed comparative studies, the lack of long-term efficacy and safety information, and the lack of a superior response from coil embolization in cases where microsurgery has failed.

A 2005 Cochrane systematic review by Van der Schaaf et al (24) evaluated patients with ruptured intracranial aneurysms with subarachnoid hemorrhage. They found that in aneurysms considered suitable for both surgical clipping and endovascular treatment, coiling is associated with a better outcome for those patients in good clinical condition with a ruptured aneurysm of either anterior or posterior circulation.

MAS Review of Studies on Ruptured Intracranial Aneurysms

Six studies (2 RCTs and 4 case series) on endovascular coil embolization of ruptured aneurysms met the inclusion criteria. These are summarized in Appendix 10.

The International Subarachnoid Aneurysm Trial (ISAT) (25) is a multicenter study that randomized 2,143 people with confirmed SAH within 28 days of a ruptured intracranial aneurysm either to coil embolization (n=1,073) or to surgical clipping (n=1,070). The study involved 26 centres in Europe, Canada, Australia, and the United States. Patients had to be eligible for both endovascular and surgical procedures and, therefore, were mostly in good clinical condition (88% were WFNS grade I or II) with predominantly ruptured small aneurysms (90% <10 mm) in the anterior circulation aneurysms (95%). The main outcome variable was combined survival and disability as assessed by a modified Rankin outcome scale (score 3–6) and a questionnaire given at 2 months and 1 year. The trial stopped recruitment after a planned interim analysis of the 1-year clinical outcome for 1,594 patients showed a 22.6% relative reduction in the combined rate of death and disability (25% with coils versus 36% for surgery, p<0.001) for coil embolization compared with surgical clipping. Post procedure rebleeding in the first year occurred in 2.4% of the patients in the coil embolization group and 1.0% of the patients in the surgical clipping group. A 2005 update of ISAT (26) reported on the outcomes of 2,118 patients with 1-year clinical follow-up (1,063 coiling; 1055 surgical), and confirmed its earlier finding that coil embolization produced better independent survival for people with SAH and good clinical conditions, in whom the aneurysm is suitable for both coil embolization and surgical clipping. These findings will be discussed in greater details under synopsis of results.

In 2000, Koivisto et al (27) reported on a RCT that randomized 109 patients fewer than 71 hours after SAH into either coil embolization (n=52) or surgical clipping (n=57). Clinical and neuropsychological outcomes were assessed at 3 and 12 months after treatment. Magnetic resonance imaging (MRI) of the brain was performed at 12 months. Follow-up angiography was scheduled after clipping and at 3 and 12 months after treatment. At 1 year, similar clinical and neurologic outcomes were reported for both the coil embolization and the surgical clipping groups. There was no late bleeding in either group. MRI showed that superficial brain deficit and ischemic lesions were more frequent in the patients that received surgical clipping.

Rabinstein et al (11) reported in 2003 on a retrospective review of a series of 415 patients who were admitted to the Mayo Clinic within 7 days of experiencing a SAH. Endovascular embolization was performed on 76 patients with poorer clinical grade on admission and more prevalent early hydrocephalus. Surgical clipping was performed on 339 patients. The patients had a median follow-up of 6 months. There were no statistically significant differences in the clinical outcome of the 2 groups, but endovascular coil embolization was associated with a lower risk of symptomatic cerebral vasospasm in patients with good WFNS grades (I–III) at presentation, but not in patients with poor WFNS grades (IV or V).

In 2001, Byrne et al. (28) reported on the outcomes of 317 patients with intracranial aneurysms treated with coil embolization in the acute and recovery phases after rupture. The initial outcomes showed that the neurological status of 89% of the patients was unchanged or improved during the first 48 hours after the procedure, but the neurological status of 11% (35/317) of the patients was worse, mainly due to procedure-related complications. The clinical outcomes at 6- to 9-month follow-up showed that patients who were treated within 6 days of experiencing a SAH had better overall outcomes than those treated after 48 hours following SAH (p= .004 by Wilcoxon rank sum).

Versari et al. (15) in 2000 reported on a multicenter series of 223 patients with ruptured intracranial aneurysms, of whom 105 were treated with coil embolization, and 118 were treated with surgical clipping. Generally, patients with posterior circulation aneurysms, poor medical conditions, poor clinical HH grades, or older age were eligible for endovascular treatment. Patient outcomes of that series were compared with those of the surgical series. Analysis of the 6-month outcomes showed that endovascular coiling increased the rate of good recovery in patients with good HH grades (I–II), decreased the rate of good recovery in patients with HH grade III scores, and increased the rates of moderate and severe disability in patients with poor HH grades (IV–V). In patients with posterior circulation, coil embolization resulted in a decrease in untreated patients, a significant decrease in mortality, and an increase in overall good outcomes.

Also in 2000, Richling et al. (19) retrospectively analyzed the clinical and angiographic outcomes of 470 patients treated for ruptured intracranial aneurysms in Austria. Surgical clipping was used in 297 of the patients and coil embolization was used in 173 of the patients. The results were analyzed for 4 anterior circulation and 4 posterior circulation locations. The mean clinical follow-up period was 43.5 months (SD, 14.3 months), and the mean angiographic follow-up period was 15.3 months (SD, 12.6 months).

The results showed that in the anterior circulation locations, coil embolization was the primary choice only in the group of paraophthalmic aneurysms, but surgical clipping was the main treatment modality for anterior communicating artery and middle cerebral artery aneurysms (81%). In the anterior circulation locations, clinical outcomes were not significantly different between surgical clipping and coil embolization. Angiographic follow-up of the embolized aneurysms showed the best results in the paraophthalmic group. It was indicated that ophthalmic and paraophthalmic aneurysms are sometimes technically challenging for the surgical approach, but they are relatively simple for the endovascular treatment, provided there is no severe atheroma or looping of cervical vessels. On the other hand, many of the middle cerebral artery aneurysms have complex vascular architecture that limits endovascular feasibility. (19)

For posterior circulation aneurysms, there was a general preference for coil embolization (66%). There was no significant difference in the clinical outcome between the 2 treatments. Angiographic follow-up in the coil embolization group showed the highest occlusion rates in basilar tip aneurysms. (19)

Overall, the study found that the elegance of the minimally invasive coil embolization procedure was disturbed by the limited angiographic occlusion in follow-up examinations. (19)

Summary Statements on Coil Embolization of Ruptured Aneurysms

- Endovascular embolization of ruptured small, anterior circulation intracranial aneurysms in patients with good clinical grade at presentation significantly reduced the combined 1-year mortality and disability rates compared with surgical clipping (7.4% absolute reduction and 23.9% relative reduction). (Level 1evidence)

- Compared with surgical clipping, endovascular embolization also resulted in improved survival during the first 7 years of follow-up. (Level 1 evidence)

- Endovascular coil embolization improved the 6-month clinical outcome and lowered the risk of symptomatic cerebral vasospasm in patients with good clinical grades at presentation (HH I–II or WFNS I–II) compared with surgical clipping (Level 4 evidence).

- Coil embolization improved the treatment of ruptured posterior aneurysms by reducing the number of untreated patients, significantly decreasing the mortality rate, and increasing the overall good outcome (Level 4 evidence).

- Ruptured aneurysms treated with coil embolization within 6 days of SAH had better overall outcomes than those treated after 6 days (Level 4 evidence).

- In terms of location of the ruptured aneurysm, coil embolization was the preferred treatment for paraophthalmic aneurysms in the anterior circulation, and for posterior circulation aneurysms, because of easier access or visualization. Surgical clipping was preferred for anterior communicating artery and middle cerebral artery aneurysms.

- The advantage of coil embolization over surgical clipping varies widely with aneurysm location, but endovascular treatment seems beneficial for aneurysms at all sites. (Level 1 evidence)

- Coil embolization provided the best angiographic results in paraophthalmic and basilar-tip aneurysms (Level 4 evidence).

MAS Review of Studies on Unruptured Aneurysms

Studies on the use of coil embolization as a treatment for unruptured intracranial aneurysms are summarized in Appendix 11.

In 1998, Wiebers set al. (29) reported on the retrospective International Study of Unruptured Intracranial Aneurysm (ISUIA), a cohort study that analyzed data from medical records of 1,449 patients with unruptured intracranial aneurysms. The patients were divided into two groups according to presence or absence of previous SAH from another intracranial aneurysm. The result of this study is discussed under Risk of Rupture of Unruptured Aneurysms and Synopsis of findings.

In 2003, Wiebers et al. (30) reported on the prospective phase of the ISUIA study of 4,060 patients with unruptured intracranial aneurysms who were enrolled at 61 centres. From 1991 to 1998, 1,917 patients were treated surgically, 451 were treated endovascularly, and 1,692 did not receive either procedure (conservative management). Ninety percent of the unruptured aneurysms were in the anterior circulation. The endovascular cohort was significantly older (mean age 53.7 vs 51.5 years, $p<0.0001$), had a greater percentage of aneurysms greater than 12 mm in diameter (41.7% vs 21.6%, $p<0.0001$), and had more aneurysms located in the vertibrobasilar system (23.8% vs 9.3%, $p<0.0001$) compared to the surgical cohort. All patients were followed-up clinically and angiographically (for the surgical and endovascular groups, at 7 days after procedure, at hospital discharge, at 30 days after treatment, and then at annual intervals). Clinical outcome was assessed using the Rankin scale.

The 5-year Kaplan-Meier mortality rate was 12.7% for the entire cohort managed conservatively. The mortality rate was 65% for the patients whose aneurysms ruptured during follow-up. For the cohort that underwent surgical clipping, the total mortality and morbidity rates at 1 year were12.6% for patients with no previous history of SAH and 10.1% for patients with a previous history of SAH. The 1-year morbidity and mortality rates of the endovascular cohort were 9.1% and 9.5%, respectively. There was no indication as to whether these results were statistically significantly different from those reported for the surgical group.

The findings of this study will be discussed in detail under Synthesis of Outcomes.

This study found that older age strongly predicts poor outcome in surgical clipping. Other variables that predicted poor surgical outcome were having an aneurysm with a diameter greater than 12 mm or located in the posterior circulation; having experienced previous ischemic cerebrovascular disease; and aneurysmal symptoms other than rupture.

The endovascular cohort had older patients with larger unruptured aneurysms and a higher proportion of aneurysms in the posterior circulation. The study also found that endovascular mortality and morbidity seem to be less dependent on age.

In 2004, Barker et al. (31) conducted a retrospective cohort study on unruptured intracranial aneurysms. They compared the end points, at discharge from the hospital, of 421 patients treated with endovascular embolization with those of 3,498 patients treated by surgical clipping from 1996 to 2000. The study was based on the Nationwide Inpatient Sample hospital discharge database, which contains information about 20% of all inpatient admissions to nonfederal hospitals in the United States.

Results showed surgically treated patients were slightly younger (median, 54 years) than those treated with coil embolization (median, 56 years; $p =0.001$). Medical comorbidity was similar between the groups. The major findings are summarized in Table 7.

Table 7: Outcomes of Surgical and Endovascular Treatment of 3,919 Unruptured Aneurysms(31)

Outcome, mean	Surgical Clipping	Endovascular	Multivariate analysis
Discharge home, %	82	91	
Discharge to short-term facilities, %	13	5	
Discharge to long-term facilities, %	3.3	2.4	
In-hospital mortality rate, %	2.1	1.7	(OR1.3, 95% CI 0.6–2.8; p=.6)
Death and discharge to long-term care facilities, %	5.4	4.1	(OR 1.4, 95% CI 0.8–2.3; p=.2)
Death and discharge to long-term care or short-term care facilities, %	18.4	9.1	(OR 2.2, 95% CI 1.6–3.1; p<.001)
Neurologic complications including infarction or hemorrhage, %	7.8	5.0	(OR 2.0, 95% CI 1.3–3.2; p=.002)
Hemiparesis or hemiplegia, %	5.3	1.9	(OR 2.8, 95% CI 1.3–5.9; p=.008)
Transfusion of red blood cells, %	3.7	0.7	(OR 5.6, 95% CI 1.2–26, p=.03)
Length of hospital stay, days	5	2	p<.001
Hospital charges, US$	21,800	13,200	p=.007

The rates of in-hospital death were not statistically significant between the 2 groups; neither were the rates of adverse outcomes that included in-hospital deaths and discharge to long-term care facilities. Endovascular embolization showed a significant advantage over surgical clipping only when discharge to a short-term rehabilitation facility was included as an adverse event. Most of the difference in discharge disposition was due to the high rate of discharge to short-term rehabilitation for patients older than 65 years in the surgical group. The difference in outcome between the 2 groups persisted in propensity score analysis, which adjusted for factors such as age, sex, race, primary payer for care, hospital geographic region, and medical comorbidity. Barker et al. (31) stated that the discharge to short-term rehabilitation could have been influenced by subjective factors, such as the preference of the physician and the patient.

Neurological complications were about twice as common after surgery compared with endovascular (31) treatment. Furthermore, hospital stay was longer and hospital costs were higher for the surgical group. The authors noted that the outcome differences increased from 1996 to 2000, suggesting that outcomes of endovascular treatments improved as physicians gained more experience in the procedure.

Johnston et al. (32) in 2001 reported on a retrospective review that compared surgical and endovascular treatment of unruptured intracranial aneurysms in California from January 1990 to December 1998. In-hospital data and data in a State database were analyzed. The review comprised 307 patients treated with coil embolization and 1,699 patients treated with surgical clipping. The primary outcome was the rate of adverse outcome, defined as death or transfer to a rehabilitation hospital.

The results showed that when compared to surgical clipping, endovascular embolization was associated with significantly less risk of adverse events (9.7% versus 25.4%), lower rates of in-hospital death (0.5% versus 3.5%), shorter hospital stays (7.1 days versus 11.8 days), and lower hospital costs ($37,000 (US) versus $64,000 (US)). The study also showed that adverse outcomes, length of stay and rates of in-hospital death decreased as the volume of endovascular embolization performed increased. This did not hold for surgical clipping.

At the 2002 Annual Meeting of the American Society of Neuroradiology, Higashida et al. (33) presented a retrospective study to examine the treatment outcomes for 2,484 cases of unruptured aneurysms in a large US twelve-state database. Of these cases, 625 were treated by endovascular means, and 1,859 by surgical clipping. At the time of discharge from the hospital, there were more adverse outcomes (coiling 7.7%, clipping 15.2% p<0.0001), more in-hospital death (coiling 1.0%, clipping 2.9%, p=0.0062), longer hospital stay (coiling 3.2 days , clipping 5.9 days, p<0.0001), and greater total charges (coiling

US$29,191 vs clipping US$35,603) in surgical clipping compared to endovascular coiling procedures. Surgical patients were approximately three times as likely to die (Death OR = 2.9, 95% CI 1.2–7.0, p=0.0274), and almost twice as likely to have adverse outcomes (OR=1.6, 95% CI 1.3–2.1, p<0.0001) compared to endovascular patients, after adjustment for age, sex, Medicaid status, region and admission source. This study has not yet been published, and details about adverse events and charges were not provided in the abstract.

Summary Statements on Coil Embolization of Unruptured Intracranial Aneurysms

- The likelihood of aneurysm rupture is low (cumulative risk 0.05% over 8 years) in people with no previous history of SAH and in whom the aneurysm is less than 10 mm in diameter. The risk of rupture for aneurysm of similar size increases 10 times (0.5%) if the person has a previous history of SAH.

- The 5-year cumulative rupture rates were higher for patients with unruptured aneurysms greater than 7 mm in diameter or patients with previous history of SAH regardless of the size of the aneurysms.

- However, these rates were often equal to or exceeded by the risks associated with surgery or endovascular repair of comparable aneurysms.

- Age over 64 years is a predictor of poor surgical outcome. Surgery-related morbidity and mortality increased significantly for people older than 64 years of age (32% vs 14.4%, p<0.001). The size and location of the unruptured aneurysms predicted both surgical and endovascular outcomes.

- The mortality and morbidity rates were related more to age in surgical clipping than in endovascular embolization.

- One observational study showed no significant difference in the in-hospital mortality rates between coiling and clipping while another showed statistically significantly lower in-hospital death in patients who received coil embolization compared to those who underwent surgical clipping.

- Patients who received coil embolization had statistically significantly lower rates of adverse outcomes, defined as in-hospital death and discharge to long-term and short-term facilities. Most of this coiling advantage was for patients older than 65 years.

- Coil embolization also significantly reduced in-hospital neurological complications, length of stay, and hospital costs compared with surgical clipping.

- The long-term risk and durability of coil embolization of unruptured intracranial aneurysms is unknown.

- The site, size, and group-specific risks of the natural history of an unruptured aneurysm should be compared with the site, size, age, and procedure-specific risks of repair for each patient.

Case Series on Ruptured and Unruptured Aneurysms

The findings of case series on ruptured and unruptured aneurysms are summarized in Appendix 12 and are discussed under the Synthesis of Outcomes.

Description of Systematic Review and Studies on High Surgical Risk Aneurysms

Outcomes of the studies on posterior circulation intracranial aneurysms are summarized in Table 8 and Appendix 13.

In 1998, Eskridge et al. (34) reported on the US multicenter Guglielmi Controlled Detachable Coil clinical trial that led to the Food and Drug Administration approval of the device. Controlled detachable coil was used to treat the basilar tip aneurysms in 150 subjects, of whom 83 had ruptured aneurysms and 67 had unruptured aneurysms. These aneurysms are considered high-risk, because of their location. All subjects were deemed to be ineligible for surgical clipping based on neurosurgical assessments prior to entering the trial. Seventy-five per cent (75%) of the subjects achieved more than 90% coil packing. Periprocedural mortality for the whole group was 2.7%. Conservative mortality rates were up to 23% for the ruptured aneurysm group and up to 12% for the unruptured aneurysm group. Rebleeding occurred in 3.3% for ruptured aneurysms and 4.1% for ruptured aneurysms. Vasospasm occurred in 8% of the patients. Permanent deficits due to stroke in patients with ruptured and unruptured aneurysms were 5% and 9% respectively. Eskridge et al (34) concluded that coil embolization using detachable platinum coils is a promising treatment for ruptured basilar tip aneurysms that cannot be treated with surgical clipping with lower mortality and morbidity rates compared to conservative medical treatment. The authors also concluded that, the role of coil embolization in unruptured basilar tip aneurysm is unclear with less supportive results.

Miyachi et al. (35) in 1999 reported on a multicentre case series of 103 patients with unruptured vertebrobasilar aneurysms. In this series, 60 patients with 63 aneurysms were treated with endovascular embolization and 43 patients, each with 1 aneurysm, received surgical clipping. Total occlusion of aneurysms was achieved in 98% of patients receiving surgery compared with 54% in patients receiving coil embolization. Complications of surgery tended to be serious and affected outcome. Excellent or good clinical outcome was reported for 92% of patients that had coil embolization and 74% of patients that had surgery. Based on these results, Miyachi et al. concluded that endovascular treatment is safer than surgical treatment for unruptured vertebro-basilar aneurysms, particularly for patients who are poor surgical risks.

Hoh et al. (36) in 2001 analyzed the outcomes of 238 paraclinoid aneurysms treated either by endovascular embolization (n=57) or by surgical clipping (n=180). Paraclinoid aneurysms are located in the segment of the internal carotid artery, from where it enters the subarachnoid space to the origin of the posterior communicating artery. They are technically challenging to treat because of poor access or poor visibility. Hoh and colleagues retrospectively graded the aneurysms using the Massachusetts General Hospital (MGH) classification system that is based on the patient's age, HH score, Fisher Scale, and the size of the aneurysm. The scale ranged from 1 to 5, with 5 being the worst grade.

Hoh et al (36) found that patients with high MGH grade (i.e., poor clinical status) tended to be treated with endovascular coiling. Angiographic efficacy of aneurysm obliteration and long-term rates of complete occlusion were higher with surgery. Better clinical outcomes were reported for patients treated with surgery compared with those treated by endovascular embolization. A high complication rate was observed in both cohorts. Mortality rates were low compared to other series. The predominant cause of morbidity and mortality in both groups was vasospasm-related ischemia in patients with SAH. The MGH classification closely predicted the outcome. Hoh et al. concluded that endovascular coiling allows treatment of surgically high-risk and inaccessible paraclinoid aneurysms.

In 2002, Lozier et al. (22) published a systematic review of 12 reports consisting of 495 patients with ruptured and unruptured posterior circulation aneurysms treated with coil embolization using controlled detachable coils. The purpose of the review was to assess the degree and durability of aneurysm occlusion and short-term outcomes after endovascular embolization of these types of aneurysms. Studies with at least 10 posterior aneurysms were included. The results showed that coil embolization was moderately effective at completely excluding an aneurysm from the posterior circulation (47.6% initially and 44.7% at a mean follow-up of 16.8 months). The incidence of recurrence in wide-neck aneurysms and incompletely occluded aneurysms was substantial. Procedural mortality was 6.7% at 30 days and 9.8% overall. About 85% of patients achieved functional independence after embolization. The annual risk of SAH after embolization was 0.8%. Lozier et al. (22) concluded that coil embolization effectively prevents early rebleeding; however, its role in the treatment of unruptured posterior aneurysms is unclear.

Also in 2002, Ogilvie et al (7) reported on a retrospective review of the outcomes of 189 patients with posterior circulation aneurysms who were treated either with coil embolization (n=65) or with surgical clipping (n=124). The mean follow-up was 19 months (range, 4–82 months). Where possible, the aneurysms were treated surgically. Lower radiographic efficacy and higher rates of hemorrhage were reported for endovascular coiling. Excellent or good clinical outcomes were reported for 66.1% of patients who received coil embolization compared with 83.7% of patients who had surgery. Outcomes were related to the patient’s clinical grade at presentation, regardless of treatment modality.

Table 8: Outcomes of Surgical Clipping or Coil Embolization of High Surgical Risk Intracranial Aneurysms

	Lozier 2002* (22) N=495 Systematic review	Ogilvy 2002 (7) N=189 Case series	Hoh 2001 (36) N=238 Case series	Miyachi 1999(35) N=103 Case series	Eskridge 1998(34) N=150 Case series
TYPE OF ANEURYSM	Posterior circulation	Posterior circulation	Paraclinoid	Vertebrobasilar	Vertibrobasilar
Status	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Unruptured	Ruptured & unruptured
Intervention	Coiling	Coiling or Surgery	Coiling or surgery	Coiling or surgery	Coiling only
Degree of occlusion	Coiling 100% occlusion 47.6% of cases =/>90% occlusion 91% of cases	100% occlusion Coiling 32.3% Surgery 95.6% =/>95 occlusion Coiling 58.5%	100% occlusion Coiling 44% Surgery 94% =/>95% occlusion Coiling 70% Surgery 100%	100% occlusion Coiling 54% Surgery 98% =/>70% occlusion Coiling 84%	>90% coil packing = 75%
Clinical outcome	Functional independence 85% Morbidity rate 5.1%	Excellent or good Coiling 66.1% Surgery 83.7%	Excellent or good Coiling 74% Surgery 90%	Excellent or good Coiling 92% Surgery 74.4%	Permanent deficits Ruptured 5% Unruptured 9%
Mortality rate	Procedural Coiling 1.4%	Total Coiling 4.6% Surgery 8.6%	Coiling 4% Surgery 3%	Coiling 3% Surgery 7%	Perioperative 2.7% Overall ruptured 23% Unruptured 12%
Complications	Total 12.5% Recurrence 22% SAH risk 0.8%/year	Risk of rebleeding Coiling 2.25% per patient year Surgery 0.17% per patient year	Overall Coiling 21% Surgery 29% Permanent morbidity Coiling 3% Surgery 6%	Coiling 3.2% (30% major) Surgery 39.5% (71.4% major)	Vasospasm 8% Rebleeding rate: Ruptured 3.3% Unruptured 4.1%

***COILING ONLY**

Summary Statements on Coil Embolization of Posterior Circulation Aneurysms

- Only evidence from cohort and case series studies is available.
- Level 4 evidence suggests that endovascular coil embolization makes it possible and less risky to treat some aneurysms that are difficult to treat surgically because of their location.
- In the short-term, endovascular coil embolization appears to be able safe and effective in the treatment of paraclinoid aneurysms and posterior circulation aneurysms such as basilar tip aneurysms, in which treatment with surgical clipping is not feasible.
- In comparison with surgical clipping, treatment using coil embolization may yield lower rates of mortality and complications.
- Coil embolization is less effective than surgical clipping at totally excluding posterior aneurysm and paraclinoid aneurysms (32%–54% versus 94%–98%); however, coil embolization was able to achieve a near total occlusion rate in 58%–91% of patients.
- Clinical outcome for patients treated with endovascular embolization may be better than that of patients treated with surgical clipping in unruptured vertebrobasilar aneurysms, but it was poorer for paraclinoid aneurysms.
- The incidence of recurrence of posterior circulation aneurysm after coil embolization is substantial in wide neck or incompletely occluded posterior aneurysms.

Coil Embolization of Poor-Grade Aneurysms

Bracard et al.(37) reported on a subset of a series of 403 patients with intracranial aneurysms treated with controlled detachable coil embolization. These 80 patients had ruptured aneurysms of HH grade 4 or 5 treated with controlled detachable coils after SAH. About 22.5% of the aneurysms were 10 mm to 20 mm in diameter, and 8.75% were greater than 20 mm in diameter. At discharge, total occlusion was achieved in 30% of the patients, and subtotal occlusion (with a neck remnant) was achieved in 53.7%. At 1 year, total occlusion and subtotal occlusion were found in 89% of patients. Furthermore, 11% that had partial occlusion (with neck and sack remnant) had additional endovascular treatment. At discharge 52.5% of patients had good outcome (GOS 1 or 2). The rate of good outcome was much higher in patients with HH grade 4 aneurysms (62%) than those with grade 5 aneurysms (25%). Mortality rates were 32.5% at discharge and 37.5% at 1 year. All deaths occurred within the first 6 months. The effect of the initial bleeding was the main cause of death of grade 5 patients, whereas the effect of rebleeding was just as important a cause of death in grade 4 patients. The early rebleeding rate was 2.5%. Bracard et al. concluded that coil embolization allows early treatment of poor-grade aneurysms to prevent rebleeding even in the presence of vasospasm. This may not be possible with surgical clipping because of the difficulty of operating on a brain that is already turgid and traumatized by hemorrhage

Synthesis of Outcomes

Risk of Rupture of Unruptured Aneurysms

Information from autopsy series showed that most intracranial aneurysms are unruptured and apparently have never caused any symptoms. (8) The International Study of Unruptured Intracranial Aneurysms (ISUIA) (29) has shed much light on the natural history of unruptured aneurysms and on their risk of rupture. In the retrospective part of the ISUIA(29), 1,449 patients with an unruptured aneurysm of at least 2 mm in diameter were followed for 7.5 years.

The study showed that the size of the aneurysm is a significant predictor of rupture only in patients with no previous of SAH from another aneurysm. In these patients the rate of rupture for aneurysms less than 10 mm in diameter at the time of discovery was 0.05% per year. However, people with aneurysms of similar size and with a previous history of SAH, the risk of rupture increased to 0.5% per year. The risk of rupture approached 1% per year when for aneurysms of 10 mm in diameter or greater regardless of previous history of SAH. This study also showed that the aneurysms located in the vertebrobasilar or posterior circulation has a higher risk of rupture.

The prospective ISUIA (30) studied 1,692 patients with unruptured intracranial aneurysms that did not receive any intervention. The results (Table 9) showed that the 5-year cumulative rupture rate increases with the size of the aneurysm and is higher for aneurysms located in the posterior circulation. This study also suggests that even with aneurysms of 7 to 12 mm in diameter in the anterior circulation, the risk of rupture may be similar to or lower than the risk associated with surgical or endovascular repair of comparable outcomes.

Table 9: 5-Year Cumulative Rupture Rates of Unruptured Intracranial Aneurysm

Location	<7 mm diameter		7–12 mm	13–24 mm	>25 mm
	No Previous SAH	Previous SAH			
Cavernous carotid artery, %	0	0	0	3.0	6.4
Anterior Communicating /Internal carotid/ / Middle communicating (%)	0	1.5	2.6	14.5	40
Posterior communicating, %	2.5	3.4	14.5	18.4	50

*SAH represents subarachnoid hemorrhage

Angiographic Efficacy of Aneurysm Treatment

Angiographic efficacy refers to the degree to which the aneurysm is obliterated as demonstrated by follow-up angiograms. Reported angiographic efficacy data are summarized in Appendix 6.

With the exception of 1 study, the percentage of aneurysms that achieved immediate total occlusion through coil embolization ranged from 27% to 79% with a median of 55%. These rates were generally lower than those obtained with surgical clipping (79% versus 86%, (27) 51% versus 100%, (15) and 71% versus 91%(17)).

A systematic review (21) of endovascular treatment of 1,383 ruptured and unruptured intracranial aneurysms found a total occlusion rate of 53.8% and near total occlusion (more than 90%)in 87.9% of cases. Wiebers et al. (30) reported in an international study that, total occlusion was achieved in 55% of 451 unruptured intracranial aneurysms treated with coil embolization; another 24% achieved partial occlusion. Most studies reported the need for repeat procedures to achieve total occlusion in some aneurysms. For example, Leber (38) reported that additional procedures were used in 34% of the cases that achieved 95% obliteration.

In ISAT, the largest randomized controlled trial on treatment of ruptured aneurysms with SAH, one-year angiographic follow-up was available for 881coiled patients and 450 neurosurgical patients. The results showed 82% complete aneurysm occlusion in the surgical clipping group compared to 66% in the coil embolization group. Subtotal occlusion or a neck remnant was observed in 26% of coiled patients compared to 12% of neurosurgical patients, and incomplete occlusion occurred in 8% of coiled patients compared to 6% of neurosurgical patients. (28)

Vinuela et al. (20) in 1997 reviewed 403 patients who were treated with controlled detachable coils for acute ruptured intracranial aneurysms within 15 days of rupture. This series had a high proportion (57%) of posterior circulation aneurysms, large or giant aneurysms, and vertebrobasilar aneurysms. The morphological results are summarized in Table 10.

Table 10: Occlusion Rates and Sizes of Ruptured Aneurysms

	Small Aneurysm with a small Neck*	Small Aneurysm With a Wide Neck†	Large Aneurysm	Giant Aneurysm
100% occlusion, %	70.8	31.2	35	50
Neck remnant, %	21.4	41.6	57.1	50

*Less than or equal to 4 mm diameter †Greater than 4 mm diameter

These results showed that endovascular embolization is particularly effective for small aneurysms with a small neck (less than or equal to 4 mm). It is less effective for large or giant aneurysms, or in small aneurysms with a wide neck. In some complex aneurysms, an incomplete aneurysm occlusion was performed to decrease the chance of rebleeding, and more aggressive endovascular and/or surgical approaches were later performed after the patient had recovered from the acute phase of SAH.

Ng et al. (39) reported similar findings. In a series of 144 patients with ruptured and unruptured aneurysms treated with controlled detachable coils, complete occlusion was achieved in 46% for the entire group. However, the percentage with complete occlusion was higher in the group with small neck

(<4mm in diameter) than large neck (48% vs 27%, p=0.001), and also higher in small aneurysms (<10 mm in diameter) than large aneurysms (43% vs 18.5%, p=0.018). Ng also reported a residual neck remnant in 16% of the cases, and residual body filling in 38%.

Raymond et al. (40) in 2003 reported on a series of 466 ruptured and unruptured aneurysms treated with coil embolization. Angiographic follow-up at more than 12 months showed that 38.3% were still totally occluded, 45.5% showed a neck remnant, 15.2% showed a sac remnant, and 1.1% were not occluded.

Batista et al. (41) in 2002 conducted a long-term angiographic follow-up of 160 saccular aneurysms treated by coil embolization using a controlled detachable coil system. Of these aneurysms, 76.5% were on the anterior circulation and 59% had SAH. Embolization failed in 9.4% of the aneurysms, and 21.5% needed more than 1 procedure. At 1-year follow-up, 24 of the 29 aneurysms with initial complete occlusion remained unchanged, and 5 of the 29 aneurysms with initial complete occlusion showed 90% to 99% occlusion. Secondary spontaneous thrombosis occurred in 27.6% of incompletely occluded aneurysms. Almost half of the aneurysms with less that 100% occlusion became completely occluded. Thirty-five aneurysms had 5-year angiographic follow-up.

Based on the results of the follow-up, Batista et al. observed the following:

For aneurysms with immediate complete occlusion that were still stable at 1 year, long-term stability was achieved. Further angiographic follow-up is not justified.

For aneurysms with immediate subtotal occlusion, but in which complete occlusion was achieved after secondary spontaneous thrombosis at 1-year angiographic follow-up, long-term stability was always obtained and confirmed. Further angiographic follow-up is not justified.

For aneurysms with immediate occlusion of less than 80%, reintervention is required.

Aneurysms that showed a loss of occlusion at 3 months or 1 year had to be re-embolized and followed-up starting from the date of reintervention.

Batista and colleagues believed that these observations are valid in cases of multiple intracranial aneurysms. However, they based their long-term observations on a small number of patients (n=35).

Summary Statements on Aneurysmal Obliteration

All of the statements are based on Level 4 evidence.

- The percentage of complete aneurysm occlusion after coil embolization (27%–79%, median 55%) remains lower than that achieved with surgical clipping (86%–100%). However, about 90% of coiled aneurysms achieve near total occlusion or better.
- About 20% of patients required more than one procedure to achieve total occlusion.
- In one study, 45.5% of patients showed a neck remnant, and 15.2% of patients showed a sac remnant 1 year after coil embolization.
- The rate of total occlusion appears to be better for small intracranial aneurysms with a small neck.
- Secondary spontaneous embolization has been observed after coil embolization and has resulted in total occlusion in about 50% of incompletely occluded aneurysms.
- Intracranial aneurysms that have achieved angiographic total occlusion at 1 year either through the initial embolization or through secondary spontaneous thrombosis have likely achieved long-term stability.
- Intracranial aneurysms that had an immediate occlusion of less than 80% or that showed a loss of occlusion at 3 months or 1 year require reintervention and follow-up from the date of reintervention.
- Reintervention rates for coil embolization were about 20%.

Post-procedure Rebleeding

In the treatment of ruptured intracranial aneurysm, the primary objective is the prevention of rebleeding. Rebleeding rates are summarized under Complications in Appendix 8.

Molyneux (25) reported in ISAT, the only large randomized controlled trial on ruptured aneurysms with SAH, that the post-treatment rebleeding rate at 1-year follow-up was 2.4% (26 patients) for coil embolization and 1% (10 patients) for surgical clipping. Confirmed rebleeding from the repaired aneurysm after the first year and up to year eight was low and not significantly different between coil embolization and surgical clipping (7 patients for coil embolization vs 2 patients for surgical clipping, log-rank p=0.22). (26)

Byrne reported rebleeding in 1.2% of 317 patients treated with coil embolization at 6 months angiographic follow-up. Vinuela (20) found a 2.2% rebleeding rate, but his series included up to 39% of large and giant thrombotic aneurysms. However, several studies with midterm angiographic and clinical follow-up data showed no rebleeding. (11;38), (41)

Rebleeding is rare after surgical clipping, reported to affect 0.5% to 3.87% of patients, with an estimated incidence of 0.79% per year. The timing of rebleeding after surgical clipping varies from as early as 1 month to a mean interval of 10.5 years.

Mortality Rate after Treatment

Mortality rates are summarized under clinical outcomes in Appendix 7.

For Ruptured aneurysms:

ISAT reported less deaths in the first 7 years following coil embolization compared to surgery clipping (10.8% vs 13.7%) that seemed to be consistent over time, and was significant (log-rank p= 0.03) (Figure 1).(26) The other RCT reported similar mortality rates for coil embolization and surgical clipping (13.5% vs 15.8%).(27)

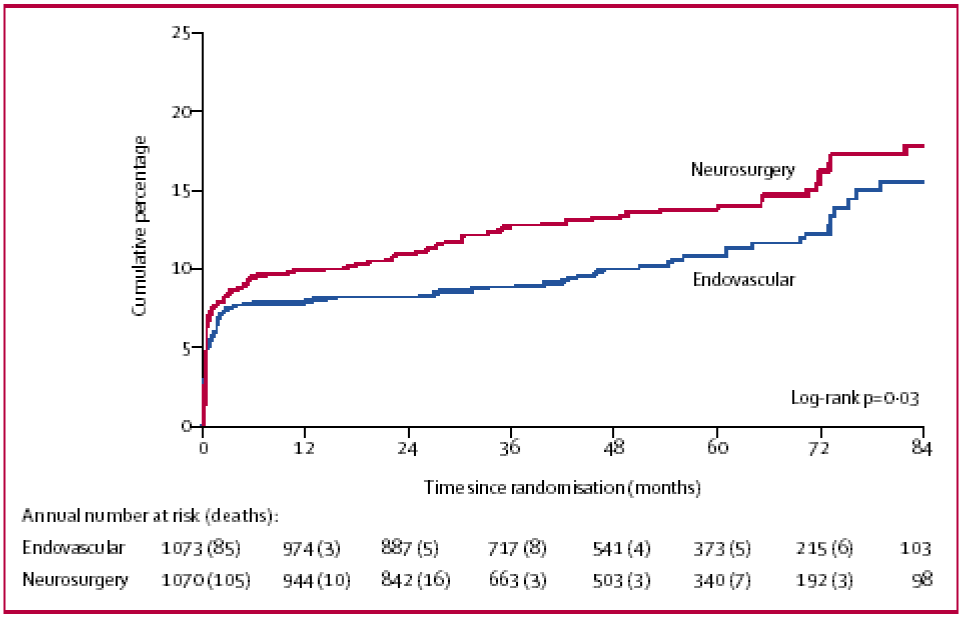


Figure 1: Kaplan Meier cumulative mortality to 7 years
Reprinted from The Lancet, 366(9488), Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion, 809-817, Copyright 2005, with permission from Elsevier.

Vinuela (20) reported that the in-hospital mortality rate for 403 patients treated for ruptured aneurysms with coil embolization was 6.2%. Of this, 1.7% was attributed to the coiling procedure.

For unruptured aneurysms:

A meta-analysis (42) of 61 studies with 2,460 patients treated for unruptured intracranial aneurysms with surgical clipping showed a mortality rate of 2.6% (at a mean follow-up of 24 weeks after treatment).

> *In hospital mortality rate following coil embolization of unruptured intracranial aneurysm reported in 3 observational studies ranged from 0.5% to 1.7%. (31); (43); (33). The in hospital mortality reported for surgical clipping in the same studies ranged from 2.1% to 3.5%. One of the studies reported that the in-hospital mortality rate was significantly higher for surgical clipping than for coil embolization.*

The mortality rates reported for the prospective cohorts (n=2,368) of the International Study of Unruptured Intracranial Aneurysm (30) that received either surgical or endovascular treatment are summarized in Table 11. The overall 1-year mortality rate for coil embolization was 3.1% and for surgical clipping 2.3%. There was no information as to whether the differences in mortality rates between the two treatment cohorts were statistically different. As previously mentioned, the endovascular cohort was older and had a higher percentage of large aneurysms and aneurysms located in the vertebrobasilar system.

Table 11: Mortality rates of the International Study on Unruptured Intracranial Aneurysms

	Surgical, No Previous SAH* (n=1,591)	Endovascular, No Previous SAH (n=409)	Surgical, Previous SAH (n=326)	Endovascular, Previous SAH (n=42)
At 30 days Procedure related death, %	1.8	2.0	0.3	0
At 1-year Procedure related death, %	2.7	3.4	0.6	0

Summary Statements on Mortality Rates

- For ruptured intracranial aneurysms suitable for either surgical or endovascular repair in patients with good clinical status, level 1 evidence showed similar 1-year mortality rate for coil embolization and surgical clipping (8.1%–13.5% for coil embolization and 10.1–15.8% for surgical clipping).
- For people in good clinical status after SAH and treated for ruptured aneurysms suitable for either surgical or endovascular repair, cumulative mortality in the first 7 years was significantly lower for the coil embolization group compared to the surgical clipping group (log rank p = 0.03).
- For unruptured intracranial aneurysms, two observational studies showed similar in-hospital mortality rates for coil embolization (0.5%-1.7%) and surgical clipping (2.1%–3.5%). One of the studies reported statistically higher in-hospital mortality rate for surgical clipping compared to coiled embolization.
- For Unruptured intracranial aneurysms, the 30-day and 1-year procedure related mortality rates were 1.8% and 3.1% for coil embolization and 1.5% and 2.3% for surgical clipping. It is not clear whether the difference in mortality rates was statistically significant.

Clinical and Neurologic Outcomes

The clinical outcomes of the studies are summarized in Appendix 7.

Ruptured Intracranial Aneurysm

The 2005 ISAT update (26) reported on the 1-year clinical outcomes of 2,118 patients (1,063 coiling; 1055 surgical) with 1-year clinical follow-up, and confirmed its earlier finding that coil embolization produced better independent survival for people with SAH and good clinical conditions, and in whom the aneurysm is suitable for both coil embolization and surgical clipping. Under these conditions, coil embolization resulted in a 7.4% absolute risk reduction and 23.9% relative risk reduction of death or dependency (Modified Rankin Score 3–6) (Table 12).

Table 12: Clinical Outcome at 2 months and 1 year (26)

	2 month outcome		1 year outcome	
	Endovascular (n = 1,065) Number (%)	Neurosurgery (n = 1,063) Number (%)	Endovascular (n = 1,063) Number (%)	Neurosurgery (n = 1,055) Number (%)
Modified Rankin Scale				
0 No symptoms	203 (19.1)	144 (13.6)	260 (24.5)	187 (17.7)
1 Minor symptoms	310 (29.1)	273 (25.7)	301 (28.3)	292 (27.7)
2 some restriction in lifestyle	274 (25.7)	254 (23.8)	252 (23.7)	250 (23.7)
(0–2 inclusive)	787 (73.9)	671 (63.1)	813 (76.5)	729 (69.1)
3 Significant restriction in lifestyle	107 (10.1)	189 (17.8)	107 (10.1)	141 (13.4)
4 Partly dependent	34 (3.2)	46 (4.3)	30 (2.8)	42 (4.0)
5 Fully dependent	62 (5.8)	73 (6.9)	28 (2.6)	38 (3.6)
6 Dead	75 (7.0)	84 (7.9)	85 (8.0)	105 (9.9)
(3–6 inclusive)	278 (26.1)	392 (36.9)	250 (23.5)	326 (30.9)

Reprinted from The Lancet, 366(9488), Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion, 809-817, Copyright 2005, with permission from Elsevier.

The advantage of coil embolization over surgical clipping varies widely with aneurysm location, but endovascular treatment seems beneficial for all sites.

In a RCT of 109 patients with ruptured intracranial aneurysms, Koivisto (27) reported no significant differences between treatment with coil embolization compared with surgical clipping in the clinical outcomes, including mortality rates.

Vinuela (20) reported in 1997 that, immediately following acute endovascular embolization in 403 patients with ruptured aneurysms and SAH, 84.9% of the patients showed improved or unchanged neurological status, 8.9% experienced post embolization clinical deterioration, and 6.2% died within 1 week of embolization. The neurological deterioration was mild in 2.48% of patients, moderate in 3.7%, and severe in 2.7%. The procedure-related mortality rate was 1.74%. Vinuela et al. (20) concluded that coil embolization of a nonsurgical acute aneurysm decreases the possibility of a repeat aneurysm rupture, and it allows for aggressive medical and/or endovascular therapy of delayed cerebral ischemia due to symptomatic vasospasm.

For Unruptured Aneurysms

Wiebers et al (30) reported that in the prospective International Study of Unruptured Intracranial Aneurysms, the overall 1-year the morbidity rate (Rankin 3-5 and/or impaired cognitive status) following endovascular treatment was 6.4% compared to 9.8% in the surgical cohort. It is not clear whether the difference is statistically significant.

Table 13: One-year outcome of the International Study of Unruptured Intracranial Aneurysms

	Surgical, No Previous SAH* (n=1,591)	Endovascular, No Previous SAH (n=409)	Surgical, Previous SAH (n=326)	Endovascular, Previous SAH (n=42)
Disability, %				
Rankin 3–5, %	1.4	1.0	0.90	0
Impaired cognitive status only, %	5.5	3.2	7.1	7.1
Rankin 3-5 & impaired cognitive status, %	3.0	2.2	1.5	0
Total morbidity	9.9	6.4	9.5	7.1
Overall morbidity and mortality for all patients†, %	12.6	9.8	10.1	7.1

*SAH represents subarachnoid hemorrhage
† Overall morbidity & mortality includes death and one of both Rankin score 3-5 and impaired cognitive status

In a 2004 retrospective database study of 3,919 patients with unruptured aneurysms in the United States, Barker et al. (31) found no significant difference between coil embolization and surgical clipping in mortality rates or discharge to long-term facilities. When discharge to short-term rehabilitation was counted as an adverse event with mortality and discharge to long-term facilities, patients treated with coil embolization had significantly better outcomes than patients treated with surgical clipping at discharge. Most of this advantage for coiling was in patients older than 65 years. Endovascular embolization was also associated with significantly fewer (about 50%) neurological complications and shorter hospital stays. Patients' age was a strong independent predictor of a poor surgical outcome in the retrospective ISUIA. (29) Surgery-related mortality and morbidity at one year was 32% for patients over 64 years and 14.4% for patients between 45 and 64 years old ($p<0.001$). Location and size of an aneurysm predict both surgical and endovascular outcomes. (30)

Ruptured and Unruptured Aneurysms

In a retrospective series of 248 patients in 2003 in the United Kingdom, Vindlacheruvu et al (44) found that, in the entire series and in patients with SAH, the length of in-patient stay, GOS outcome, and delayed ischemic neurologic deficits were similar after either coil embolization or surgical clipping. Good-grade patients were more likely to be discharged directly home, but poor-grade patients were generally transferred either to the referring hospital or to the neuro-rehabilitation ward; there was no significant difference between the surgical or endovascular cohorts. Coil embolization of unruptured aneurysms resulted in fewer days in the hospital stay compared with surgical repair (4.8 days for coiling versus 10.3 days for surgical clipping, p<.001). There was no significant difference between Glasgow Outcome Score and modality of treatment.

In a 1998 series of 248 patients with intracranial aneurysms followed-up for a mean of 2.6 years, Leber et al. (38) found no significant difference between the Glasgow Outcome Scores, including mortality, of patients treated with either coil embolization or surgical clipping, in either the ruptured or unruptured cohort. Furthermore, there was no rebleeding in either group during follow-up. Leber et al concluded that coil embolization is not associated with a higher risk of morbidity and mortality than surgical clipping.

In a systematic review of 48 case series in 1999, Brilstra et al. (21) reported that coil embolization of ruptured and unruptured intracranial aneurysms using controlled detachable coils resulted in a lower rate of aneurysm occlusion but better functional outcomes than treatment with pushable coils. The review also showed that patients with ruptured aneurysms had worse functional outcomes despite higher rates of occlusion when compared to patients with unruptured aneurysms.

Lot et al. (17) in 1998 reviewed a single centre French series of ruptured and unruptured aneurysms treated with coil embolization (n=293) or with surgical clipping (n=102). All patients were followed-up at 1 month, 6 months, and 1 year. All grades 1 to 3 ruptured aneurysms were treated in the early phase whenever possible. Grades 4 and 5 were treated only after sufficient recovery had occurred, with the exception of emergency surgery for compressive hematoma. A larger number of poor-grade aneurysms (84% in small aneurysms and 69% in large aneurysms) were treated with coil embolization. For small aneurysms, the clinical outcomes as measured by GOS were similar in the coil embolization and surgical groups. In large aneurysms, coil embolization achieved better results than surgical clipping. In large poor-grade aneurysms (HH Grades 4–5), 72% of patients treated with coil embolization had a good clinical outcome compared to 25% in those treated with surgical clipping. Mortality was 17% for coil embolization compared with 50% for surgical clipping.

Ng et al. (39) reported on the midterm clinical outcomes of 66 patients in an Australian series of 144 patients with ruptured and/or unruptured aneurysms treated with controlled detachable coil embolization. All patients with unruptured aneurysms were discharged in an independent status with GOS grade 1 or 2. At 2-year follow-up, 94% of these patients remained independent. For patients with ruptured aneurysms, 88% of those with Hunt and Hess Grade I to II on admission were discharged in an independent status compared to 30% of patients with Hunt and Hess Grade IV to V (p<0.0001). The clinical status of these patients at 2-year follow-up correlated with the HH grade on admission (Table 14).

Table 14: Clinical Outcome with Ruptured Aneurysms at 2 years after Coil Embolization(39)

	Midterm Outcome n (%)		
H&H	Independent (GOS=/<2)	Disabled (GOS>@)	Dead
I-II (n=44)	36 (82)	2(4.5)	6(13.5)*
III (n=12)	7 (47)	1(6.5)	4(26.5)†
IV & V (n=10)	3 (30)	0 (0)	7 (70)‡

N=66
* Four died in hospital of SAH sequelae; 2 died of unrelated causes
† Three died in hospital of SAH sequelae; 1 died of an unrelated cause
‡ All died of SAH sequelae

Summary Statements on Clinical and Neurological Outcomes

- Patients with small ruptured intracranial aneurysms in the anterior circulation and good clinical status had a 23.9% relative reduction and 7% absolute risk reduction in the 1-year combined rate of death and dependency when treated with endovascular coil embolization (level 1 evidence).
- Coil embolization of ruptured aneurysms was associated with less frequent MRI-detected superficial brain deficits and ischemic lesions at 1-year (level 2 evidence).
- The short-term clinical outcomes of patients with SAH were not dependent on treatment modality but on the clinical grade of the patient on admission (level 4 evidence).
- Patients with SAH and good clinical grade had better 6-month outcomes and lower risk of symptomatic cerebral vasospasm after coil embolization compared to surgical clipping (level 4 evidence)
- Ruptured aneurysms treated with coil embolization within 6 days of SAH had better overall outcomes than those treated after 6 days (level 4 evidence)
- There is no direct RCT comparison in the neurological outcome of endovascular and surgical treatment of unruptured intracranial aneurysms.
- The overall 1-year morbidity rate following treatment of unruptured aneurysm in a large prospective observational study was 6.4% for coil embolization and 9.8% for surgical clipping. The statistical significance is unknown.
- Advanced age did not have a negative impact on the outcome of endovascular embolization of unruptured aneurysms, and it may be more suitable for older patients (level 4 evidence)
- Coil embolization may yield better clinical outcomes in poor grade aneurysms compared to surgical clipping (72% vs 25%).
- At discharge from the hospital, coil embolization of unruptured intracranial aneurysms was associated with a significantly lower rate of adverse events, defined as the composite rate of in-hospital mortality and discharge to any institution (long-term or short-term) other than home (10.6% vs 18%, p=0.002) (levels 4 evidence). The advantage was mostly for people older than 65 years.
- Coil embolization of unruptured aneurysms was associated with shorter stay in the hospital and intensive care compared to surgical clipping.

Recurrence of Aneurysms after Coil Embolization

Recurrence is the refilling of the neck, sac, or dome of a successfully treated aneurysm as shown on an angiogram. The risk of recurrence has been reported to be 1.5% over 4 to 5 years in a properly surgically clipped aneurysm. In a 9-year angiographic follow-up of 112 patients treated for SAH with surgical clipping, Tsutsumi et al. (45) reported a regrowth rate of 2.9%.

The issue of recurrence of intracranial aneurysm after coil embolization has been addressed in only a few studies, because most of the studies have been short. Recurrence rates are summarized in Table 15.

Table 15: Recurrence Rates after Coil Embolization

	Cognard 1999(46)	Raymond, 2003(40)	Byrne 1999(28)	Koivisto 2000(27)	Leber 1998(38)	Murayama 2003(47)	Ng 2002 (39)
Sample size	148 berry aneurysms	50	259	109	248	818	160 Aneurysms
Follow-up	Up to 3 years	55% >1 year Some up to 58 months	At 6 months	Mean 39+/-18 months		Mean 11 months	Up to 3 years
Recurrence rate	Overall 14% Ruptured 17% Unruptured 7%	Overall 33.6% Major 20.7% Ruptured 39% Unruptured 27.4%	Recurrent refilling Ruptured 14.7%	Refilling aneurysm neck Ruptured 22%	Ruptured & unruptured 9%	Overall recanalization 20.9%	Decrease in degree of occlusion Year 1 -28% Year 2 20% recanalization Year 3- 14% increased in neck remnant size

Cognard et al. (46) in 1999 conducted an angiographic follow-up of 169 ruptured and unruptured berry aneurysms at 3 months, 18 months, and at 3 to 4 years after coil embolization. Overall, total occlusion of the sac and neck was achieved in 148 (88%) of the aneurysms. Recurrence occurred between 3 and 40 months in 20 (14%) of the 148 totally occluded aneurysms, and 5 patients underwent a successful second treatment. Recurrence was observed in the very late follow-up of some aneurysms that had persistent total occlusion in previous follow-up angiograms. The rate of recurrence was higher in ruptured aneurysms (17% versus 7% in unruptured) and in large aneurysms (22% versus 8% in small). The ratio between the size of the sac and the size of the neck and the location of the aneurysm did not correlate with the frequency of recurrences.

Remnant regrowth after subtotal occlusion was more frequent than true recurrences (30% versus 14%, respectively) and may be an indication for retreatment. Cognard et al. (46) believed that recurrence may involve 2 mechanisms: coil compaction due to arterial blood flow, and true persistent growth of the aneurysm due to the initial disease of the arterial wall.

In a Canadian series in 2003, Raymond et al. (40) retrospectively analyzed the follow-up angiograms of 501 aneurysms to assess the incidence and factors responsible for angiographic recurrences after coil embolization. Of the 501 aneurysms, 54.1% were acute ruptures and 45.9% were unruptured. Angiographic follow-up was performed at 6 months and then for incremental periods (18 months, 3 years, etc.). The mean follow-up was 31.32 months (SD, 24.96 months).

Short-term (less than or equal to 1 year) angiograms were available for 353 (70.5%) aneurysms. Long-term (greater than 1 year) angiograms were available for 277 (55%) patients. Recurrences were found a mean 12.31 months (SD, 11.33 months) after coil embolization in 33.6% of the aneurysms. Of these recurrences, 20% were considered major with 49.4% retreated with coils. Of the aneurysms treated for recurrence, 48.6% showed a second recurrence.

Logistic regression showed that the most significant predictors of recurrence for the entire group were treatment during the acute phase after rupture (p=.013); aneurysm size greater than or equal to 10 mm in diameter (p<.001); the neck of the aneurysm wider than 4 mm (p<.001); incomplete initial occlusion (residual neck or residual aneurysm; p<.001); and duration of follow-up (more frequent in follow-up longer than 17 months; p=.003).

Raymond et al. (40) concluded that recurrences are more frequent after coil embolization than after surgical clipping, and that long-term angiographic follow-up is mandatory after endovascular embolization.

In 2003, Murayama et al. (47) assessed the long-term angiographic results of 489 coiled aneurysms with a mean followed-up period of 11 months (range 3 months to 8 years). Overall recanalization was observed in 20.9% of the aneurysms. The recanalization rate was 5.1% in small aneurysms with a small neck, 20% in small aneurysms with a wide neck (more than 4 mm), 35.3% in large aneurysms, and 59.1% in giant aneurysms. Lesions with neck remnants and larger lesions were more likely to recanalize.

Ng et al. (39) followed the angiographic outcome of 135 patients after successful coil embolization treatment for their intracranial aneurysms. In the first year, the recanalization rate was 28%. Twenty per cent (20%) of completely occluded aneurysms developed small neck remnants. Three percent (3%) developed body filling and 8% that had a body remnant showed an increase in remnant size. There was a constant decline in the recanalization rate up to 3 years after coil embolization (20% in year 2, and 14% in year 3). Ng et al (39) also reported that body filling resolved over time (44% between 6–12 months, 30% at or after 2 years). There was a tendency for the occlusion status of small neck remnants to remain unchanged. Narrow-neck (<4mm in diameter) aneurysms demonstrated a higher rate of resolution of body filling and displayed greater angiographic stability throughout a 2-year period.

Summary Statement of Aneurysm Recurrences After Endovascular Coil Embolization

- The rate of recurrence was low after surgical clipping (2.9% over a 9-year follow-up).
- Rates of recurrence after coil embolization ranged from 14.7% to 39% in ruptured aneurysms and from 7% to 27% in unruptured aneurysms.
- Recurrences occurred in aneurysms that were totally occluded by coil embolization as late as 3 years after coil embolization.
- About 10% of recurrences were serious enough to require retreatment. In 1 series, the recurrence rate after retreatment was 49%.
- The risk factors for recurrence after endovascular embolization were treatment during the acute phase of rupture, aneurysms bigger than 10 mm in diameter, neck size wider than 4 mm, incomplete occlusion, and duration of follow-up (more than 17 months).

Complications

There has been very little head-to-head RCT comparison of complication rates from coil embolization and from surgical clipping. The findings are based on case series and meta-analysis of case series. Complications related to coiling or surgical clipping of intracranial aneurysms are summarized in Appendix 8.

Direct RCT comparison:

Koivisto et al reported in a small RCT that superficial brain deficit and ischemic lesions detected by magnetic resonance imaging was more frequent following surgical clipping compared to coil embolization. However, no specific data is provided.

Surgical Clipping:

Raaymakers et al. (42) reported a meta-analysis of 61 studies on surgical clipping yielded a permanent morbidity rate of 10.9% (95% CI, 9.6%–12.2%). The analysis also showed that one half of the patients with surgical morbidity became dependent.

Coil Embolization:

Brilstra et al. (21) conducted a meta-analysis of 48 case series on coil embolization of ruptured and unruptured aneurysms. They found the total complication rate with controlled detachable coils was 12%, and the rate of permanent complications was 3.7%.

In a prospective review that mimicked a RCT, Johnston et al. (1) reported that the complication rate in patients treated with coil embolization (23%) was significantly lower than that in those treated with surgical clipping (46%; p=.009).

In a cohort study of 223 patients, Versari (15) reported a higher complication rate in coil embolization (16%) than in surgical clipping (6.8%).

Ng et al. (39) reported in a series of 144 patients treated with controlled detachable coil, that the overall procedure related morbidity was 6.9% with a higher rate in ruptured aneurysms compared to unruptured aneurysms (8.6% vs 5.1%).

Complications that are common to coil embolization and surgical clipping are listed below.

Permanent complications were reported for 3% to 7.1% of patients following coil embolization, (21) and 10.9% for following surgical clipping. (42)

Rates of ischemic deficit were 8.5% for controlled detachable coils and 13.4% for pushable coils in a systematic review.(21)

Barker et al. (31) identified 13 types of complications resulting from treatment of 3,919 patients with unruptured intracranial aneurysms. Multivariate analysis showed 3 of the complications were significantly more frequent in the surgical group than in the coil embolization group. These were infarction or hemorrhage (Odds ratio (OR) 2.0; 95% CI, 1.3–3.2, p=.002), hemiparesis (OR 2.8; 95% CI, 1.3–5.9, p=.008), and transfusion of red blood cells (OR 5.6; 95% CI 1.2–26, p=.03). (31)

Rates of thrombo-embolic events following coil embolization were 2.5% in a series of 317 patients with acute SAH (48), 9.5% in another series of 223 patients with ruptured aneurysms, (15) and 14.5 % in a series of 160 ruptured and unruptured aneurysms.

The rate of intraoperative rupture was 3% for patients treated with coil embolization and 6.8% for patients treated with surgical clipping in a series of 223 patients with intracranial aneurysms. (15)
Hematoma was reported in 3.8% of patients who had coil embolization and 2.2% of patients who had surgical clipping.(31)

Across studies, the overall rate of technical complications of coil embolization ranged from 8.6% to 18.6%. The complications that are unique to coil embolization are as follows:

Perforation of aneurysms happened in 2.3% to 4.7% of cases. It was more frequent in ruptured aneurysms (4.1% versus 0.7% in unruptured aneurysms) (49) and in pushable coils (7.1% versus 3.7% in controlled detachable coils). (21) Cloft et al (49) conducted a meta-analysis of 17 published retrospective reports consisting of 2,008 patients on perforation of intracranial aneurysms during embolization using controlled detachable coils. The review showed that the risk of perforation during embolization was higher for patients with previously ruptured aneurysms (4.1% versus 0.7% in unruptured aneurysms). Perforations caused by the coils or microcatheters during coil embolization tended to result in substantial combined morbidity and mortality rates (39% and 33%, respectively), whereas perforations caused by microguidewires did not result in any morbidity or mortality.

Unintended parent artery occlusion occurred in 2% to 3% of cases. Murayama (47) reported a rate of 2%, resulting in the death of 3 patients. Barker (31) reported rates of 8.8% in coil embolization and 6.4% in surgical clipping. The difference was not statistically significant:
Other complications of coil embolization were collapsed coils (7.7%)(27),coil rupture (0.4%).(47). coil migration (0.5%–3%) (15); (20); (47), and coil malposition (14.6%).(44)

Summary Statements on Complications

- Complications resulting from coil embolization of intracranial aneurysms ranged from 8.6% to 23%.
- Meta-analysis showed that permanent complication rates were 3.7% for controlled detachable coil embolization and 10.9% for surgical clipping.
- Large observational studies showed that complications such as hemiparesis, hemiplegia, and cerebral infarction were significantly more frequent in surgical clipping than in coil embolization of unruptured aneurysms. A systematic review showed that one half of the patients with post surgical complications became dependent in daily life.
- The most common complications of coil embolization were perforation of the aneurysm, ischemic deficit, thrombo-embolic events, intraoperative rupture, parent artery occlusion, collapsed coils, coil migration, and coil malposition.
- The risk of perforation during coil embolization was higher in previously ruptured aneurysms (4.1%). The combined morbidity and mortality rates from perforation caused by microcatheters and coils were substantial (33% and 39%, respectively).

Cerebral Vasospasm in Ruptured Aneurysms

Cerebral vasospasm often results in delayed ischemic neurologic deficits, and is the main cause of morbidity and mortality in patients with ruptured aneurysms and SAH. Previous studies have shown that the most powerful prognostic factors for vasospasms are the extent of the hemorrhage, a poor admission clinical grade, and loss of consciousness at presentation. (11)

Rabinstein et al. (11), in 2003, studied symptomatic vasospasm and outcomes of 415 patients with ruptured intracranial aneurysms following treatment with either coil embolization (n=76) or with surgical clipping (n=339). All patients were admitted to hospital within 7 days of SAH. Vasospasm was considered present when there was unequivocal narrowing of the lumen of the artery on angiogram. Symptomatic vasospasm was defined as documented vasospasm that was consistent with new neurologic deficits presented from 4 to 14 days after the onset of SAH and that could not be explained by other causes of neurological deterioration. The median follow-up duration was 6 months. After the diagnosis of vasospasm, hemodynamic augmentation therapy with crystalloids, colloids, and inotropic medications was initiated.

Rabinstein et al. reported no statistically significant differences in the overall outcome between the surgical clipping cohort and the coil embolization cohort. Logistic regression analysis showed that treatment modality did not affect the rate of symptomatic vasospasm among patients with poor WFNS grades (4–5) at presentation. For patients with good admission WFNS grades (1–3), coil embolization was associated with a lower risk of symptomatic vasospasm (OR 0.34; 95% CI 0.14–0.8) and death or permanent neurological deficit due to vasospasm (OR 0.28; 95% CI 0.08–1) compared with surgical clipping.

In 2003, Manabe et al.(50) reported that in a series of 151 ruptured aneurysms, surgical clipping was used whenever possible and coil embolization was chosen as a second line of treatment in 13% of the cases. The results showed that patients receiving coiled embolization group had a good prognosis (85%) compared with patients receiving surgical clipping (73%), even though patients in this group were surgically difficult or at high risk for general anesthesia or craniotomy. They found that vasospasm occurred in 5% of the patients in the coil embolization group and 11% of the patients in the surgical clipping group.

Summary Statements on Vasospasm

Limited evidence suggests that coil embolization treatment of ruptured aneurysm accompanied by SAH may be associated with a lower incidence of vasospasm (5% vs 11%) and the resulting death and permanent deficits (Odds ratio 0.28) especially in patients with good WFNS grades (1–III) on admission compared to surgical clipping. (Level 4 evidence)

Indications for Endovascular Coil Embolization

The selection of coil embolization in the treatment of intracranial aneurysms appears to be based mainly on the morphology, location and accessibility of the aneurysm and the age, clinical condition, and comorbidity of the patient. Examples of indications for endovascular coil embolization used in the studies are provided below.

Richling 2002 (Austria)(19)

Factors favoring surgical clipping:

- Broad-necked aneurysm (dome diameter/neck diameter <1)
- **Imaging gives unclear microanatomic results**
- Intracranial hematoma requiring evacuation
- **Aneurysm in easily accessible location without previous hemorrhage**
- Factors favoring endovascular coiling
- Aneurysms with clear neck (dome diameter/neck diameter >1)
- Critically ill and medically unstable patients
- Poor neurologic condition after hemorrhage
- Patients age >65 years plus significant comorbidity
- Threatening vasospasm
- Incipient brain edema
- Coagulopathies

Anticipated surgical difficulties, especially in some posterior circulation aneurysms.

Vinuela 1997(20)

Exclusion from surgical clipping was the primary factor considered in the selection of the coil embolization technique as the therapeutic alternative. The causes for surgical exclusion in this group included: anticipated surgical difficulty because of aneurysm size or location (69.2%), attempted and failed surgical exploration in 12.7%; poor neurological grade in 12.2%; poor medical status in 4.7% and refusal of surgery by 1.2% of patients.

Murayama 2003(47)

In the early phase of the study, there was a dominant referral pattern of surgically difficult aneurysms such as those located in the posterior circulation or large lesions. After FDA approval of the Guglielmi Detachable Coil® system in 1995, the referral pattern became similar to that experienced in a standard neurosurgical practice, although there was still a higher incidence of posterior circulation aneurysms.

Rabinstein 2003(11)

Main factors for selecting endovascular coil occlusion during the early study period included poor clinical grade and an aneurysm located in the posterior circulation. More recently, the type of treatment was selected on the basis of a consensus reached between the treating neurosurgeon and the interventional neuroradiologist after they had analyzed the risks and chances of success of both therapeutic modalities in each particular case. Factors considered during the decision-making process included the dome/neck ratio of the aneurysm, the presence of major or perforating arterial branches of the aneurysm, and surgical or endovascular accessibility

Summary Statement on Indications for Coil Embolization

Indications for coil embolization are sufficiently well described to develop guidelines for institutions. While data on long-term follow-up are lacking, careful surveillance following coil embolization may mitigate this concern.

Coil embolization has been generally considered when surgical treatment is not feasible or unsafe. Decision-making should be based on a consensus reached between the treating neurosurgeon and interventional neuroradiologist after an analysis of the risks and chances of success of both therapeutic modalities for the individual patient.

Follow-up Strategy for Coil Embolization

Murayama(47) conducted a study on the long-term follow-up of 489 intracranial aneurysms treated with coil embolization. This study suggests that long-term angiographic follow-up is necessary after coil embolization, particularly in aneurysms that showed less than total occlusion at 1-year follow-up.

In this study, completely embolized aneurysms received angiographic follow-up at 6 months and 1year. If follow-up angiogram demonstrated any evidence of recanalization, another 6-month follow-up was usually recommended. Additional embolization or direct clipping was suggested if the remnant was morphologically significant. After a follow-up of 3 years, only plain skull x-ray films were used to evaluate coil mass deformity.

If a neck remnant occurred after initial embolization, a 3-month follow-up angiography session was scheduled. If significant recanalization was observed a second embolization was usually planned if possible.

Limitations of Evidence

Paucity of randomized controlled studies

With the exception of two randomized controlled trials on ruptured intracranial aneurysms, all the other studies are observational studies. Most of these are retrospective analyses. Although there were general guidelines for the selection of patients, very few studies have clear inclusion and exclusion criteria. All the above factors contribute to bias in patient selection. The lack of randomization and controls makes it difficult to make direct comparisons between coil embolization and surgical clipping.

Limitations of randomized controlled trials

One of the randomized controlled trials only had a one-year follow-up. Of the two RCTs, the study by Koivisto et al (27) had a very small sample size (Total n=109).

The large international randomized controlled trial(30) was under criticism for having to pool the modified Rankin scales 3 to 6 to achieve statistical significance, while there was no statistically significant difference in each individual Rankin score. There is a concern that by grouping Rankin outcome scores, the results are diluted significantly. The outcome scores were based on patient reports rather than physician assessment. The study was also questioned about the percentage of poor outcome from surgical clipping because it is much higher than those reported by other surgical series. Moreover, this study provided no long-term angiographic data or recurrent rates. Finally, of 9,559 patients with SAH who were assessed for eligibility for this study, 7,416 (77.6%) were excluded for refusal or unspecified reasons. Most of the patients included in the study were in good clinical condition prior to treatment (88% with WFNS grade 1 or 2) and had small anterior circulation aneurysms (97.3%). Hence, the results of this study can only be generalized to similar patients but not to all patients with SAH or to any patients with an unruptured aneurysm.

Bias in patient selection

Most series showed a higher percentage of elderly patients, patients with poor clinical status and posterior aneurysms in the endovascular group. These patients tend to have less favorable outcome from treatment.

Heterogeneity of definitions of outcome measures

There is heterogeneity in the definitions of outcomes that were reported, making inter-study comparisons difficult. For example, definitions for partial occlusion and suboptimal occlusion varied among the studies. Different scales were used to evaluate the clinical outcome of treatment.

Lack of statistical data

In some series that included both a surgical cohort and an endovascular cohort, comparative data were provided but sometimes without indications as to whether the differences were statistically significant.

Bias in follow-up procedures

Serial angiographic follow-up evaluations were performed in patients treated with coil embolization in all studies. However, surgically treated patients had relatively few angiographic follow-ups.

Economic Analysis

Literature Review

Bairstow et al (51) compared the costs of aneurysm treatment of a subset of 22 subjects from the International Subarachnoid Aneurysm Study. Ten of the patients were treated with coil embolization and 12 with surgical clipping. Costs included procedural costs (staffing and consumables) and postprocedural cost associated with the patient's stay in intensive care, general ward and rehabilitation ward. Because of the wide variation of costs among the patients, the median values were used. All costs were given in Australian currency. The analysis showed that endovascular procedure tended to have higher consumable costs. This expense was more than compensated by lower staffing costs, and lower costs of postprocedure hospitalization.(51)

Table 16: Cost Comparison for Coil Surgical Clipping and Coil Embolization (ISAT)

Costs	Neurosurgery (median)		Endovascular (median)	
Consumables (A$)	1,034		4,351	
Staffing (A$)	985		738	
Total Procedural (A$)	2,020		5,078	
Intensive care (A$)	10,068	(4 days)	11,327	(4.5 days)
General ward (A$)	4,476	(12 days)	2,984	(8 days)
Rehabilitation ward (A$)	10,819	(31 days)	5,933	(11.5 days)
Total Postprocedure (A$)	19,718		13,005	

Kallmes et al (52) applied a decision tree and Markov analyses to determine the incremental cost-utility ratio for coil embolization versus no therapy for unruptured intracranial aneurysms considered inappropriate for surgical clipping procedures. The cost-effectiveness ratios were calculated using the following formula:

Incremental cost-utility ratio = (cost of COIL embolization - cost of no therapy)/(utility of COIL embolization - utility of no therapy)

Clinical values required as input data were estimated from the literature. Utilities were quantified by using quality factors (1.0 for perfect health to 0.0 for death). Quality factors and time spent within a given health state are used to calculate quality-adjusted life years (QALYs) saved with COIL embolization versus no treatment. Simulations were performed for two coil embolization scenarios (A: unfavorable aneurysmal morphology; B: comorbid disease). Sensitivity analyses were also performed. All costs were given in American dollars and a discount rate of 5% was applied. Incremental cost-utility ratios below $50,000/QALY were considered acceptable.

The results showed that:

For scenario A, calculation using baseline input data yielded an incremental cost of $13,000, an incremental QALY of 0.56 and an incremental cost-utility ratio of $23,000/QALY.

For scenario B, calculation using baseline input data yielded an incremental cost of $10,000, an incremental QALY of 0.53 and an incremental cost-utility ratio of $19,000/QALY. These ratios were found to be acceptable.

Sensitivity analyses using wide ranges of various input parameters showed that the above ratios remained within the acceptable limits.

These analyses also showed that cost-effectiveness was markedly affected by the natural course of unruptured, untreated aneurysms; rates of spontaneous rupture greater than 2% per year resulted in favorable cost-utility ratios that were relatively unaffected by variation in coil embolization efficacy. Ruptured rates less than 1% per year resulted in unfavorable ratios that were highly dependent on coil embolization efficacy.

Coil embolization efficacy indexes such as rate of failed coiling, early recanalization and progressive aneurysmal thrombosis, have mild effects on the cost-utility ratios.

Coil embolization complication rate and life expectancy had moderate effects on the analysis.
The influence of late aneurysmal recanalization was mild unless high rates of rupture for partially coiled aneurysms were applied.

Suboptimal clip placement resulting from the presence of coils within a ruptured aneurysm had no demonstrable consequence on cost-utility rates.(52)

Johnston et al (53) used decision trees and Markov models to perform a comprehensive cost-utility analysis that compared surgical clipping and endovascular coil embolization to no treatment for asymptomatic unruptured intracranial aneurysms. Eight clinical scenarios were defined based on aneurysm size, symptoms, and history of SAH from different aneurysms. A Markov model for each of the treatment option was constructed to track the health outcomes of a hypothetical cohort of 50-year old women over the projected lifetime of the cohort. Patients were classified into four health states: healthy, mild disability (independent), moderate–severe disability (dependent) or dead. Yearly rates of SAH and all-cause mortality were applied to the cohort and the number of patients in each health state recorded for each year. The total cost and QALYS per hypothetical patient were totaled for each model. The net QALYs and cost per QALY of each therapy were compared to persons with no treatment.

The following assumptions were applied.

Surgical clipping is associated with an initial risk of death or disability due to surgical complications, but if the patient survives, it was assumed that there is no subsequent risk of SAH because the aneurysm is fully treated.

For endovascular coiling, the analysis included both an early, procedure-related risk and a delayed risk of SAH; lack of long-term follow-up raised the possibility that coil embolization reduces but does not eliminate risk of SAH.

Modeled all direct medical costs associated with the clipping and coiling procedures and with SAH (hospital, physician fees, outpatient, rehabilitation, and nursing home/home care) regardless of who pays.

The analyses showed that:

For an asymptomatic unruptured aneurysm <10 mm in diameter in patients with no previous history of SAH from a different aneurysm, both coil embolization and surgical clipping resulted in a net loss in QALYs. The confidence intervals were not compatible with a benefit from treatment, suggesting a worsening of clinical outcomes from treatment (loss of 1.6 QALY for clipping, [95% CI 1.1–2.1]; loss of 0.6 QALY for coiling [95% CI 0.2–0.8]). Sensitivity analysis showed that the rupture rate for the base case would need to be at least sevenfold higher for coiling and 15-fold higher for clipping before these treatments would reach a borderline cost-utility ratio of $100,000 per QALY.

For aneurysms that are >/=10mm or symptomatic, or in patients with a history of SAH, treatment appears to be cost-effective. Coiling appeared more effective and cost-effective than clipping but these differences depended on relatively uncertain model parameter. In univariate analysis, cost-effectiveness depended most sensitively on patient age and SAH rates of untreated aneurysms.

The studies evaluating costs are summarized in Appendix 14.

Ontario-Based Economic Analysis

Notes and Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analysis of technologies. The main cost categories and the associated methodology from the province's perspective are as follows:

Hospital: Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are ten or more hospital separations or one-third or more of hospital separations in the ministry's data warehouse are for the designated ICD-10 diagnosis and CCI procedure codes. Where appropriate, costs are adjusted for both hospital specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are utilized. Adjustments may need to be made to ensure that the relevant Case Mix Group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis/procedure, the MAS normally defaults to considering direct treatment costs only.

Historical costs have been adjusted upward by 3% per annum representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals. Non-Hospital: These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long Term Care, device costs from the perspective of local health care institutions and pharmaceutical costs from the Ontario Drug Benefit formulary list price. Discounting: For all cost-effective analysis, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and the Washington Panel of Cost-Effectiveness, respectively. Downstream cost savings: All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methodologies that have been explicitly stated above. These estimates will change if different assumptions and costing methodologies are applied for the purpose of developing implementation plans for the technology.

ICD-10: (International Classification of Diseases)
CCI: Canadian Classification of Health Interventions

Budget Impact

From an estimated 12.4 million Ontario residents in 2004 (54), there is an estimated annual incidence of intracranial aneurysms—asymptomatic, symptomatic but unruptured and ruptured--of between 1% and 4% of the population with an annual incidence of ruptured aneurysms at 0.01% (10 per 100,000). These incidence figures result in an estimate of between 125,000 and 500,000 intracranial aneurysms per year in the province of which approximately 1,230 ruptured. The total number of treated aneurysms is approximately 120% of the total number of ruptured aneurysms (Expert opinion). Also important with regard to coil embolization is that approximately 90% of intracranial aneurysms can be classified as saccular, berry, or congenital—potentially suitable for endovascular repair. Of 660 cerebral aneurysm repairs performed during FY 2004 in Ontario, 251 or 38% were treated by coil embolization which is considered to be near the minimum percentage that could benefit from this treatment. We assume that this percentage could increase to 60% of total cerebral aneurysm repairs by FY 2007 with the potential to increase to 450 cases per year (out of 750 total repairs) in the future if resources to do so were made available.

The largest component of cost differences between neurosurgical repair and endovascular repair involves differences in equipment costs. A neurosurgical clip costs approximately $300 and a controlled detachable coil costs $750 per coil (median value), with an average of 10 coils needed per procedure. An additional $10,000 is needed for a small percentage of cases that require a supporting stent in addition to the coils.

Based on device cost differences only, the direct incremental budget impact of increasing the current caseload of 251 rupture cases to 450 is approximately $1.5 million (=$7,500 * 199) for the added cases and $1.8 M (=$7,500 x. 251) for the current volume. If a 15% recurrence rate is factored in, the total incremental cost would be $3.8 M (($1.5 M + 1.8 M) x 1.15). There is also the one-time expenditure of approximately $3 million for a biplane angiosuite at each centre to properly engage in endovascular intracranial aneurysm repair; however, the number of new centres/suites that would be needed/demanded in the coming years is still unclear (there are currently 8 centres in the province). Costs of follow-up treatments were not included in these estimates.

All of these expenditures are offset partially by shorter operating room times and hospitalization stays for endovascular repair of unruptured aneurysms; however, the realization of these cost savings is probably not likely to be greater than 25% of the total outlay since the majority of cases involve ruptured aneurysms. For these cases, the total downstream cost savings from endovascular repair are likely to be minimal even though the savings for individual cases may be substantial due to lower perioperative complications for endovascular aneurysm repair.
Furthermore, the recent growth in aneurysm repair has predominantly been in the area of coil embolization presumably for patients for whom surgical clipping would not be advised; therefore, no offset of surgical clipping costs could be applied in such cases.

Cost-Effectiveness

The literature on cost-effectiveness indicates that treating unruptured aneurysms less than 10 mm in diameter by either technique is not effective or cost-effective when compared to no therapy, with a loss of 1.6 QALYs (95% CI 1.1 to 2.1 QALYs) from neurosurgical clipping and 0.6 QALYS from endovascular repair (95% CI 0.2 to 0.8 QALYs). (52) With larger unruptured aneurysms, or with a history of SAH of another aneurysm, both procedures had a CE ratio of less than $50,000 per QALY, with endovascular repair generally more favourable than neurosurgical clipping (however the ranges overlapped to a great degree). Regarding relative effectiveness between the two procedures in such cases, coiling produced between 0.9 and 1.0 greater QALYs than did neurosurgical clipping. (52) It should be noted that as techniques have improved from the time of the aforementioned study, the outcomes of endovascular repair may be greater such that asymptomatic aneurysm repair may now be considered potentially cost-effective. The biggest impact on the cost-effectiveness of endovascular repair is rupture rate of intracranial aneurysms, with rates of at least 2% producing favourable cost-effectiveness, while with rates of rupture lower than 1%, cost-effectiveness depends highly on surgical skill and effectiveness. Also of importance is life expectancy, with younger patients often experiencing higher cost-effectiveness ratios due to longer post-surgical life expectancy. (51)

Guidelines on Treatment of Intracranial Aneurysms

The most recent guidelines were published by the National Institute for Clinical Excellence of the United Kingdom. These are summarized below.

2005 Evidence-based Guidance on Ruptured Intracranial Aneurysm (NICE, United Kingdom)(55)

"Current evidence on the safety and efficacy of coil embolization of ruptured intracranial aneurysm appears adequate to support use of the procedure, provided that normal arrangements are in place for consent, audit, and clinical governance."

"The procedure should only be performed in specialist units with expertise in the endovascular treatment of intracranial aneurysms. Clear arrangements should be in place for the involvement of different clinical disciplines in treatment and follow-up."

"Patients with subarachnoid hemorrhage should have rapid access to appropriate specialist care."

2005 Guidance on Coil Embolization of Unruptured Intracranial Aneurysms (NICE, United Kingdom)(56):

This guidance states that:

“Current evidence suggests that coil embolization is efficacious in obliterating unruptured intracranial aneurysms and that its safety is similar to that of surgical treatment.”

“….the decision to treat unruptured intracranial aneurysms by coil embolization requires judgement of the risks for each patient, and recognition of the importance of patient choice. Clinicians wishing to undertake this procedure should ensure that:

Normal arrangements are in place for audit and clinical governance
Patients understand the relative risks of coil embolization and surgery compared to the risk of having no treatment when giving their consent for this treatment.”

“The procedure should only be performed in specialist units with expertise in the endovascular treatment of intracranial aneurysms.”

Guidelines Issued before the publication of the ISAT results:

Two other guidelines were found, and both were issued before the publication of the ISAT results.

2000 Recommendation for the Management of Patients with Unruptured Intracranial Aneurysm (UIA): A Statement for Healthcare Professionals from the Stroke Council of the American Heart Association (6)

Recommendations:

The existing body of knowledge supports the following recommendations (options) regarding the treatment of UIAs:

1. The treatment of small incidental intracavernous ICA aneurysms is not generally indicated. For large symptomatic intracavernous aneurysms, treatment decisions should be individualized on the basis of patient age, severity, and progression of symptoms, and treatment alternatives. The higher risk of treatment and shorter life expectancy in older individuals must be considered in all patients and favors observation in older patients with asymptomatic aneurysms.

2. Symptomatic intradural aneurysms of all sizes should be considered for treatment, with relative urgency for the treatment of acutely symptomatic aneurysms. Symptomatic large or giant aneurysms carry higher surgical risks that require a careful analysis of individualized patient and aneurysmal risks and surgeon and center expertise.

3. Coexisting or remaining aneurysms of all sizes in patients with SAH due to another treated aneurysm carry a higher risk for future hemorrhage than do similar sized aneurysms without a prior SAH history and warrant consideration for treatment. Aneurysms located at the basilar apex carry a relatively high risk of rupture. Treatment decisions must take into account the patient’s age, existing medical and neurological condition, and relative risks of repair. If a decision is made for observation, reevaluation on a periodic basis with CT/MRA or selective contrast angiography should be considered, with changes in aneurysmal size sought, although careful attention to technical factors will be required to optimize the reliability of these measures.

4. In consideration of the apparent low risk of hemorrhage from incidental small (<10 mm) aneurysms in patients without previous SAH, treatment rather than observation cannot be generally advocated. However, special consideration for treatment should be given to young patients in this group. Likewise,

small aneurysms approaching the 10-mm diameter size, those with daughter sac formation and other unique hemodynamic features, and patients with a positive family history for aneurysms or aneurysmal SAH deserve special consideration for treatment. In those managed conservatively, periodic follow-up imaging evaluation should be considered and is necessary if a specific symptom should arise. If changes in aneurysmal size or configuration are observed, this should lead to special consideration for treatment.

5. Asymptomatic aneurysms of ≥10 mm in diameter warrant strong consideration for treatment, taking into account patient age, existing medical and neurological conditions, and relative risks for treatment.

2002 Recommendations for the Endovascular Treatment of Intracranial Aneurysms: A Statement for Health Care Professionals from the Committee on Cerebrovascular Imaging of the American Heart Association Council on Cardiovascular Radiology (57)

The major recommendations were:

Given the absence of data from randomized trials, all recommendations are based on expert opinion. Endovascular coil embolization is an option for treatment of ruptured and unruptured intracranial aneurysms. Special consideration for coil embolization should be given when surgery is impossible or is high risk. This may include patients with aneurysms in the posterior circulation. Results of a randomized trial are required to define the appropriate role of endovascular coil embolization in the treatment of patients who are candidates for surgery.

Endovascular occlusion of the artery from which an aneurysm arises is a treatment option when an aneurysm cannot be treated directly with surgery or endovascular coil embolization and when that aneurysm is at high risk for subsequent rupture or when neurological symptoms are progressive.
All patients whose aneurysms are treated by coil embolization should have follow-up catheter angiography performed 1 to 6 months after initial treatment. Follow-up imaging should occur sooner in patients with aneurysms that are not completely occluded. Subsequent angiography should be performed in patients whose aneurysms remain incompletely occluded.

Synopsis of Findings

Safety

Coil embolization of intracranial aneurysms appears to be safe.

Technical complications associated with coil embolization ranged from 8.6% to 18.6% with a median of about 10.6%.

Permanent complication rates were lower in coil embolization (3.7%) than in surgical clipping (10.9%).

The most common complications were perforation of the aneurysm, ischemic deficit, thrombo-embolic events, intraoperative rupture, parent artery occlusion, collapsed coils, coil migration, and coil malposition.

Neurological complications, hemiparesis, and transfusion of red blood cells occurred significantly less frequently in patients with unruptured aneurysms treated with coil embolization rather than with surgical clipping.

Clinical Outcomes: Ruptured Aneurysms

Randomized controlled trials showed that for ruptured intracranial aneurysms with SAH, suitable for both coil embolization and surgical clipping (mostly saccular aneurysms <10 mm in diameter located in the anterior circulation) in people with good clinical condition:

Coil embolization resulted in a statistically significant 23.9% relative risk reduction and 7% absolute risk reduction in the composite rate of death and disability compared to surgical clipping (modified Rankin score 3–6) at 1-year.

The advantage of coil embolization over surgical clipping varies widely with aneurysm location, but endovascular treatment seems beneficial for all sites.

There were less deaths in the first 7 years following coil embolization compared to surgery clipping (10.8% vs 13.7%) that seemed to be consistent over time, and was significant (log-rank p= 0.03).

Coil embolization is associated with less frequent MRI-detected superficial brain deficits and ischemic lesions at 1-year.

The 1- year rebleeding rate was 2.2% after coil embolization and 1% for surgical clipping. Confirmed rebleeding from the repaired aneurysm after the first year and up to year eight was low and not significantly different between coil embolization and surgical clipping (7 patients for coil embolization vs 2 patients for surgical clipping, log-rank p=0.22).

Observational studies showed that:

Patients with SAH and good clinical grade had better 6-month outcomes and lower risk of symptomatic cerebral vasospasm after coil embolization compared to surgical clipping.

The short-term clinical outcome (GOS and rate of delayed ischemic neurological deficits) of patients with SAH depends on their clinical grade on admission. Patients with SAH and good clinical grade had better 6-month outcomes and lower risk of symptomatic cerebral vasospasm after coil embolization compared with surgical clipping.

Ruptured aneurysms treated with coil embolization within 6 days of SAH had better overall outcomes than those treated after 6 days.

Clinical Outcomes: Unruptured Aneurysms

The annual risk of rupture in unruptured aneurysms less than 10mm in diameter is about 0.05% per year for patients with no previous history of SAH from other aneurysms. The risk of aneurysm rupture is 10 times higher (0.5%) in patients with similar size aneurysms and a previous history of SAH. The risk of rupture for larger aneurysms approaches 1%.

There is no direct RCT comparison between coil embolization and surgical treatment of unruptured intracranial aneurysms.

Based on observational studies: In hospital mortality rate following treatment of unruptured aneurysm was 0.5% to 1.7% for coil embolization and 2.1% to 3.5% for surgical clipping. One-year mortality rate was 3.1% for coil embolization and 2.3% for surgical clipping and 1-year morbidity was 6.4% for coil embolization and 9.8% for surgical clipping. It is not clear whether these differences were statistical significant.

For unruptured aneurysms, coil embolization is associated with shorter hospital stay and lower composite rate of in-hospital death and discharge to any facility other than home following coil embolization was lower than that of surgical clipping (10.6% vs 18%, p=0.002). The improvement in discharge disposition was highest in people older than 65 years.

Clinical Outcome: Ruptured and Unruptured Aneurysms

The rates of mortality and morbidity after coil embolization are not dependent on age, contrary to surgical clipping, which showed worse outcomes in patients older than 64years.

The long-term durability of coil embolization has not been established.(26)(27)(27)(149)(27)(28)(29)(29)(29)(26)(28) Controlled detachable coils resulted in lower aneurysm obliteration but better functional outcome than pushable coils.

Aneurysm Obliteration

Coil embolization occludes intracranial aneurysms less efficiently than does surgical clipping. Total occlusion was achieved in a median of 55% of coiled aneurysms (range 28%–79%) compared to about 86% to 100% of surgically clipped aneurysms. (15;17;27)

The rate of total occlusion appears to be better for small aneurysms (less than 10 mm in diameter) with a small neck (less than or equal to 4 mm wide) (70.8%) than for large aneurysms (35%) or small aneurysms with a wide neck (31.2%). (20)

Secondary spontaneous embolization has been observed after the initial procedure.

Intracranial aneurysms that achieved total occlusion at 1 year were more likely to be stable in the long-term.

Intracranial aneurysms with an immediate occlusion of less than 80% or with a loss of morphology during follow-up required repeat treatment and further follow-up.

Recurrence and Rerupture

Recurrences have occurred in aneurysms that have been totally occluded by coil embolization for more than 3 years.

The rate of recurrence ranged from 14.7% to 39% in ruptured aneurysms and from 7% to 27% in unruptured aneurysms compared with a recurrence rate of 1.5% over 4 to 5 years after a surgically clipped aneurysm.

Major recurrences were found in 20% of all patients treated with coil embolization, and about 50% of these were serious enough to require treatment. The rerecurrence rate after reintervention was about 49%.

The risk factors for recurrence of intracranial aneurysms after coil embolization are treatment during the acute phase of rupture, an aneurysm bigger than 10 mm in diameter, neck size wider than 4 mm, incomplete occlusion, and duration of follow-up.

The rerupture and rebleeding rates were reported to be from 0% to 2.2% for coil embolization and 0% to 0.17% per patient per year for surgical clipping at 6 months.(7;20).

Clinical Outcomes: High-Risk Intracranial Aneurysms

In the short-term, endovascular coil embolization appears to be safe and effective in treating posterior circulation aneurysms, paraclinoid aneurysms, and basilar aneurysms that are in areas with difficult access or poor visualization. Some of these aneurysms would not otherwise have been treated.

Coil embolization improved the treatment of ruptured posterior aneurysms by reducing the number of untreated patients, significantly lowering the mortality rate, and improving overall outcomes.

The incidence of recurrence after coil embolization of posterior circulation aneurysm is substantial in wide neck or incompletely occluded posterior circulation aneurysms.

Limitations of Endovascular Coil Embolization

Endovascular treatment offers less assurance of a permanent cure than surgical clipping because of the low complete obliteration rate, and possible coil compaction, especially in giant or thrombotic aneurysms, and aneurysms with a wide neck. It is not clear whether patients with partially occluded aneurysms are still subject to the same risk as patients with unsecured but ruptured aneurysms.

Patients undergoing endovascular procedure require heparin. Long-term postoperative anticoagulation is needed to avoid embolic complications. The impact of short-term heparin in poor-grade patients has not been studied.

Studies have shown that although coil embolization is an alternative to some patients that are at high surgical risk, only select patients with the appropriate aneurysm anatomy are suitable candidates.

Because coil embolization is performed under fluoroscopic guidance, the lengthy x-ray exposure and the ongoing angiographic follow-up are additional concerns.

Limitations of Surgical Clipping

The risks of surgical clipping are associated with the retraction of the brain and dissection or isolation of small vessels and nerves adhering to the aneurysmal sac. There are also risks of mechanical injury to surrounding normal tissues from the surgical maneuver. These risks increase with the treatment of deep-seated anatomically complicated aneurysms, such as those involving the paraclinoid and cavernous, internal carotid and the vertebrobasilar system aneurysms.(35)

Surgical clipping may not be feasible for patients with serious potential problems such as hemorrhagic tendencies, or a high-risk profile for general anesthesia.

Costs and Cost-Effectiveness

A few studies have reported that coil embolization of intracranial aneurysm costs less than surgical clipping. One analysis showed that for ruptured aneurysms, the procedure cost of coiling is higher than clipping, but the total cost of coiling is less than clipping because of shorter hospital stays after treatment. Markov analysis showed that neither surgical clipping nor coil embolization is cost-effective for treating unruptured intracranial aneurysms less than 10 mm in patients with no previous history of SAH from another aneurysm.

For aneurysms that are 10mm or greater or are symptomatic, or in patients with a history of SAH, treatment appears to be cost-effective. Coil embolization appears to be more effective and cost-effective than clipping, but these differences are based on relatively uncertain model parameters and are highly dependent on patient age and SAH rates of untreated aneurysms.

Literature search failed to identify any economic analysis on coil embolization of ruptured intracranial aneurysm or Ontario-based economic studies on coil embolization.

Existing Guidelines

Guidance issued by the National Institute of Clinical Excellence (UK) in 2005 supports the use of coil embolization for both unruptured and ruptured (SAH) intracranial aneurysms provided that procedures are in place for informed consent, audit, and clinical governance, and that the procedure be performed in specialist units with expertise in the endovascular treatment of intracranial aneurysms.

Policy Considerations

Regulation

Health Canada has approved numerous endovascular coils and delivery systems for coil embolization procedures in the brain. (see Appendix 4).

Clinical Expertise Available in the Geographic Region

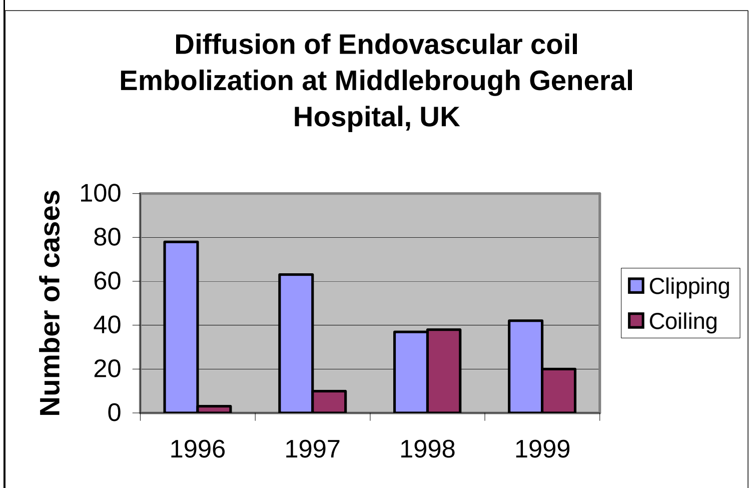
Evidence shows that early treatment of ruptured intracranial aneurysms is necessary to prevent another hemorrhage and, therefore, it may be better for the patient to be treated within the region rather than being transported out of the region, which would cause delay and negatively affect the patient's clinical status. The availability of clinical expertise available in the patient's geographic region would likely have some influence on the modality of treatment chosen.

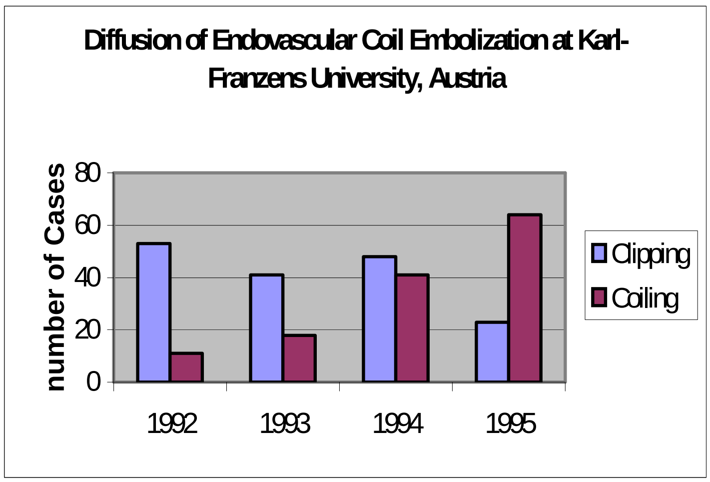
Diffusion

Information from Europe and the United States indicates that coil embolization of intracranial aneurysm has diffused rapidly since the mid 1990s. For example, in the United Kingdom, 30% of intracranial aneurysms were treated endovascularly in 1998. This was predicted to rise to 44% in 2003.(44)

Figures 2a and 2b illustrate the diffusion of coil embolization at the Middlesbrough Hospital in the United Kingdom and the Karl-Pranzens University in Austria.(44); (19)

Figure 2: Diffusion of Coil Embolization at a British Hospital (2a) and an Austrian Hospital (2b)





At the Mayo Clinic, 5% (11) of the patients with aneurysmal SAH were treated endovascularly before 1996. Between 1996 and 2000, 27% (58) of 215 patients treated for SAH at the same institution underwent endovascular coil embolization.(11)

In Ontario, utilization data show that the overall uptake of coil embolization in the province is close to 40% of all intracranial aneurysm treatments (Table 17). The uptake is likely higher in major neurointerventional centres in the province. Diffusion of coil embolization in the province is probably moderated by the high cost of devices for coil embolization, which is being covered by hospitals' global budgets. The professional fee is the same for both open surgical and endovascular repair. It should be noted that recent increases in the number of MRI scanners in the province has led to an upswing in the number of asymptomatic intracranial aneurysms being detected secondarily to the initial indication for the scan. These are often referred for treatment (Source: Expert consultants). With the 2005 publication of the ISAT results (26) which show survival benefits from coil embolization up to seven years after the procedure, the pressure for increasing the use of coil embolization will likely continue to escalate.

TABLE 17: CURRENT INFORMATION ON THE UTILIZATION OF COIL EMBOLIZATION IN ONTARIO

	2003/2004	2004/2005
Total number of cerebral aneurysm repairs	594	660
Total number of cerebral repair by coil embolization	202	251
% of cerebral repair by coil embolization	34%	38%

Coil embolization performed in Ontario in Fiscal Year 2004-2005 by Hospital

	Number	%
St. Michael's Hospital	39	16%
Hamilton Health Sciences Centre	18	7%
Hotel Dieu, Windsor	2	1%
London Health Science Centre	35	14%
University Health Network	60	24%
Trillium Health Centre	20	8%
Sunnybrook & Women's Health Science Centre	8	3%
Ottawa Hospital -Civic	69	27%
Total	251	100%

Multidisciplinary Team Approach

Evidence suggests that endovascular embolization and surgical clipping are complementary technologies. The randomized ISAT protocol (25) required all patients to be evaluated by both a neurosurgeon and an endovascular specialist (e.g. an interventional neuroradiologist). This multidisciplinary team approach is believed to be key to selecting the most appropriate treatment approach, and improving outcomes of aneurysm treatment. This means that coil embolization should only be performed in centres with expertise in both neurosurgery and endovascular neurointerventions.

Learning Curve and Critical Volume

Studies have shown a learning curve effect in the performance of coil embolization of intracranial aneurysms.

In a large cohort study in the United States, Barker et al. (31) found diversity in the quality of endovascular treatment of unruptured intracranial aneurysms among the 469 hospitals involved, on the basis of hospital and surgeon caseload.

Singh et al. (58) analyzed the impact of physician experience on the rates of procedure-related complication rates of 94 patients treated with coil embolization for unruptured aneurysm. A procedure-related complication was defined as an adverse event that was clearly a result of the procedure and that led to prolonged hospitalization or a change in the Rankin Scale score of 1 or more points at discharge. The results showed that the risk of complications decreased from 53% of the first 5 cases that each of the three physicians treated to 10% of the later cases ($p<0.001$). After adjusting for all other predictors, the odds of a complication decreased with increasing physician experience (odds ratio, 0.69 for every 5 cases treated; 95% CI: 0.50–0.96; $p=0.03$). This corresponds to a 30% odds reduction in complication for every 5 cases treated. Singh et al. (58) cautioned that this may not be generalized to other centres because the physicians involved in the study were already highly experienced in other endovascular techniques at the study onset.

When planning the distribution of endovascular and surgical services, it is necessary to ensure an adequate volume of such procedures at each centre for the physicians to acquire and maintain their expertise. Evidence supports centralizing coil embolization to a few provincial centres that have the equipment and expertise to perform both surgical clipping and coil embolization.

Resource Implications

Cost is likely one of the factors moderating the diffusion of the technology. Endovascular coiling requires a biplane angiography suite that costs $3 million. The cost of the devices for coil embolization is also considerable. There is, however, evidence that endovascular embolization may reduce the demands on hospital and short-term rehabilitation beds after the treatment of unruptured aneurysms because of shorter lengths of stay.

Informed Consent

Although endovascular coils and delivery systems have been licensed by Health Canada for the treatment of intracranial aneurysms, patients should be informed of the risks associated with surgical clipping and coil embolization before giving consent, because the long-term outcome of coil embolization is unknown.

Conclusion

For people in good clinical condition following subarachnoid hemorrhage from an acute ruptured intracranial aneurysm that is suitable for either surgical clipping or endovascular repair, coil embolization results in better independent survival in the first year, improved survival for up to seven years, and low rebleeding rates after the first year. However, there is uncertainty regarding the long-term occlusion status, durability of the stent graft, and long-term complications.

For people with unruptured aneurysms, level 4 evidence suggests that coil embolization may be associated with comparable or less mortality and morbidity, shorter hospital stay, and less need for discharge to short-term rehabilitation facilities. The greatest benefit was observed in people over 65 years of age. In these patients, the decision regarding treatment needs to be based on the assessment of the risk of rupture against the risk of the procedure, as well as the morphology of the aneurysm.

In people who require treatment for intracranial aneurysm, but for whom surgical clipping is too risky or not feasible, coil embolization provides survival benefits over surgical clipping, even though the outcomes may not be as favourable as in people in good clinical conditions and have small aneurysms. The procedure may be considered under the following circumstances provided that the aneurysm is suitable for coil embolization:

- Patients in poor/unstable clinical or neurological state
- Patients at high risk for surgical repair (e.g. people>age 65 or with comorbidity), or
- Aneurysm(s) with poor accessibility or visibility for surgical treatment due to their location (e.g. ophthalmic or basilar tip aneurysms)

Compared to small aneurysms with a narrow neck in the anterior circulation, large aneurysms (> 10 mm in diameter), aneurysms with a wide neck (>4mm in diameter), and aneurysms in the posterior circulation have lower occlusion rates and higher rate of hemorrhage when treated with coil embolization.

The extent of aneurysm obliteration after coil embolization remains lower than that achieved with surgical clipping. Aneurysm recurrences after successful coiling may require repeat treatment with endovascular or surgical procedures. Experts caution that long-term angiographic outcomes of coil embolization are unknown at this time. Informed consent and long-term follow-up after coil embolization are recommended.

The decision to treat an intracranial aneurysm with surgical clipping or coil embolization needs to be made jointly by the neurosurgeon and neuro-intervention specialist, based on the clinical status of the patient, the size and morphology of the aneurysm, and the preference of the patient.

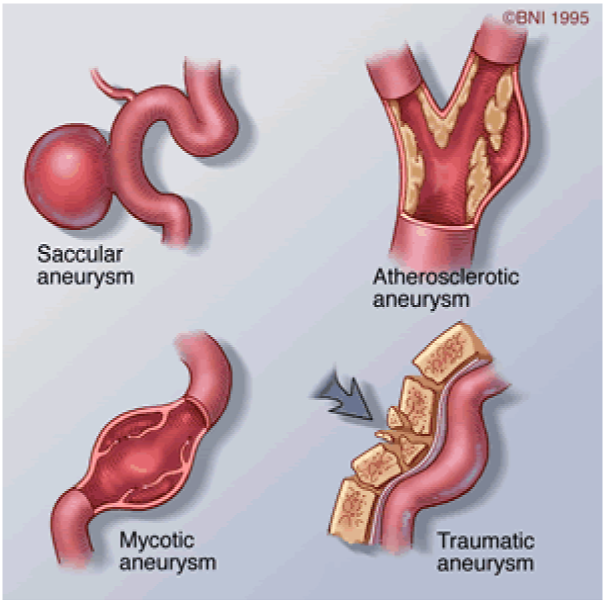
The performance of endovascular coil embolization should take place in centres with expertise in both neurosurgery and endovascular neuro-interventions, with adequate treatment volumes to maintain good outcomes. Distribution of the technology should also take into account that patients with SAH should be treated as soon as possible with minimal disruption.

Glossary

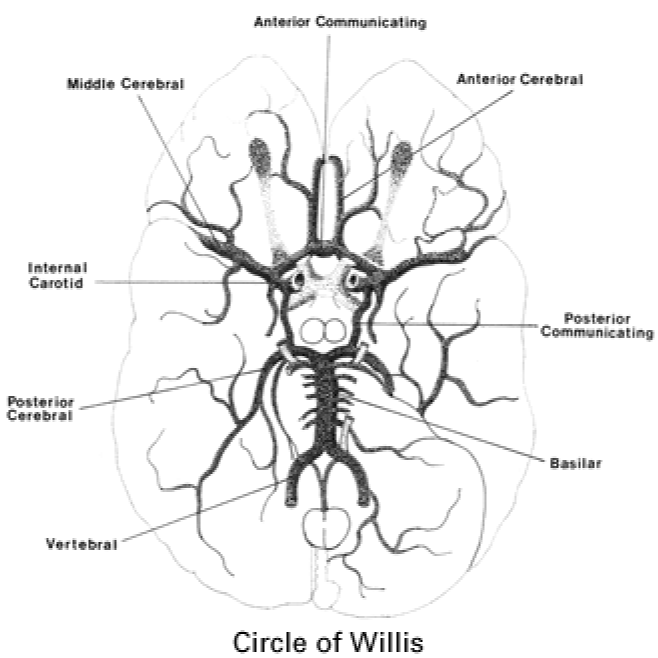
Atherosclerosis	A common form of arteriosclerosis in which deposits of yellowish plaques containing cholesterol, lipoid material, and lipophages are formed within the intima and inner media of large and medium-sized arteries
Coil embolization	Introduction of microcoils into a vessel in order to occlude it.
Fisher Grade	A system for grading the extent of subarachnoid bleeding in a computed tomography scan
Glasgow Outcome Score (GOS)	A scale used to describe outcome after serious head injury, based on the general level of social functioning regained.
Endovascular	Within a vessel
Hunt and Hess Classification	A system for grading the clinical status of a person with intracranial aneurysm
Hyponatremia	Deficiency of sodium in the blood
Hydrocephalus	An accumulation of water in the brain
Intracranial aneurysm	An abnormal, localized dilatation that bulges or balloons out of an artery supplying blood to the brain
Procedure-related morbidity	Neurological deficit lasting >7 days that was attributable to the coil embolization
Rankin Score	A 6-point scale to define the degree of a patient's functional disability and assess neurologic disability
Subarachnoid hemorrhage	Bleeding into the fluid-filled spaces surrounding the brain
Subdural bleeding	Bleeding into the area between the dura mater and the arachnoid
Vasospasm	Narrowing of the artery at the base of the brain following subarachnoid hemorrhage; may result in symptomatic ischemia and infarction
World Federation of Neurological Surgeons Scale (WFNS)	A system used to measure the level of consciousness following subarachnoid hemorrhage

Appendices

Appendix 1: Types and Locations of Intracranial Aneurysms

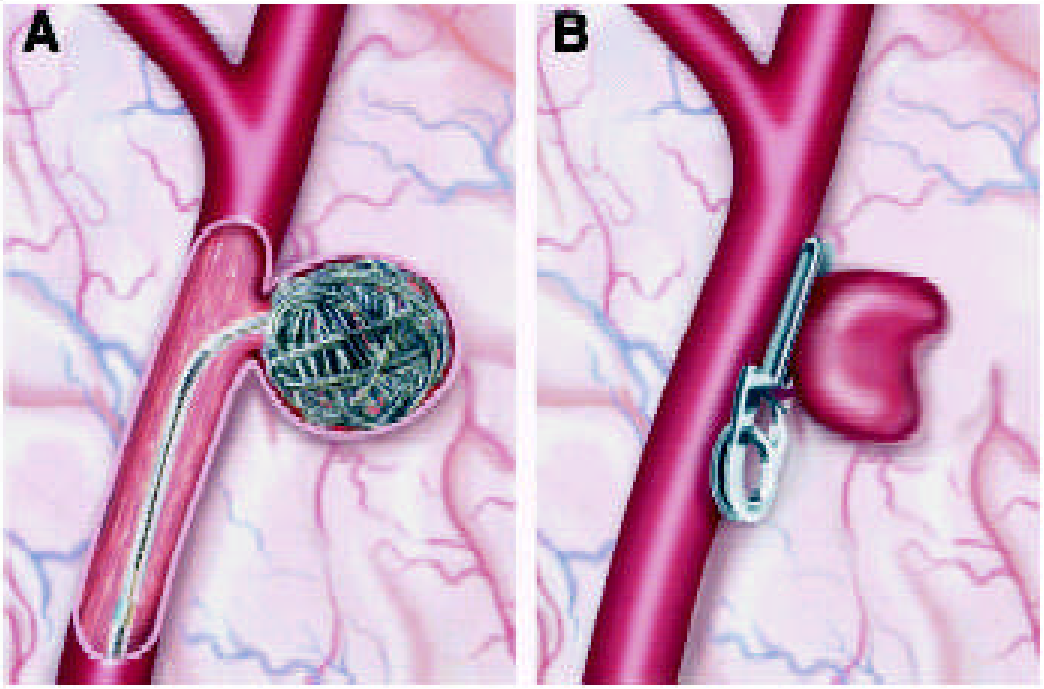


From the Barrow Neurological Institute; available at:
http://www.thebni.com/index.asp?catid=oc&pg=lc_aneur_types&supnav=lc_aneur_supnav



From: Micrus Endovascular; available at:
http://www.micrusendovascular.com/phyinfo.html

Appendix 2: Illustration of Coil Embolization and Surgical Clipping of Intracranial Aneurysm



A. Coil Embolization B. Surgical Clipping

(Reproduced with permission from John Wiley & Sons; Johnston et al, Annals of Neurology 2000; 48(1):11–19)(1)

Appendix 3: Original Glasgow Outcome score

Grade		Clinical Condition at Presentation
GOS - 5	Good recovery	Resumption of normal lifestyle, despite possible minor neurobehavioural or neurophysical sequelae. Implies the capacity to return to work.
GOS - 4	Moderate disability	Capacity of independence in performing daily activities. Can use public transport and work in a sheltered environment.
GOS - 3	Severe Disability	Dependent upon others for daily support due to neurophysiological or physical disability. May be institutionalized, but not necessarily (family support may be available).
GOS - 2	Persistent vegetative state	Exhibit cycles of sleeping and waking with eye opening, but are unresponsive to commands, speechless, and do not demonstrate cognitive functions
GOS - 1	Dead	Dead

From: Vindlacheruvu RR, Crossman JE, Dervin JE, Kane PJ. The impact of interventional neuroradiology on service in a neurosurgical unit. British Journal of Neurosurgery 2003; Vol 17(2):-159. (44)

Appendix 4: Embolization Coils and Delivery Systems Licensed as Class 4 Device in Canada as of February 23, 2006

Embolization Coils			February 23, 2006
Company Name	Licence	Licence Name	Indications
BOSTON SCIENTIFIC CORPORATION	1106	PLATINUM COILS	DESIGNED TO OBSTRUCT OR REDUCE BLOOD FLOW IN THE PERIPHERAL AND NEUROVACULATURE. THE DEVICES ARE INTENDED FOR USE IN THE INTERVENTIONAL RADIOLOGIC MANAGEMENT OF ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAS WHEN DEVACULARISATION PRIOR TO DEFINITIVE SURGICAL RESECTION IS DESIRABLE.
	1155	CONTOUR EMBOLI ARTIFICIAL EMBOLIZATION DEVICE.	CONTOUR EMBOLI ARTIFICIAL EMBOLIZATION DEVICE
	1248	INTERLOCKING DETACHABLE COIL	DESIGNED TO OBSTRUCT OR REDUCE BLOOD FLOW IN THE PERIPHERAL AND NEUROVASCULATURE. IN THE INTERVENTIONAL RADIOLOGIC MANAGEMENT OR ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAS WHEN DEVASCULARISATION PRIOR TO DEFINITIVE SURGICAL RESECTION IS DESIRABLE
	1249	BERENSTEIN LIQUID COIL	TO OBSTRUCT OR REDUCE BLOOD FLOW IN THE PERIPHERAL AND NEUROVASCULATURE. FOR USE IN THE INTERVENTIONAL RADIOLOGIC MANAGEMENT OR ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAS WHEN DEVASCULARISATION PRIOR TO DEFINITIVE SURGICAL RESECTION IS DESIRABLE.

1653	GDC-GUGLIELMI DETACHABLE COILS	THE GDC IN INTENDED FOR EMBOLIZING CERTAIN INTRACRANIAL ANEURYSMS THAT ARE CONSIDERED TO BE VERY HIGH RISK FOR MANAGEMENT BY TRADITIONAL OPERATIVE TECHNIQUES OR INOPERABLE AND DETACHED USING AN ENERGY SOURCE.
9527	FIBERED PLATINUM COIL	TO OBSTRUCT OR REDUCE RATE OF BLOOD FLOW IN THE PERIPHERAL AND NEUROVASCULATURE
15362	GDC-GUGLIELMI DETACHABLE COILS	INTENDED FOR EMBOLIZING CERTAIN INTRACRANIAL ANEURYSM THAT ARE CONSIDERED TO BE VERY HIGH RISK FOR MANAGEMENT BY TRADITIONAL OPERATIVE TECHNIQUES OR INOPERABLE AND FOR OTHER NEURO VASCULAR ABNORMALITIES SUCH AS ARTERIOVENOUS MALFORMATIONS & ARTERIOVENOUS FISTULAE. ALSO FOR ARTERIAL& VENOUS EMBOLIZATIONS IN THE PERIPHERAL VASCULAURE.
15364	PLATIUM COILS	DESIGNED TO OBSTRUCT OR REDUCE BLOOD FLOW IN THE PERIPHERAL AND NEUROVASCULATURE. THE DEVICES ARE INTENDED FOR USE IN THE INTERVENTIONAL RADIOLOGIC MANAGEMENT FO ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAS WHEN DEVASCULARISATION PRIOR TO DEFINITIVE SURGICAL RESECTION IS DESIRABLE.
18843	PLATINUM COILS	DESIGNED TO OBSTRUCT OR REDUCE BLOOD FLOW IN THE PERIPHERAL AND NEUROVASCULATURE. THE DEVICES ARE INTENDED FOR USE IN THE INTERVENTIOANL

		RADIOLOGIC MANAGEMENT OF ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAS WHEN DEVASCULARISATION PRIOR TO DEFINITIVE SURGICAL RESECTION IS DESIRABLE.
18914	FIBERED PLATINUM COIL	TO OBSTRUCT OR REDUCE RATE OF BLOOD FLOW IN THE PERIPHERAL AND NEUROVASCULATURE
18942	GDC - GUGLIELMI DETACHABLE COILS	INTENDED FOR EMBOLIZING CERTAIN INTRACRANIAL ANEURYSM THAT ARE CONSIDERED TO BE VERY HIGH RISK FOR MANAGEMENT BY TRADITIONAL OPERATIVE TECHNIQUES OR INOPERABLE. THE COILS ARE DETACHED USING AN ENERGY SOURCE .(GDC POWER SUPPLY)
26574	GDC-GUGLIELMI DETACHABLE COIL	INTENDED FOR EMBOLIZING CERTAIN INTRACRANIAL ANEURYSM THAT ARE CONSIDERED TO BE VERY HIGH RISK F OR MANAGEMENT BY TRADITIONAL OPERATIVE TECHNIQUES OR INOPERABLE. THE COILS ARE DETACHED USING AN ENERGY SOURCE. (GDC POWER SUPPLY)
27484	GDC TRISPAN COIL	INTENDED AS A SUPPLEMENTAL DEVICE FOR CONCURRENT USE WITH BOSTON SCIENTIFIC/TARGET'S GDC FAMILY OF DEVICES IN THOSE ANEURYSMS FOR WHICH USE OF GDC IS INDICATED, BUT WHOSE MORPHOLOGY MAY NOT ALLOW FOR ADEQUATE RETENTION OF COILS WITHIN THE ANEURYSMAL SAC.

	35479	MATRIX DETACHABLE COILS	INTENDED FOR EMBOLIZATION OF THOSE INTRACRANIAL ANEURYSMS THAT ARE CONSIDERED BY THE TREATING NEUROSURGICAL TEAM TO BE VERY HIGH RISK FOR MANAGEMENT BY TRADITIONAL OPERATIVE TECHNIQUES OR INOPERABLE AND FOR EMBOLIZATION OF OTHER NEURO VASCULAR ABNORMALITIES SUCH AS ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAE.
MICRO THERAPEUTICS INC	15133	ONYX LIQUID EMBOLIC SYSTEM	IS INDICATED FOR ENDOVASCULAR EMBOLIZATION OF ARTERIOVENOUS MALFORMATIONS. EMBOLLYX IS AN EJECTABLE LIQUID EMBOLIC AGENT COMPRISED OF ETHYLENE VINYL ALCOHOL COPOLYMER (EVOH) DISSOLVED IN DIMETHYL SULFOXIDE (DMSO) WITH MICRONIZED TANTALUM POWDER SUSPENDED IN THE POLYMER/SOLVENT SOLUTION TO PROVIDE CONTRAST FOR VISULIZATION UNDER FLUROSCOPY. FOR INTRA CRANIAL ANEURYSMS
	63475	EMBOLIZATION COILS	INTENDED FOR THE ENDOVASCULAR EMOBILIZATION TREATMENT OF INTRACRANIAL ANEURYSMS OR OTHER NEUROVASCULAR DISEASES INCLUDING ARTERIOVENOUS MALFORMATIONS OF THE BRAIN OR FISTULAS OF THE DURA MATER THAT BECAUSE OF THEIR MORPHOLOGY, THEIR LOCATION, OR THE PATIENTS GENERAL MEDICAL CONDITION

WILLIAM COOK EUROPE A/S, A COOK GROUP COMPANY	1336	JACKSON DETACHABLE EMBOLIZATION COILS	ARE USED FOR EMBOLIZATION OF SELECTIVE VESSEL SUPPLY TO ARTERIO-VENOUS MALFORMATIONS AND OTHER VASCULAR LESSIONS. SUPPLIED STERILE. ADDITION OF THE MREYE JACKSON DETACHABLE EMBOLIZATION COIL. THE COIL ITSELF IS MADE OF AN MRI COMPATIBLE MATERIAL CALLED INCONEL.
	1407	EMBOLIZATION COILS - MREYE	EMBOLIZATION OF SELECTIVE VESSEL SUPPLY TO ARTERIO-VENOUS MALFORMATIONS AND OTHER VASCULAR LESIONS. SUPPLIED STERILE.
	1457	EMBOLIZATION MICROCOILS - PLATINUM	EMBOLIZATION COILS ARE USED FOR EMBOLIZATION OF SELECTIVE VESSEL SUPPLY TO ARTERIO-VENOUS MALFORMATIONS AND OTHER VASCULAR LESIONS. SUPPLIED STERILE.
	13457	DETACH-11/18 EMBOLIZATION COIL SYSTEM	THE DETACHABLE EMBOLIZATION COIL SYSTEM CONSISTS OF AN INTRODUCER SYSTEM WITH A PREMOUNTED DETACHABLE PLATINUM COIL. THIS SYSTEM IS USED FOR INTERVENTIONAL NEURORADIOLOGY PROCEDURES.
	13458	EMBOLIZATION COILS FOR PDA CLOSURE	USED FOR THE OCCLUSION OF THE PATENT DUCTUS. THE DUCTUS ARTERIOSUS IS A LARGE MUSCULAR ARTERY THAT SHUNTS BLOOD FROM THE FETAL PULMONARY ARTERY TO THE AORTA.
CORDIS NEUROVASCULAR, INC.	22555	TRUFILL PUSHABLE COIL	USED TO REDUCE OR BLOCK THE RATE OF BLOOD FLOW IN SMALL OR TAPERING VESSELS. INDICATED FOR USE IN THE INTERVENTIONAL RADIOLOGIC MANAGEMENT OR ARTERIOVENOUS MALFORMATIONS AND OTHER LESIONS OF THE BRAIN, SPINAL CORD AND SPINE,

			WHEN DE-VASCULARIZATION PRIOR TO DEFINITIVE SURGICAL RESECTION IS DESIRED
	38687	TRUFILL DCS DETACHABLE COIL SYSTEM	IS INDICATED FOR EMBOLIZING CERTAIN INTRACRANIAL ANEURYSMS AND FOR EMBOLIZING OTHER VASCULAR MALFORMATIONS SUCH AS ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAE OF THE NEUROVASCULATURE. ALSO INTENDED FOR ARTERIAL AND VENOUS EMBOLIZATION IN THE PERIPHERAL VASCULATURE.
	63169	TRUFILL DCS ORBIT DETACHABLE COILS	INTENDED FOR EMBOLIZING CERTAIN INTRACRANIAL ANEURYSMS AND FOR EMBOLIZING OTHER VASCULAR MALFORMATIONS SUCH AS ARATERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAE OF THE NEUROVASULATURE
COOK INCORPORATED, A COOK GROUP COMPANY	658	GIANTURCO-GRIFKA VASCULAR OCCLUSION DEVICE	STERILE , ONE-TIME USE DEVICE USED TO OCCLUDE SELECTIVE VESSEL SUPPLY TO ARTERIOVENOUS MALFORMATIONS OR OTHER VASCULAR ABNORMALITIES.
	1350	DETACHABLE EMBOLIZATION COILS	EMBOLIZATION COILS ARE USED FOR ARTERIAL AND VENOUS EMBOLIZATION. SUPPLIED STERILE. INTENDED FOR ONE-TIME USE.
	1357	EMBOLIZATION COILS	EMBOLIZTION COILS ARE USED FOR ARTERIAL AND VENOUS EMBOLIZATION. SUPPLIED STERILE. INTENDED FOR ONE-TIME USE.
	1396	EMBOLIZATION COILS	EMBOLIZATION COILS ARE USED FOR ARTERIAL AND VENOUS EMBOLIZATION. SUPPLIED STERILE. INTENDED FOR ONE-TIME USE.

	2829	HILAL EMBOLIZATION MICROCOILS	EMBOLIZATION COILS ARE USED FOR ARTERIAL AND VENOUS EMBOLIZATION. SUPPLIED STERILE.
	66349	MREYE EMBOLIZATION COILS	EMBOLIZATION COILS DESIGNED FOR ARTERIAL AND VENOUS VESSEL EMBOLIZATION PROCEDURES.
MICRUS ENDOVASCULAR CORPORATION	29118	MICRUS MICROCOIL SYSTEM	IS USED FOR THE ENDOVASCULAR EMBOLIZATION OF INTRACRANIAL ANEURYSMS. INDICATION FOR USE FOR ALL INTRACRANIAL ANEURYSMS
MICROVENTION, INC.	61528	MICROPLEX COIL SYSTEM (MCS)	INTENDED FOR EMBOLIZATION OF INTRACRANIAL ANEURYSMS. ALSO INTENDED FOR EMBOLIZATION OF ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAE AND FOR ARTERIAL AND VENOUS EMBOLIZATIONS IN THE PERIPHERAL VASCULATURE.
	61530	HYDROCOIL EMBOLIC SYSTEM (HES)	INTENDED FOR EMBOLIZATION INTRACRANIAL ANEURYSMS, ALSO INTENDED FOR EMBOLIZATION OF ARTERIOVENOUS MALFORMATIONS AND ARTERIOVENOUS FISTULAE AN FOR ARTERIAL AND VENOUS EMBOLIZATIONS IN THE PHERIPHERAL VASCULATURE

Appendix 5a: Search Strategy (2003)

Search date: October 22, 2003
Databases searched: Cochrane, INAHTA, MEDLINE, EMBASE, and MEDLINE In-Process and Not Yet Indexed Citations (formerly PREMEDLINE) (INAHTA and Cochrane databases searched extensively by keyword and results sent separately; PREMEDLINE searched by keyword.)

Database: MEDLINE <1966 to October Week 3 2003>
Search Strategy:
----
1 coil$ emboli$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (745)
2 (Guglielmi adj2 coil).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (129)
3 endovascular coil emboli$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (40)
4 endovascular coil treatment.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (1)
5 (coil$ adj2 treatment).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (229)
6 endovascular coil occlusion.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (17)
7 (emboli$ adj2 treatment).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (1829)
8 exp Embolization, Therapeutic/ (13233)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (14369)
10 exp Intracranial Aneurysm/ (13183)
11 cerebral artery aneurysm.mp. (301)
12 cerebral aneurysm.mp. (1010)
13 *aneurysm, ruptured/ (1758)
14 exp subarachnoid hemorrhage/ (9845)
15 10 or 11 or 12 or 13 or 14 (20008)
16 9 and 15 (1128)
17 limit 16 to (human and english language and yr=1998-2003) (764)
18 Case Report/ (1108549)
19 17 not 18 (386)
20 limit 19 to (comment or editorial or letter or review or review, academic or review, multicase or review, tutorial or review literature or review of reported cases) (97)
21 19 not 20 (289)

Database: EMBASE <1988 to 2003 Week 42>
Search Strategy:
----
1 coil$ emboli$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (728)
2 (Guglielmi adj2 coil).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (146)
3 endovascular coil emboli$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (43)
4 endovascular coil treatment.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1)

5 (coil$ adj2 treatment).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (227)
6 endovascular coil occlusion.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (21)
7 (emboli$ adj2 treatment).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1166)
8 exp Artificial Embolism/ (11278)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (11957)
10 exp Intracranial Aneurysm/ (5798)
11 cerebral artery aneurysm.mp. (210)
12 cerebral aneurysm.mp. (639)
13 *aneurysm, ruptured/ (1425)
14 exp subarachnoid hemorrhage/ (6885)
15 10 or 11 or 12 or 13 or 14 (11645)
16 9 and 15 (1012)
17 limit 16 to (human and english language and yr=1993-2003) (748)
18 Case Report/ (544642)
19 17 not 18 (441)
20 limit 19 to (comment or editorial or letter or review or review, academic or review, multicase or review, tutorial or review literature or review of reported cases) [Limit not valid in: EMBASE; records were retained] (68)
21 19 not 20 (373)

Appendix 5b: Search Strategy (2006)

Search date: January 9, 2006
Databases searched: Cochrane DSR and CENTRAL, INAHTA, OVID Medline, Embase, and Medline In-Process and Not Yet Indexed Citations (INAHTA, Cochrane, and In-Process databases searched by keyword.)

Database: Ovid MEDLINE(R) <1966 to December Week 4 2005>
Search Strategy:
----
1 exp Intracranial Aneurysm/ (14274)
2 exp Subarachnoid Hemorrhage/ (10680)
3 (cerebral adj2 aneurysm).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1526)
4 or/1-3 (20914)
5 exp Embolization, Therapeutic/ (15358)
6 coil$ emboli$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (972)
7 (Guglielmi adj2 coil).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (156)
8 (emboli$ adj2 treatment).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (593)
9 endovascular coil occlusion.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (24)
10 or/5-9 (15872)
11 4 and 10 (1342)
12 limit 11 to (humans and english language and yr="2004 - 2006") (230)

13 limit 12 to meta analysis (0)
14 (systematic review$ or systematic overview$ or metaanalysis or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (25749)
15 12 and (13 or 14) (1)
16 limit 12 to (case reports or comment or editorial or letter or "review") (134)
17 12 not 16 (96)
15 or 17 (97)

Database: EMBASE <1996 to 2006 Week 01>
Search Strategy:
----
1 exp Intracranial Aneurysm/ (5121)
2 exp Subarachnoid Hemorrhage/ (5907)
3 ((cerebral or intracranial) adj2 aneurysm).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2555)
4 or/1-3 (9266)
5 exp Coil Embolization/ (707)
6 coil$ emboli$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1368)
7 (Guglielmi adj2 coil).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (193)
8 (emboli$ adj2 treatment).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1039)
9 endovascular coil occlusion.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (25)
10 or/5-9 (2434)
11 4 and 10 (596)
12 limit 11 to (human and english language and yr="2004 - 2006") (202)
13 Meta Analysis/ (20888)
14 exp "Systematic Review"/ (7704)
15 12 and (13 or 14) (3)
16 12 (202)
17 limit 16 to (editorial or letter or note or "review") (64)
18 16 not 17 (138)
19 15 or 18 (140)
20 Case Report/ (383194)
21 19 not 20 (83)

Appendix 6: Angiographic Efficacy of Endovascular Coil Embolization (Obliteration of aneurysms)

Angio-graphic Efficacy	Koivisto 2000 (27) n=109	Versari 2000 (15) n=223	Vinuela 1997 (20) n=403	Wiebers 2003 (30) n=4,060	Lot 1998 (17) n=248	Brilstra, 1999 (21) n=1,383	Murayama 2003 (47) n=818	Batista 2002(41) n=160 aneurysms	Raymond 2003 (40) n=466	Ng 2002 (39) n=144
Type of aneurysm	Ruptured	Ruptured	Acute ruptured	Unruptured	Unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & Unruptured	Ruptured and unruptured
Interventio n	Coiling or surgery	Coiling or surgery	Coiling	Coiling or surgery	Coiling or surgery	Coiling	Coiling	Coiling	Coiling	Coiling
Initial Total Occlusion	Coiling 79% Surgical 86%	Coiling 51% Surgery 100%	Coil small 70.8% Giant 50%	Coiling 54% Surgery No data	Coiling 71% Surgery 91%	Coiling 53.8%	Coiling 55%	Coiling 27.6%	Coiling 35.9%	Overall 46% Neck <4mm 48% Neck >/=4mm 27%
Initial Subtotal Occlusion		23.4%	Neck Rem. Small 21.4% Giant 50%	24%	Not expanding 3.5–20%	Near complete 87.9%	Neck remnant 35.4%	52.3%	Neck remn 46.3%	Neck remnant 16% Residual body filling 38%
Initial incomplete occlusion		25.2%		18%	Expanding 8.5%		3.5%	18.1%	Sac 13.8%	
Failed			Small 3.6% Large 2.9%				5%	<80% occlusion = 2%	4%	16% of aneurysms
Follow-up								@ 5 year	>12 months	Up to 3 years
Total occlusion								35/53	38.3%	Recanalization Year 1 28% Year 2 20% Year 3 14%
Subtotal Occlusion								7/53	Neck remnant 45.5%	
Incomplete Occlusion								8/53	Sac 15.2%	
Failed								3/53	1.1%	

Rem. = Remnant

Appendix 7: Summary of Clinical Outcomes of Treatment of Intracranial Aneurysms (Endovascular vs Surgical)

	Molyneux 2005 (24;25) n=2,143	Koivisto 2000 (27) n=109	Rabinstein 2003 (11) n=415	Wiebers 2003 (30) n=4,060	Barker 2004 (31) n=3,919	Johnson 2001 (32) n=2,164	Murayama 2003 (47) n=818	Vindlachervu, 2003 (44) n=248	Brilstra, 1999 (21) n=1,383	Leber 1998 (38) n=248	Lot 1998 (17) n=395	Ng 2002(39) n=144
Type of aneurysms	Ruptured	Ruptured	Ruptured SAH	Unruptured	Unruptured	Unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & Unruptured	Ruptured & Unruptured
Intervention	Coiling or surgery	Coiling or surgery	Coiling or surgery	Coiling or surgery	Coiling or surgery	Coiling or surgery	Coiling	Coiling or surgery	Coiling	Coiling or surgery	Coiling or surgery	Coiling
Mean follow-up	1 year	1 year	6 months	1 year	At discharge	At discharge	11 months	6 months			13 months	>2 years
Mortality	Coiling 8.1% Surgery 10.1% (1 yr)	Coiling 13.5% Surgery 15.8%		Coiling 3.1% Surgery 2..3%	Coiling 1.7% Surgery 2.1%	Coiling 0.5% Surgery 3.5%	New neuro deficits Initial 6% F-up 4.8%		CDC 5.3% Pushable coil 13.8%		Coiling 4% Surgery 2.7%	In-hospital Ruptured 19% Unruptured 0, Procedure related 1.2% 6 month 10.4%
Evaluation tool used	Modified Rankin	GOS	GOS	Rankin				GOS	Rankin			GOS
Good recovery & moderate disability	Coiling 76.5% Surgery 69.1	Coiling 79% Surgery 75%	Coiling 74% Surgery 73%				Immediate Improved or unchanged 90.6%	Coiling 77.8% Surgery 84.8%	CDC 89.6% Pushable C 76.7%		Good outcome Coiling 92% Surgery 90%	GOS 1–2 Unruptured 100% at discharge Ruptured depends on HH grade
Severe disability to fully dependent	Coiling 15.5% Surgery 21%	Coiling 7.7% Surgery 8.8%	Coiling 26% Surgery 27%	Coiling † 6.4% Surgery 9.8%			Follow-up Improved or unchanged 86.2%		CDC 5.1% Pushable C 9.5%			

	Molyneux 2002 (25) n=2,143	Koivisto 2000 (27) n=109	Rabinstein 2003 (11) n=415	Wiebers 2003 (30) n=4,060	Barker 2004 (31) n=3,919	Johnson 2001 (32) n=2,164	Murayama 2003 (47) n=818	Vindlachervu, 2003 (44) n=248	Brilstra, 1999 (21) n=1,383	Leber 1998 (38) n=248	Lot 1998 (17) n=395	Ng 2002(39) n=144
Death & dependent (Rankin scale 3–6)	Coiling* 23.5% Surgery 30.9% RR 0.71 p<.0001											
Death & discharge to facility other than home					Coiling 9.1% Surgery 18.4% Significant	Coiling 9.7% Surgery 25.4%						
Morbidity rate				Coiling 9.5% Surgery 10.1%						DIND Coiling 25% Surgery 40.6%		
Comment		Clinical outcome & mortality not significantly different	Clinical outcome not significantly different	No statement on statistical significance	In hospital death not significant	Significant difference				No statistical significance		

* Modified Rankin score 3–6; † Rankin score 3–5 and/or impaired cognitive status

Appendix 8: Complications of Treatment of Intracranial Aneurysms

	Koivisto 2000 (27) n=109	Versari 2000 (15) n=223	Vinuela 1997 (20) n=403	Byrne 2001(48) n=317	Barker 2004 (31) n=3,919	Bilstra, 1999 n=1,383 (21)	Murayama 2003 (47) n=818	Batista 2002 (41) n=160 A	Cloft 2002 (49) n=2,008	Vindlachervu 2003 (44) n=248	Ng 2002 (39) n=144
Type of aneurysms	Ruptured	Ruptured	Acute ruptured	Ruptured SAH	Unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & unruptured	Ruptured & Unruptured
Intervention	Coiling or Surgery	Coiling or surgery	Coiling only	Coiling only	Coiling or surgery	Coiling only	Coiling only	Coiling only	Coiling only	Coiling or surgery	Coiling only
Complication rate -overall		Coiling 16% Surgery 9.3%	Coiling 9.18%	Coiling 9.8%		Coiling CDC 12% PC 19%	Coiling Technical 8.6%				Ruptured 8.6% Unruptured 5.1%
Neurological complications					Coiling 5% * Surgery 7.8%			Coiling 3.05%			8.5%
Hemiparesis or hemiplegia		Hemiparesis Surgery 0.8%			Coiling 1.9%* Surgery 5.3%						
Perforation			Coiling 2.73%	Coiling 3.5%		Coiling CDC 2.4% PC 4.7%	Coiling 2.3%		Coiling Ruptured: 4.1% Unruptured 0.7%		Intraprocedural rupture Ruptured 16%
Ischemic deficit	More in surgical					CDC 8.5% PC 13.4%				SAH Coiling 0% Surgery 3.2%	
Parent artery occlusion			Coiling 2.98%	Coiling 2.5%	Coiling 8.8% Surgery 6.4%		2% (3 deaths)				
Intraoperative rupture		Coiling 3% Surgery 6.8%									
Thrombo-embolic events		Coiling 9.5%		Coiling 2.5%	Coiling 1.0% Surgery 0.8%						14.6%
	Koivisto 2000 n=109	Versari 2000 n=223	Vinuela 1997 n=403	Byrne 2001 n=317	Barker 2004 n=3,919	Bilstra, 1999 n=1,383	Murayama 2003 n=818	Batista 2002 n=160 A	Cloft 2002 n=2,008	Vindlachervu 2003 n=248	Ng 2002 n=144
Intracerebral hematoma		Coiling 1% Surgery 1.7%		Coiling 0.6%	Coiling 3.8% Surgery 2.2%						
Collapsed coils	Coiling 7.7%						Coil rupture 0.4%				

Coil migration/ malposition		Coiling 3%	Coiling 0.5%				Coil migration 0.5%			SAH Coil malposition 14.6%	
Transfusion of red blood cell					Coiling 0.75* Surgery 3.7%						
Aphasia					Coiling 1.7% Surgery 2.9%						
Hydro-cephalus					Coiling 2.5% Surgery 1.95						
Mechanical ventilation					Coiling 3.3% Surgery 5.1%						
Cardiac complications					Coiling 0.5% Surgery 1.7%						
Permanent complication						Coiling CDC 3.7% PC 7.1%					

GOS Glasgow Outcome Score
CDC Controlled detachable coils
PC Pushable coils

Appendix 9a: Summary of Systematic Reviews (English-language)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding	Complication	Conclusion
Brilstra 1999(21) Systematic review 48 case series N = 1,383	Compared controlled detachable coils (CDC) vs pushable coils (PC) (ruptured & unruptured aneurysms) 714 prospective (58% of patients)	100% occlusion CDC 53.8% PC 78.2% >90% occlusion CDC 87.9% PC 97.7% Significant	CDC 5.3% PC 13.8%	Independent (Rankin 0-2) CDC 89.6% PC 76.7% Dependent (Rankin 3-5) CDC 5.1% PC 9.5%	In 16 patients with SAH before embolization,, 12 with incomplete occlusion rebled. 25% acute, 75% after 6 months.	Total CDC 12% PC 19% Permanent CDC 3.7% PC 7.1% NS Perforation CDC 2.4% Pushable 4.7% Ischemic CDC 8.5% 13.4%	Short-term : coil embolization is a reasonably safe treatment for patients with unruptured aneurysm and for patients with SAH. The effectiveness in terns of complete occlusion of aneurysm is moderate. RCT needed to compare coil embolization to surgical clipping.
Cloft 2002 (49) Meta-analysis Total N = 2,008 Ruptured n=1,248 Unruptured n=760	Meta-analysis of 17 published retrospective reports on perforation during embolization using Guglielmi detachable coils (GDC)			Combined mortality & morbidity with perforation caused by: Coils = 39% Microcatheter = 33% Microguidewire = 0%		Perforations during GDC embolization Ruptured Perforation 4.1% Death 33% Disability 5% Unruptured Perforation 0.7% Death 14% Disability 14%	The risk of rupture during GDC embolization is higher in patients with previously ruptured aneurysms. The morbidity & mortality rates are substantial for perforations caused by coils (39%) and mircocatheters (33%) whereas they seem to be much lower for perforations caused by microguidewires (0%)

Appendix 9b – Summary of Systematic Reviews (2006 update)

Studies	Design	% Occlusion	Mortality	Clinical Outcome	Rebleeding	Complication	Conclusion
Van der Schaff, 2005 (24) (Systematic Review) Cochrane Collaboration	Included: 2 published RCT 1 unpublished RCTs (1996 - February 2005) on ruptured aneurysm with SAH Results mainly from ISAT Meta-analysis of rates of poor outcome, cerebral ischemia, rebleeding , death, & incomplete occlusion	Incomplete occlusion after 1 year Coiling vs clipping: RR =1.37 (95% CI 1.29 –2.17, p=0.0001) Siginificantly lower for coiling	Up to 1 year: No significant difference coilng vs clipping RR = 0.81 (95% CI 0.63–1.05, p=0.1)	Death or dependency coiling vs surgical clipping at 2–3 months (RR 0.71, p<0.00001) & at 12 months (RR 0.76, 95% CI 0.67–0.88, p=0.0001), absolute risk reduction of 7% (95% CI 4% to 11%), Worst case scenario: RR 0.81 (95% CI 0.7 –0.92), absolute risk reduction of 6% Anterior circulation: RR 0.78 (95% CI 0.68–0.90) & absolute risk reduction of 7% Posterior circulation RR 0.41 (95% CI 0.19-0.92) & absolute risk reduction of 27%,	Significantly higher for coiling compared to clipping up to 1 year: RR = 2 (95% FI 1.08–3.70, p=0.03)	Procedure related: Not statistically different: RR = 1.05 (95% CI 0.44–2.53, p=0.9)	For patients with good clinical condition with ruptured aneurysm of either anterior or posterior circulation, there is evidence that if the aneurysm is considered suitable for both surgical clipping and endovascular treatment, coiling is

Appendix 10: Summary of Findings on Ruptured Aneurysms

Study	Design	% Occlusion	Mortality	Clinical outcome	Refilling/ Rebleeding	Complication	Conclusion
Molyneux, 2002 & 2005(25) (26) International RCT N=2,143 Level 1	RCT, Coils = 1,073 Surgical n =1,070 1 year follow-up	At 1 year Complete occlusion Coils 66% Surgical 82%	Coils = 8.1% Surgical = 10.1% @ 1 yr In 7 yrs Coils 116/1073 Surgical 147/1070 (log-rank p=0.03)	Death & dependency (Rankin 3-6) Coils = 23.5% Surgical = 30.9% (p=0.0019)	Rebleeding Year 1 Coils = 45/1073 Surgical = 39/1070 Year 2–7 Coils = 7/1073 Surgical = 2/1070 (Log rank p=0.22)	Non-procedural bleeding Coils = 5% Surgical = 4.1%	Relative risk reduction = 23.9% (95% CI 8.9 - 34.2) Absolute risk reduction = 7.4% Trial stopped because of significant benefit of coils
Koivisto 2000 (27) RCT N = 109 Level 2	RCT Endovascular n = 52 Surgical n = 57 Mean follow-up = 39+/-18 months	100% occlusion endo = 77% surgical 86% nearly complete surgical = 12% Cross over Endo 20% Surgical 6%	Endo = 13.5% Surgical = 15.8% Not significant, KM analysis showed equal survival in both groups	Glasgow outcome score Good - moderate recovery Endo = 79% Surgical 75% Severe disability/ vegetative Endo = 7.7% Surgical = 8.8% Not significant	Refilling: Aneurysm neck Endo = 22% No late rebleeding in either group	Collapsed coils = 7.7% Repeat Procedure Endo = 7% Surgical = 3.5% MRI - superficial brain deficit & ischemic lesion more frequent in surgical group	Endovascular treatment of acutely ruptured intracranial aneurysms results in similar clinical & neurologic outcomes as surgical clipping and is suitable for a selected group of patients -its long-term efficacy in preventing rebleeding remains unknown.
Rabinstein 2003 (11) Single centre case series (1990–2000) N=415 patients Admitted within 7 days of SAH Follow-up median 6 months	Retrospective review Endovas n=76 Surgical n= 339 Mean age 54 years (17–88 yrs) 65% women Endovascular Poorer clinical grade on admission with more prevalent early hydrocephalus		27% of all patients had died or remained severely disabled	Glasgow outcome score Coil Surgery GOS 1 16% 8% GOS 2 0% 1% GOS 3 11% 19% GOS 4 11% 15% GOS 5 63% 58% No statistically significant difference (GOS 1–3 = poor outcome GOS 3–4 Good outcome)	Rebleeding Coil = 0% Surgical = 2/339 during hospital stay due to small aneurysm remnant.	Clinical spasm Coil Surgery None 70% 61% Moderate 6% 24% Severe 14% 15% Global neuro deficits 23% 27% Permanent deficit None 71% 62% None/spasm 11% 8% Deficit/spasm 9% 20% None of the above were significant. About 20% with permanent deficit	-Symptomatic vasospasm occurred in 37% of patients overall. -Treatment modality did not affect the rate of symptomatic vasospasm among patients with poor WFNS grades (IV or V). -Endovascular coil embolization was associated with a lower risk of symptomatic cerebral vasospasm in patients with good WFNS grades (I– III) at presentation (OR 0.34, 95% CI 0.14–0.8).

Study	Design	% Occlusion	Mortality	Clinical outcome	Refilling/ Rebleeding	Complication	Conclusion
Versari 2000 (15) Multicenter (4) case series N = 223 patients Level 4 Italy	Coils = 105 (111 aneurysms) Surgical = 118 6 month follow-up	Success rate Coil : 94% Surgery: 100% Coils Total occlusion 51% Subtotal 23.4% Partal 25.2% 2nd endov 8.5% cross over 4.7% Surgery Total occlusion 76.2% Subtotal 3.4% No angiography 22.7%	Coil = 4.7% Surgery? Overall Dead 17.5%	Overall (all treated patients) At 6 months: Good recovery 56.4% Moderate disability 12.8% Severe disability 10.3% Vegetative state 3% Dead 17.5% Grade I & II increase in Good recovery Grade III - decrease in good recovery. Grade IV & V - increase in moderate & severe disability	Rebleeding Coil = 2/105 Surgery = 0 Posterior circulation: decrease in untreated patients; significant decrease in mortality & increase in overall good outcome. increase in treated	Coiling Procedure related complication rate 16% Thrombo-embolic events = 9.5% Intra-operative rupture 3% Coil migration 3% Hematoma 1% Surgery Surgery related complication 9.3% Intraoperative rupture 6.8% Post-op hematoma 1.7% Hemiparesis 0.8% Early unfavorable evolution 22/118	Endovascular coiling seems an effective choice in selected grade I–II patients. Surgery more advantageous for grade III. Results for grade IV &V patients are unsatisfactory & probably early surgery should be considered. GDC is probably an advantageous choice for the elderly and should be considered the first therapeutic choice for patients with posterior circulation aneurysm.
Byrne 1999 (28) Consecutive case series Endovascular only N=317 patients	317 patients with SAH treated within 30 days following rupture. Clinical follow-up median 22.3 months (range 6–65 months) Angiography at 6 months post treatment Annual questionnaire	For 259 aneurysms (at 6 months?) Stable angio occlusion 86.4% of small and 85.2% of large aneurysms			Recurrent filling 14.7% Rebleeding 4 patients between 11 and 35 months. Annual rebleeding rate 0.8% in the 1st year 0.6% in the 2nd year 2.4% in the 3rd year after embolization. No rebleeding in subsequent years. Rebleeding occurred in 7.9% of 38 recurrent aneurysms and in 0.4% of 221 aneurysms that appeared stable on angiography.		Periodic follow-up angiography after coil embolization is recommended to identify aneurysm recurrence and those patients at high risk of late rebleeding.

Study	Design	% Occlusion	Mortality	Clinical outcome	Refilling/ Rebleeding	Complication	Conclusion

Byrne 2001(48) Single center consecutive case series Endovascul-ar only N=317 patients	317 patients with SAH treated acutely (within 30 days) following rupture. Clinical follow-up median 22.3 months (range 6–65 months) Angiography at 6 months post treatment Annual questionnaire	Procedure related mortality 3.5% Procedure related morbidity 3.2%	Perioperative Conditions same or improved 89% Neurological deterioration Clinical outcome 6–9 months WFNS 1or2, early treatment Good outcome (93%) Late treatment good outcome 84% WFNS 3–5 Early treatment Good outcome 61% late treatment good outcome 53%	Neurological deterioration in 35/317 patients within first 48 hours. In 21/35 patients, these were due to procedural complications No correlation was found in the incidence of such deterioration and the timing of treatment, or with patient's outcome at 6 months. Patient treated within 6 days of SAH had better outcomes than those treated later.	Procedural complications Total 9.8% Aneurysm perforation 3.5% (resulted in transient neurological deterioration in 5 patients & delayed deaths) Thrombo-embolism 2.5% (clinical deterioration in 7 & 4 died) Parent artery occlusion 2.5% (neurological deterioration in 6 & 4 died) Serious hematoma at the arterial puncture 0.6%	Procedural complications occurred in 9.8% of cases.	Patients should be treated as soon as possible after presentation with a ruptured intracranial aneurysm since the technique appears less susceptible to the adverse effect of vasospasm in the 3–10 day period after SAH.

Appendix 10: Summary of Findings on Ruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Neuropsychological outcome	Refilling/ Rebleeding	Complications	Conclusion
Vinuela 1997(20) Multicenter case series Endovascular only (acute) N= 403 patients Texas, US	1990–1995 Acute ruptured aneurysms treated with GDC within 15 days of rupture 70.2% female 40.9% 51–70 years old; 13.9% =70–90 years old Size of aneurysm Small=60.8% Large =34.7% Giant =4.5% Size of aneurysm neck: </=4mm 53.6% (>4mm 36.2% Fusiform 6% 57% in the posterior circulation. H&H grade 1=20.3% Grade II 26.1% Grade III 30% Grade IV 7.1% Grade V 6.5% Follow-up until discharge or death	Initial complete occlusion Small A small neck 70.8% Small aneurysm with wide neck 31.2% Large aneurysms 35%.1% Giant aneurysms 50% Neck Remnant Small A small neck 21.4% Small aneurysm with wide neck 41.6% Large aneurysms 57.1% Giant aneurysms 50% Failure Small A small neck 3.6% Small aneurysm with wide neck 16.9% Large aneurysms 2.9% Giant aneurysms	Within 1 week of GDC treatment Total 6.2% (1.74% death related to GDC technical complications; 4.47% death due to severity of primary intracranial hemorrhage By location of Aneurysm Anterior circulation A 8.1% morbidity & 6.4% mortality rates Posterior circulation 9.6% morbidity & 6.1% mortality	Immediate Clinical Outcome Unchanged or improved 84.9% Deterioration 8.9% (mild 2.48% moderate 3.72% severe 2.73%) Dead 6.2%		Technical complications Overall 9.18% Perforations 2.73% Cerebral embolizations 2.48% Unintentional parent artery occlusion 2.98% Coil migration 0.5% Arterial vasospasm 0.5%	Findings demonstrate the safety of the GDC system for the treatment of ruptured intracranial aneurysms in anterior and posterior circulation. Additional randomized studies will further identify the role of this technique in the management of acutely ruptured intracranial aneurysm.

Appendix 11: Summary of Findings on Unruptured Aneurysms

Studies	Design	% Occlusion	Mortality	Neuropsychological outcome	Rebleeding/ Complication	Others	Conclusion
Wiebers, 2003 (30) Prospective cohort in 61 centres N = 4,060 Level 3	Non-randomized cohort Unruptured No operation n = 1692 Endo n = 451 Surgical n = 1,917 Mean follow-up = 4.1 years	Coils Complete occlusion = 51% Partial occlusion = 24% No occlusion = 18% Unknown = 3%	1-year total mortality rate Endo 9.1% Surgical 12.6%	Morbidity rate Endo 9.5% Surgical 10.1%	No data	Ruptured during follow-up No OR = 3% Rupture during Surgical = 6% Surgical outcome dependent on age, location of aneurysm & history of ischemic CV disease Outcome of endo less dependent on age but more on morphology	Risk of Rupture <7mm = 0.1% >7 mm with previous SAH, 5 yr cumulative rupture rate higher but equal or exceed by risk of intervention 7-24 mm and age<50 with unruptured aneurysm of posterior communicating artery would benefit most from open surgery Long-term outcome & durability of endo not known.
Johnston 2001 (32) (unruptured) Comparative case series N =2,164 State if California	Review of in-hospital and follow-up data in state database On both surgical and endovascular treatment Coiling n=307 Surgical n=1,699	No data	In-hospital deaths Endovascular 0.5% Surgery 3.5%	Adverse outcome (death or transfer to Rehab) Endovascular 9.7% Surgery 25.4% Adverse outcomes, length of stay and in-hospital deaths decreased with volume for endovascular, not surgery.	No data	Length of stay Endovascular 7.1 days Surgery 11.8 days Hospital charges Endovascular $37,000 Surgery $64,000 (significant)	Endovascular therapy of unruptured aneurysms in California is associated with less risk of adverse outcomes and in-hospital deaths, shorter hospital stay and lower hospital charges compared to surgery. Differences between the two therapies become more distinct throughout the years.

Appendix 11: Summary of Findings on Unruptured Aneurysms (Continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding/ Complication	Others	Conclusion
Johnston 2000 (1) Single centre case series N=130 Follow-up 3.9 years US	Blinded prospective review to mimic RCT Compare outcomes of patients deemed suitable for surgical & coiling Coiling n=62 Surgery n=68	** follow-up survey	Rankin 6 (death) Coil =2% Surgery = 37% (p=0.003)	Rankin sc at discharge Coil Rankin 1–2 79% Rankin 3–6 21% Surgery Rankin 1–2 68% (p<0.001) Rankin 3–6 31% Less coil patients reported diminished function, quicker recovery	Total procedure related complications Coil =23% Surgery 46% (p=.009)	Length of stay total days Coil =5 days Surgery = 7.7 days (p<.001) ICU days Coil = 2.6 days Surgery =1.9 days (p=.003) Predictors of poor outcome Surg/endo OR 9 Signif Poster/Anterior, OR 3.8 significant Symptomatic OR 5.3 Signif Age OR 1.7 signifc	Coil embolization of unruptured intracranial aneurysm seems to be associated with significantly fewer complications, shorter hospital stay & lower hospital charges than surgical clipping at 3.9 years of follow-up. -more long-term data on aneurysm rupture rates are required to confirm efficacy.
Johnston 1999 (43) Muticenter case series N=2,612 60 University hospitals in US	Retrospective review Coiling n=255 (GDC) Surgery n=2,357 Adverse outcome = in-hospital death or discharge to nursing/rehab -bilitation home	No data	In-hospital death Coiling 0.4% Surgery 2.3% (p=0.039)	Adverse outcome Coiling 10.6% Surgery 18.5% (p=0.002) Odds ratio Surg/Endovas 1.9 (95% CI 1.3-2.9, p=.001) ; still significant after adjustment for differences in the 2 cohorts.	No data	Mean length of stay Coiling 4.6 days Surgery 9.1 days (p<.0001) Odds ratio Surg/endovasc Not significant after adjustment Mean charges Coiling $30,000 Surgery $43,000 (p<.0001)	-Endovascular coil embolization resulted in fewer adverse outcomes than surgery for unruptured cerebral embolism treated at university hospitals. Comment: Surgical patients were younger, more likely to be Black, less likely to be Asian and more likely to be admitted through the emergency room than coisl.

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding	Complication	Conclusion
Vindlacheruvu 2003 (44) Single centre case series N=248 UK	Retrospective analysis Coiling n=86 aneurysms Surgery n=220 aneurysms GOS and delayed ischemic neurologic deficit (DIND) Follow-up 6 months	No data	No data	For all Aneurysms DIND Coil 25% Surgery 40.6% not significant good recovery or moderate disability GOS Coil 77.8% Surgery 84.8% NS Unruptured aneurysm Inpatient stay Coil 4.8 days Surgery 10.3 days P<.001 Good recovery similar	No data	Wound infection ? Coil malposition 14.6% Coil failure 2.1% Patient with SAH - permanent ischemic deficit at 6 months - 3.2% in surgery, 0 in coil	-No significant difference in GOS @ 6 months (coiling vs surgery). -Coiling of unruptured aneurysms reduced in-patient stay -Fewer complications with coiling (non significant) Good grade patients more likely to be discharged directly home. -Long-term morbidity following SAH not related to treatment modality but to the clinical grade of the aneurysm.
Raftopoulos 2000 (59) Single centre prospective case series N=112	Evaluate coiling as first option Coil n=60 Surgery n = 49 Coil & surgery =12 Intervention GDC Follow-up 2 months - 3 years 57% with SAH	Coil Complete obliteration 68.8% 95–99% = 12.5% <95% = 18.7% Surgery Complete =98.4% 95–99% = 0 <95% =1.6% Coil+surgery Complete =100%	Coil =3/60 Surgery =1/49	@2–6 months Coil GOS good =86.7% GOS poor =13.3% WRNS grade I–III deteriorated post op =10% Surgery GOS good 93.9% GOS poor 6.1% WFNS grade I–III deteriorated post-op =0 (1 improved	No data	Coiling: higher number of small aneurysms and posterior circulation A (21.9% vs 1.6% in surgery) Unsuccessful coiling is due to unstable coils, recanalization and sac perforation.	-Coiling resulted in lower complete obliteration of the aneurysm than surgical clipping. -even with cautious preselection, coiling can have a significant rate of failure -coiling should be avoided in wide neck aneurysms especially on the middle communicating artery -surgical procedure have better clinical results than coiling in complex aneurysms in the anterior circulating artery (esp the MCA)

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding/ Complication	Complications/ others	Conclusion
Lot G 1998 (17) Case series N=395	Endovascular as first choice Endovascular n=293 cases Surgical n=102 cases Angiography @1, 6 &12 months for endovascular , Surgical- 78 had follow-up angiograph Mean follow-up =13 months (maximum 36 months)	Complete : Endovasc 71% Surgical 91% Endovascular Incomplete but satisfying Small: 3.5% Large: 20% Unsatisfying: 8.5% 92% treated to satisfying with complementa-ry procedures Surgical Incomplete 9% Small 6.9% large 15% 5% had endovasc. complementary treatment	Small Aneurysms Endo 4% Surgery 2.7% Large Aneurysms Endo 4.4% Surgery 17.2% High grade small A =10.4% High Grade large A = 3/18	Good Outcome Small Aneurysms Endovascular 92% Surgery 90% Small Aneurysms Endovascular 91% Surgery 72% Small, Poor Grade HH III–V Aneurysms Surgical Total=9 Good outcome 5/9 Severe deficit 3 Dead 1 Endovascular total = 48 Good 75% Severe deficit 14.6% Dead 10.4% Large, Poor Grade HH III–V Aneurysms Surgical Total =8 Good 25% Severe deficit 25% Dead 50% Endovascular total=18 Good = 13/18 Severe deficit =2/18 Dead = 3/18	No data	No data	Good results in terms of efficiency and clinical outcomes were achieved. They were as good as the best surgical series. With appropriate selection, endovascular treatment is a good alternative for treatment for the majority of saccular aneurysms.

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Neuropsychological outcome	Rebleeding/ Complication	Complications/others	Conclusion
Leber 1998 (38) Single centre case series Austria N=248	Reviewed 248 consecutive patients treated for intracranial aneurysm with either surgical or endovascular treatment Endovascular n N=106 patients (138 aneurysms) Surgery N=142 patients (162 aneurysms)	95% obliteration Endovascular 94% 34% with additional procedures Failure: 21 patients Surgery 89% 3.7% with additional wrappings	Unruptured Endo 4.5% Surgery 6.2% Unruptured Ruptured HH 1&2: 5.3–9.1% HH 3: 5.7–5.8 HH 4&5: ?	Unruptured Endov Surgery GOS 1 87.5% 77.8% GOS 2 11% 6% GOS 3 7% 0% GOS 4 0 0 GOS 5 .5% 6.2% (death) No significant difference Ruptured No significant difference between coiling & clipping H&H 1or2 GOS 1 70.8%–83% GOS 3&4 (morbid) 0%–12.5% GOS 5 5.3%–9.1% H&H Grade 3 GOS 1 Endo 47% Surgery 48.6% GOS 3&4 up to 14% GOS 5 5.7-5.8% H&H score 4 &5 GOS 1 up to 50%	Recurrence rate: Endovascular 9% No rebleeding in either group.	Treatment related complications were due to fatal rupture of aneurysm during treatment or occlusion of the parent vessel as a result of a thromboembolic event.	GDC embolization is not associated with higher risk of morbidity and mortality than open surgery. This risk may even be lower for lesions in surgically unfavorable locations. The GDC technique is less invasive, effective option to prevent rebleeding the early stage even in poor-grad patients. However, these encouraging medium-term results have to be confirmed by a longer observation period. Risk of endovascular treatment is not associated with the localization of the aneurysm.

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding/Refilling	Complication	Conclusion
Raymond 2003 (40) Case series (1992–2002) Endovascular only N=466 patients 501 aneurysms Montreal, Canada	Retrospective analysis of prospective data. Selective endovascular coiling =466 Ruptured = 54.1% Mean age = 54.2+/-12.54 years; Mean aneurysm size = 9.67+/-5.91 mm Intervention: GDC coiling Occlusion Class 1= complete occlusion Class 2 = residual neck Class 3 = residual aneurysm Mean clinical follow-up 31.32+/-24.96 months	Treated once 91.4% >1 treatment 8.6% Initial (n=501) Class 1 35.9% Class 2 46.3% Class 3 13.8% Failure 4.0% Early follow-up (3–12 months, n=353) Class 1 44.6% Class 2k 41.1% Class 3 12.8% Failure 0.6% Late Follow-up (>12 months, n=277) Class 1 38.3% Class 2 45.5% Class 3 15.2% Failure 1.1%	1 patient died despite re-treatment.	Recurrence by aneurysmal dimensions A Size All recur major 3–9 mm 21.3% 10.9% >10 mm 50.6% 34.4% P value <0.001 <0.001 Neck Size All recur major <4mm 23.7% 13.3% >4mm 52.3% 34.8% P value <0.001 <0.001 Recurrence by follow-up period All recur Major 1–16 mo 22.1% 14.5% 17–37mo 39.3% 23.8% >37 mo 39.8% 24.2% P value 0.003 0.094 All recurrence Rupture 39.8% Unruptured 27.4% (p=0.013) Major recurrence Ruptured 25.1% Unruptured 16.3% (p=0.043)	Total Recurrences 33.6% of treated aneurysms(at mean of 12.31+/-11.33 months) Major recurrence In 20.7% of all patients (16.49+/-15.93 months); 49.4% re-treated with coils; 48.6% showed a second recurrence at 15.56+/-18.43 months Minor recurrence In 22.1% of cases (33.6+/-25.6 months) Rebleeding 0.8% (at 13.25+/-8.62 months)	Risk factors for recurrences (from logistic regression) Residual aneurysm (p=0.002, relative risk =3.60, CI 1.60–8.09) Aneurysms> 10 mm (p=0.002, Relative risk 2.49, CI 1.4–4.43) Residual neck (p=0.002, relative risk 2.44, CI 1.40–4.23) Ruptured aneurysm (p=0.007, relative risk 1.96, CI 1.21–3.17) Neck >4mm (p=0.086, Relative risk 1.69, CI 0.93–3.09) NS Follow-up (months) (p=0.000, relative risk =1.02, CI 1.01-1.03)	The most significant predictor of a recurrence for the entire groups were: treatment during the acute phase after rupture (p=0.013), aneurysm size >/=10 mm (p<0.001), width of the neck of the aneurysm (p<0.001), incomplete initial occlusion (class 2 or 3, p<0.001); and duration of follow-up (p=0.003). Long-term monitoring of patients treated by endovascular coiling is mandatory.

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% occlusion	Mortality	Clinical outcome	Rebleeding/Refilling	Complication	Conclusion
Casasco 1998(60) Case series GDC only N=217 patient, 295 aneurysms	Case series 4 groups Ruptured treated early 45% Ruptured treated after 30th day 29% Unruptured 22% No hemorrhage but with a mass effect	Complete 78% Subtotal (80%) 19% Partial (<80%) 3%	11.6%	Good results 80.2% Moderate disability 5.81% Severe disability 2.3% Death 11.6%		Technical complication 18.6% Permanent neurological deficit 3.05%	
Ng 2002 (39) Case series GDC only N=144 patients, 160 anuerysms Australia	July 1992–Aug. 1998 Retrospective review medical record, questionnaire & telephone interviews. 87.5% berry aneurysms 61% ruptured (35% >/=H&H grade III) 39% unruptured (95% Asymptomatic) 129/144 Patients had clinical follow-up =/> 2years 82 patients had angiographic follow-up >6 months, 54 had angiographic follow-up >2 years -3 patients required surgical clipping	Technical success: Ruptured 90% Unruptured 90% Neck<4mm 92% Neck>4mm 70% (p<0.0001) Complete 46% (neck<4mm 48% neck≥4mm 27%, p=0.001) (size<10mm 43%, size>/=10mm 18.5%, p=0.018) Overall recanalization 23% Neck remnant 16% Residual body filling 38% No statistically significant difference between ruptured and unruptured groups.	In hospital mortality Ruptured 19% Unruptured 0% Procedure related mortality Overall 1.2% Ruptured 2.5% Unruptured 0% Total mortality at 6 months 10.4%	Unruptured 100% GOS 1 or 2, independent at discharge Ruptured: HH grade I-2 on admission 88% discharged independent HH grade grade IV-V, 30% discharged independent (p<0.0001) At 2 years Unruptured: 44/48 (94%) patients remained independent Ruptured: midterm clinical outcome correlated with HH grade HH grade I-II Independent GOS</=2 82% HH grade III independent 47% HH grade IV-V independent 30%, dead 70%	1.5% (delayed rebleeding) after a mean period of 9 months.	Overall procedure related morbidity 6.9% Ruptured 8.6% Unruptured 5.1% Intraprocedural rupture Overall 14/144 Ruptured aneurysm 16% Unruptured aneurysm 1.3% (p<0.001) Thromboembolic complications 21/144 Sustained neurologic deficits 8.5% Internal carotid artery dissection 1/144 Coil fracture 1/144 16% required a subsequent procedure at 2 years after coil embolization.	Coil embolization is safe and effective for both ruptured and unrutpured aneurysms. Increasing angiogrphic stability is demonstrated in treated aneurysms up to 3 years from coil embolization. Follow-up angiography until this time is advisable. Limitations: -patients requiring further procedure were excluded from follow-up analysis

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding/ Refilling	Complication	Conclusion
Murayama 2003 (47) Single center case series (endovascular only) n=818 patients 916 aneurysms UCLA	Coiling with GDC 71% female 43.4% age 51–70 years group A (treated Dec1990–Dec1995) = 230 patients group B (treated Jan 1996–Sept 2002) =588 patients 49.4% Acute SAH 41.8% unruptured Mass effect 10% HH grade I 30% Grade II 19.5% Grade III 25.5% Grade IV 17.1% Grade V 6.2% Aneurysm size Small with small neck 36.5% Small with wide neck 26.7% Large 21.6% Giant 8% Anterior circulation 70.7% Posterior circulation 29.2% Complete 0cclusion complete = no contrast filling of the dome, body or neck of the aneurysm.	Initial Complete occlusion 55% Neck remnant 35.4% Incomplete 3.5% Failed 5% Group A- higher rate of complete (56.8% vs 50.2%) + less frequent neck remnant & incomplete embolization. Follow up 53.4% of cases at a mean of 11 months (3 months –8 years) Recanalization 26.1% (group A) 17.2% (group B) 20.9% overall. Small A small neck 5.1% Small A wide neck 20% large aneurysms 35.3% Giant aneurysms 59.1%	Total mortality rate 3.4% Patients who presented with acute SAH, the morbidity rate was 7.2% and mortality rate was 6.4%. Incidental Morbidity 4.5% Mortality 0.8% Patients with mass effect or nonacute SAH Morbidity rate 4.9% &6.9% with no death.	Immediate clinical outcome Overall rate of patient with no change or with improved conditions =90.6% Had new neurological deficits =6% long-term clinical outcome 768 patients Overall Improved 17.1% Unchanged 69.1% Had neurological deficits 4.8% Delayed rupture 1.6% 10/12 delayed rupture were large or giant aneurysms. The rate was improved in the recent 5 years.		Technical complications during GDC placement in 8.6% cerebral embolization 2.4% aneurysm perforation 2.3% (associated with 6 deaths) Parent artery occlusion 2% (3 deaths) Less frequent complications: Arterial dissection/spasm (0.7%) (1 death) Coil migration 0.5% Coil rupture (0.4%) New mass effect (0.1%) Group B was associated with an overall lower rate of technical complications than group a (7.3% vs 11.3%)	

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding /Refilling	Complication	Conclusion
Batista 2002 (41) Case series (prospective database) Endovascular only N=102 patients 160 saccular intracranial aneurysms At least 5 year clinical follow-up + angiographic follow-up	Retrospective analysis of 102 patients treated by Intervention GDC (1993–1997). Saccular aneurysms: 76.5% on anterior circulation, 59% with SAH, 39% unruptured. H&H grade 1or 2 76.6%,, Grade 4or 5 (5/102). Follow-up DSA at 3 months & 1 year after treatment, with further angiography at 3 and 5 years. Immediate control angiograms at 6 months- in cases of partial occlusion, recanalization or aneurysm regrowth. 100% occlusion =complete angio exclusion of the sac.	Failed embolization 9.4% 21.5% needed >1 procedure Initial occlusion 100% occl 27.6% 90–99% 52.3% 80–89% 18.1% <80% 2% @ 1 year (85 pts, 98 AA) 24/29 AA remained completely occluded -5/29 AA with immediate complete occlusion showed 90–99% occlusion -27.6% incomplete showed secondary spontaneous thrombosis, 30/75 become completely occluded 5 year angio (45 patients) 100% 35/53 90-99% 7/53 89–90% 8/53 <80% 3/53	mortality 1 year unruptured =0 ruptured =6/61 Overall =6/102 (5.8%)	86% had good clinical outcome (equivalent to GOS 1) at 1 year.	No bleeding or rebleeding has occurred since the beginning of experience in saccular AA treated with GDC coil.	Complications Causing permanent neurological deficits 3.8% Transient complications 12.7%	- immediate compete occlusion & stable @ 1 year, or immediate subtotal occlusion but complete occlusion achieved after secondary spontaneous thrombosis at 1-year control angio, long-term stability achieved. Further control angiogram not justified - As that showed loss of morphology at 3-month or 1-year & had to be re-embolized , followed-up according to the date of the re-intervention - immediate occlusion of <80%, reintervention is required. The above observations are valid in the presence of multiple As (37.2%). -Coil embolization or properly selected patients is effective in protecting against bleeding or rebleeding at short & long-term with stable morphological results provided a strict follow-up control is established at short term.

Appendix 12: Summary of Cohort Studies of Ruptured and unruptured Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding/Refilling	Complication	Conclusion
Cognard 1999 (46) Case series Endovascular only N=203 berry aneurysms	203 berry aneurysms treated with detachable coils Size <15 mm Intervention: Follow-up angiography at least 3 months (in 169 cases)	Initial Occlusion Complete occlusion of sack & neck 148/169 Subtotal 18/169 Incomplete 3/169 Last follow-up angiography (n=169) Total occlusion 133/169 Subtotal 30/169 Incomplete 6/169	No data	No data	Recurrence in 14% (20) of the 148 totally occluded aneurysms (between 3& 40 months) Repeat treatment 5 cases -Neck remnant grew in 3 cases but did not require repeat treatment - neck remnant remained stable in 10 cases. In the subtotally occluded aneurysm: remnant regrowth occurred in 6/18 cases	No rebleeding occurred	A very small recurrence may be observed at the level of the neck of the aneurysm at long-term follow-up angiography despite achieving total occlusion initially with detachable coils.
Dowd 1999(61) Single center case series Endovascular only N=435 patients US	Retrospective review Intervention GDC 55% anterior circulation AA 45% posterior circulation AA 55% with SAH 45% unruptured						Factors that hindered optimal coiling: wide aneurysm neck in relation to the overall aneurysm size, mural thrombus, giant aneurysm, arteries originating from the aneurysm sac, and middle cerebral aneurysms especially in the non-ruptured group. Epidemiological data suggests that the natural history of unruptured aneurysms. is significantly lower than previously thought.

Appendix 13: Summary of Findings on High-Surgical Risk Aneurysms

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding	Complication	Conclusion
Lozier 2002 (22) Systematic review of GDC embolization of posterior circulation aneurysms Systematic review N = 495 posterior aneurysms	Included 12 reports with at least 10 aneurysms 82% of the aneurysms arose near the basilar apex ruptured = 81% small = 63%	100% = 47.6% 90–99% occlusion = 43.4% Incomplete = 9%	Procedural 1.4% 30-day 6.7% Overall 9.8%	Morbidity rate =5.1% Functional independence 85% Dependent = 5.3%	Recurrence 22% in a subset of 234 patients (92% had wide neck aneurysms) Annual risk of SAH after embolization = 0.8%	Procedural complication rate 12.5%	GDC embolization is moderately effective in completely excluding an aneurysm from the posterior circulation. The incidence of recurrence in wide-neck aneurysms and incompletely coiled aneurysms is substantial. Coil embolization is effective in preventing early rebleeding.; its role in the treatment of unruptured aneurysms remain unclear.
Ogilvy 2002 (7) Posterior circulation aneurysms Single center case series N=189 MGH US	Retrospective review of case series of Posterior circulation aneurysm Coil n=65 patients Surgery n= 124 patients -52 coil patients mean follow-up of 19 (range 4–82) months	Coil (n=65 patients) 100% occl= 32.3% > 95% = 26.2% <95% = 41.5% Coil impaction 42% Surgery (113 pts) 100% occl= 95.6% Residual = 4% No growth to time of report		Clinical outcome Good or excellent Coil 66.1% Surgery 83.7%	Coil 2.25% risk of hemorrhage per patient year Surgery 0.17% risk of hemorrhage per patient year	-Lower radiographic efficacy & a higher hemorrhage rate reported for endovascular coiling	-patients selected for coiling thought to be at higher risk for surgery -Regardless of treatment modality, outcomes were related to patient's clinical grade at presentation -Good outcomes with acceptable radiographic efficacy can be achieved in patients with posterior circulation aneurysm by a combined treatment algorithm.

Appendix 13: Summary of Findings - High Surgical Risk Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Clinical outcome	Rebleeding	Complication	Conclusion
Hoh 2001 (36) Paraclinoid aneurysms Retrospective analysis of a single center case series N=238 aneurysms	Grading of pts at presentation applied retrospectively Coil n=57 Surgery n=180 MGH Score based on age, H7H score, Fisher score & aneurysm size GDC coil	Coil 100% Occl =44% 95–99% = 26% <95% =30% Regrowth/compaction = 26% Retreatment = 9% Surgery 100% occl = 94% 95–99% =6% <95% = 0 Regrowth =0 Retreatment =0	Coil 4% Surgery 3% Death from complication Coil 2% Surgery 0% All deaths related to vasospasm	GOS score Coil Excellent or good 74% Fair 12% Poor outcome 10% Dead 4% Surgery Excellent or good 90%% Fair 6% Poor outcome 2% Dead 3%	Relation between grade of patient at presentation and outcome: MGH grade 0–2 89.7% had excellent or good outcome MGH grade >2 21.4% had excellent or good outcome (p<0.0001)	Overall complication rate Coil 21% Surgery 29% Procedure related permanent morbidity Coil 3% Surgery 6% (See text for types of complications) Patients with high MHG grades tended to be treated with coiling	-Angiographic efficacy & long-term rates of complete occlusion seem to be higher with surgery than coiling. -A high rate of complications was seen in both cohorts. -Vasospasm was the cause of death in both in both cohorts -Endovascular coiling allow treatment of patients with paraclinoid aneurysms with high surgical risk who would not otherwise have been treated.
Eskridge J (34) 1998 Multicenter US N=150	(submitted to FDA) Basilar tip aneurysm Ruptured n= 83 patients Unruptured n=67 patients Subjects deemed ineligible for surgical clipping Mean follow-up time Ruptured 13.7 months (range 0–43) Unruptured 9.8 months (range 0–40 months)	>90% coil packing achieved in 75% of patients	Ruptured 23% Unruptured 12% Peri-operative mortality 2.7% of total cohort		Ruptured up to 3.3% Unruptured up to 4.1%	Permanent deficit due to stroke: Ruptured up to 5% Unruptured up to 9% Vasospasm 8% of all patients (2 deaths)	Detachable platinum coil embolization a promising treatment for ruptured basilar tip aneurysms that are not surgically clippable. The role of this procedure in unruptured basilar tip aneurysms is unclear. More long-term evaluation is necessary.

Appendix 13: Summary of Findings - High Surgical Risk Aneurysms (continued)

Studies	Design	% Occlusion	Mortality	Neuropsychological outcome	Rebleeding	Complication	Conclusion
Miyachi S 1999 (35) Unruptured Vertebro-basilar aneurysms Multicenter case series (1990–1998) (35 affiliated hospitals in a network) n= 103 patients	Endovascular n=60 patients & 63 Aneurysms Surgery n= 43 patients & 43 aneurysms Size of aneurysms (endo) Small = 36/63 large = 15/63 giant = 2/63 Intervention 50/63 saccular embolization 8/63 endovascular trapping occlusion of parent artery 5/63 Types of coils Interlocking coils 29/63 GDC 23/63 Detachable balloons 3/63 Fibre covered coils 4/63	Endovascular embolization Total occl 54% 70–99% occl 30% 50–70% occl = 16% Surgical Incomplete clipping = 1/43	Endovascular =3% Surgical = 7%	Endovascular Excellent or good =92% Fair = 5% Poor = 0% Dead = 3% Surgical Excellent or good = 74.4% Fair = 11.6% Poor = 7% Dead = 7%		Endovascular Total = 30.2% Minor = 70% Major = 30% Basilar artery 90% Vertebral 5% Peripheral artery = 5% By type Perforation 10.5% Vascular occlusion 36.8% Coil migration 15.8% Regrowth 21% Management related 0% Others 15.8% Surgical: Total = 39.5% Minor = 28.6% Major = 71.4% Basilar artery 70.6% Vertebral artery 23.5% Peripheral artery 5.9% By type Vascular occlusion 64.7% Nerve injury 7.6% Incomplete clipping 5.9% Management related 11.8%	Complications of surgery tend to be serious and affect outcome, and endovascular treatment is safer than surgical for vertebro-basilar aneurysms. Embolizations are particularly advantageous for patients who are poor surgical risks.

IDC Interlocking detachable coils (Target Therapeutics, Fremont, CA); GDC Guglielmi detachable coils (Target Therapeutics, Fremont, CA)
Fibre-covered coils (Cook, Bloomington, IN) Occl.=Occlusion; pt.=patients

Appendix 14: Summary of Studies on Cost-effectiveness

Studies	Design & method	Assumptions	Costs Analysis	Cost-Effectiveness Analysis	Conclusion
Bairstow P et al 2002 (51) Comparison of cost and outcome for ruptured intracranial aneurysm Participating centre of the ISAT (Australia)	A subset of patients from an international RCT Endovascular n=10 Surgery n=12 No significant pre-randomization differences Collection of procedural data at 2 & 12 months follow-up.	Cost data includes direct costs of procedure & follow-up. Overhead & acquisition cost NOT included. All costs in Australian currency Due to wide variation in data among patients, the median values were used. Median value Findings Coiling / Surgery Procedure Time: 180 min / 120 min Anesthetic consumables: $292 / $209 $Procedure consumables: $742 / $4,142 Intensive care: 4 days / 4.5 days General ward: 12 days / 8 days Rehab ward: 1 days / 17 days Total post procedure: 22 days / 11.5 days	Median Value Surgery / Coiling Staffing: $985 / $738 Consumables: $1,034 / $4,351 Total Procedure: $2,020 / $5,078 Intensive care: $10,068 / $11,327 General ward: $4,476 / $2,984 Rehab ward: $10,819 / $5,933 Total post-procedure: $19,718 / $13,005	**NOT PERFORMED**	-Endovascular tended to be more expensive in terms of the cost of consumables, the expenses was more than compensated by lower staffing costs and lower cost of postprocedure hospitalization. -following an endovascular procedure, patients tended to return to normal activity or paid employment sooner and have a more favourable functional outcome compared to patients following a neurosurgical procedure.

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