# *Endovascular neurointerventional procedures*

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

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

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Alun Cameron, Ms Philippa Middleton, Ms Christine Barber, Mr Nicholas Marlow and Ms Amber Watt from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). The report was edited by members of the Advisory Panel (see Appendix B). This recommendation was endorsed by the Minister for Health and Ageing on 30th August 2006.

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## Endovascular neurointerventional procedures

Five different topics are covered in this review:

1. Endovascular embolisation of brain and spinal arteriovenous malformations (AVMs).
2. Endovascular embolisation of dural arteriovenous fistulae (DAVF) and carotid-cavernous fistulae (CCF).
3. Endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage (SAH).
4. Endovascular treatments for arterial atherosclerosis.
5. Endovascular treatment of intracranial arteries in acute stroke.

Many different procedures requiring endovascular access to intracranial blood vessels were investigated. This is where a catheter is directed through a blood vessel, commonly the femoral artery or vein at the groin, through which can be passed numerous devices.

AVMs, DAVF, and CCF are various types of abnormalities of intracranial blood vessels which cause incorrect blood flow and swelling or rupture of the blood vessels. These can be removed from the circulation by filling them with various devices such as: coils, glue or detachable balloons, depending on the size and shape of the abnormality and blood flow through the abnormality.

Vasospasm is a common complication following SAH which causes the contraction of intracerebral arteries and a reduced blood flow in the brain tissue, which can lead to long-term neurologic effects or death. This can be treated using an angioplasty balloon, which is introduced into the affected area by passing it over a microguide wire through a catheter and then inflating it to re-canalise the constriction. Angioplasty balloons can also be used in a similar method to improve blood flow through constrictions in arteries seen in intracranial atherosclerosis or acute stroke.

## Medical Services Advisory Committee – role and approach

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

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) in South Australia was engaged to conduct a systematic review of literature on endovascular neurointerventional procedures (Application 1093). An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

## MSAC's assessment of endovascular neurointerventional procedures

### Clinical need

Brain and spinal AVMs are rare diseases:

- in the UK, the crude detection rate was approximately 1 per 100,000 adults per year (Al-Shahi et al 2001);
- Western Australian figures suggest a prevalence of 5 per 100,000 adults per year (ApSimon et al 2002);
- DAVF account for 10-15% of all intracranial malformations (Klisch et al 2004), and dural CCF are a subset of DAVF;
- most CCF are direct and are caused by trauma to the skull base (Ringer et al 2005). The numbers of people presenting with direct CCF has dropped dramatically following the introduction of safety belts and air bags in motor vehicles.

Brain AVMs are responsible for a small proportion of strokes and haemorrhages:

- in young adults where they can be responsible for one-third of all intracerebral haemorrhages (Al-Shahi and Warlow 2001).

Vasospasm is the main cause of morbidity and mortality for people who survive an aneurysmal SAH and:

- is thought to account for about 4% of all strokes (Australian Cooperative Research on Subarachnoid Haemorrhage Study (ACROSS) Group 2000);
- can be detected with angiography in around 70% of untreated patients following aneurysmal SAH (Dorsch 2002). This becomes clinically relevant when this leads to a reduction in blood flow through the affected arteries, causing possibly irreversible ischaemic effects in the brain tissue.

Intracranial atherosclerosis accounts for between 8-29% of ischaemic strokes (Schumacher et al 2004), and can occur as a consequence of systemic atherosclerotic disease.

Strokes are common in Australia:

- stroke is the third most common cause of death and is a major cause of disability (Hankey 2000);
- 50,000 Australians have a stroke annually (almost three-quarters are first-ever strokes), with 33,416 hospitalisations for stroke in 2003-4;
- in 2003, a total of 9,006 Australians died of a stroke, accounting for 7% of all deaths during that year (see www.aihw.gov.au).

Few comparative studies which investigated intracranial endovascular procedures used devices which were registered for this indication with the Therapeutic Goods Administration (TGA). There was only one randomised controlled trial which was not directly relevant. Therefore it is not possible to comment on the safety, effectiveness or cost-effectiveness of these procedures compared to the current standard treatment or no treatment; however, available information has been summarised.

## Safety

Studies for treatment of AVMs, showed:

- mortality decreased for patients in one study who were treated with endovascular embolisation compared to conservative treated;
- mortality was lowest for patients in two studies who were treated with surgery, radiosurgery, or endovascular embolisation with surgery or radiosurgery;
- in these studies embolisation was often used when the AVM was unable to be treated by any other method, due to nidus location or size, or patient condition;
- DAVF - the only deaths reported in the two available comparative studies occurred in patients treated with conservative treatments. Other adverse events were transient for embolisation, and a vision defect was seen in one patient treated with radiosurgery.
- CCF - no deaths were reported in any study for any treatment technique. The only long-term morbidity recorded was in a patient treated with radiosurgery.
- Vasospasm - two studies investigated the use of balloon angioplasty used as a prophylaxis measure to treat possible vasospasm after SAH. Most deaths and adverse events were seen in the conservatively-treated group, mostly as a result of vasospasm. In patients treated with angioplasty there was one death from a complication and no other reported adverse events.

One historical comparative study was available for investigation of endovascular treatment of intracranial atherosclerosis. There was no conservatively-treated group. The fewest adverse events were seen using the latest balloon angioplasty technique, which could be as a result of improved technique and increasing experience of the neurointerventional team.

Two stroke studies used balloon angioplasty treatment following failed intra-arterial thrombolysis. This technique is not registered for intracranial use in Australia. There were no deaths in one study. In the second an equal number of deaths in the angioplasty-treated group and the control group included patients who were rated in worse clinical condition than the first study.

## Effectiveness

Studies for effectiveness of treatment of:

- AVMs - one study showed that patient outcome was significantly improved with endovascular occlusion followed by surgery compared to surgery alone. In another study, patient outcome was improved in endovascular occlusion compared with conservative treatment; however, in two other studies patients treated with embolisation had poor outcomes compared to surgery alone, radiosurgery alone or surgery following embolisation.

- DAVF - the most successful techniques used were surgery or multimodal approaches such as endovascular embolisation followed by surgery; however, one study reported endovascular embolisation alone was an improvement over conservative treatment.

- CCF in available studies:

    - patients were mainly treated with endovascular embolisation, followed in some cases by radiosurgery and no CCF were treated with surgery;

    - in two studies, radiosurgery alone provided improvement in 100% of the patients treated.

    - embolisation alone provided improvement in 100% of patients in another study;

    - embolisation with radiosurgery gave mixed patient outcome in the studies, possibly as this method was used to treat large or difficult CCF. Recurrent symptoms were only seen in this group of patients, who were treated with further embolisation.

- Vasospasm - there was an improved clinical outcome in both studies in patients treated with balloon angioplasty compared with control patients. This difference was statistically significant in one study. None, or very few patients, suffered vasospasm after treatment with angioplasty compared with around half of all those treated conservatively.

- Intracranial atherosclerosis - the most improved patient outcomes were seen using the latest balloon angioplasty technique, which could be from improved technique and increasing experience of the neurointerventional team.

- Stroke - there was an improved clinical outcome for the patients treated with angioplasty compared to the control group in both studies. This reached statistical significance in one study at one-day postoperative, but there was no statistical difference at one-month postoperative in either study.

## Cost-effectiveness

Due to a lack of published literature, it was not possible to determine cost-effectiveness of any of the intracranial endovascular procedures investigated in this report.

## Expert opinion

Many different types of endovascular techniques are used intracranially, and reported in published studies. It was not possible to report on some of them as they are not indicated on the TGA for use in Australian hospitals. There are only a small number of patients who can receive these treatments, and little economic reason for a company to trial and register their devices for these intracranial indications. Often there is no comparator procedure available to a particular endovascular technique, therefore there were limited comparative studies from which to gauge the safety and effectiveness of these procedures.

In Australia:

- DAVF and CCF are treated mostly with endovascular techniques rather than surgery;
- the endovascular technique used for some conditions often differs from techniques discussed in published studies;
- the treatment of choice in Australian hospitals for medically-refractory symptomatic vasospasm (given experience and technical backup), is the intra-arterial infusion of vasodilators; however, vasodilators are not indicated for this use by the TGA and are only used in this manner after local hospital ethics approval has been granted;
- balloon angioplasty is considered too dangerous to be used prophylactically as not all individuals who suffer SAH will go on to develop vasospasm where a symptomatic reduction in blood flow requires immediate and intensive management. Balloon angioplasty is not used to treat vasospasm, mainly due to the inability to guide a reasonably large device through the delicate intracranial arteries, as there is the possibility of causing arterial rupture through balloon inflation.

## Recommendation

MSAC made the following recommendation for the first two indications:

MSAC has considered the respective evidence for safety, effectiveness and cost effectiveness for brain arteriovenous amalgamations and endovascular remobilisation of dural arteriovenous fistulae and carotid cavernous fistulae.

MSAC finds that there is evidence of safety compared with alternative therapies.

There is insufficient evidence to assess effectiveness and cost effectiveness. Given that there are limited treatment options MSAC recommends that current public funding arrangements should continue.

MSAC made the following recommendation for the final three indications:

MSAC has considered the strength of evidence for the safety and effectiveness for endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage, endovascular treatments for arterial atherosclerosis and endovascular treatment of intracranial arteries in acute stroke and finds that there is insufficient evidence of safety and effectiveness.

MSAC recommends that public funding for these interventions should not be supported.

- The Minister for Health and Ageing endorsed this recommendation on 30th August 2006 -

# Introduction

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

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

This report summarises the assessment of current evidence for endovascular treatments of five different neurointerventional procedures.

# Background

The treatment of neurovascular disease is a complex field of neurology, neuroradiology and surgery. It must balance the delicate nature of the intracerebral vasculature and related problems of complications with the urgency of intervention to save the neurological function and life of the patient. The range of diseases involving brain and spinal cord blood vessels include those associated with:

- atherosclerotic disease (stenosis of intracranial vessels and acute ischaemic stroke);
- vascular malformations caused by congenital effects or trauma (arteriovenous malformations (AVM);
- dural arteriovenous fistulae (DAVF);
- carotid-cavernous fistulae (CCF);
- vasospasm of intracerebral arteries caused from subarachnoid haemorrhage.

The endovascular treatment of neurovascular diseases is a specialised and growing area of neuro-intervention. Recent advances in endovascular technology, including soft atraumatic microcatheters and steerable microguidewires, enable safer access of the intracranial vessels. A number of different devices have been developed which can allow the relatively safe treatment of intracranial problems. The possible benefits include a much less invasive treatment than surgery and a more effective intervention than medical regimens; however, these techniques are relatively new and their effectiveness is not fully confirmed for all diseases.

The safety and efficacy of these interventions was assessed by examining and analysing the available published literature, and investigated whether each particular endovascular intervention was an improvement over current surgical interventions or medical treatments.

The review assesses the following five groups of endovascular approaches:

1. Endovascular embolisation of brain and spinal arteriovenous malformations
2. Endovascular embolisation of dural arteriovenous fistulae and carotid-cavernous fistulae
3. Endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage
4. Endovascular treatments for arterial atherosclerosis
5. Endovascular treatment of intracranial arteries in acute stroke.

## Questions of the review

### 1. Endovascular embolisation of brain and spinal arteriovenous malformations

The primary objective of this review is to compare the safety, effectiveness and cost-effectiveness of endovascular treatments for occlusion of AVMs with the current standard treatments (surgical excision, stereotactic radiosurgery or no treatment).

There are a number of subsidiary questions which may be answered by this review:

- Are there malformation characteristics such as location, size or type which affect the safety or effectiveness of endovascular or surgical treatment?
- Is there variability in the safety and effectiveness of the types of endovascular devices used (eg coil, glue, stent, balloon)?
- Are there patient characteristics such as the clinical grade of the patient at presentation, age or presence of comorbidities which affect the safety or effectiveness of endovascular or surgical treatments?
- Are there differences in outcomes for patients who have been treated with an endovascular approach alone, compared with those who have been treated with endovascular techniques together with surgery or radiosurgery?

### 2. Endovascular embolisation of dural arteriovenous fistulae and carotid-cavernous fistulae

The primary objective of this review is to compare the safety, effectiveness and cost-effectiveness of endovascular treatments for occlusion of CCF and DAVF with the current standard treatments (stereotactic radiosurgery, conservative treatment or no treatment).

There are a number of subsidiary questions which may be answered by this review:

- Are there fistula characteristics such as size, location or type (direct or indirect) which affect the safety or effectiveness of endovascular or surgical treatment?
- Is there variability in the safety and effectiveness of the types of endovascular devices used (eg coil, glue, stent, balloon)?
- Does the endovascular route have an effect on the safety and effectiveness of the treatment (eg intra-arterial, intravenous (IV) (femoral) or intravenous (superior ophthalmic vein (SOV)))?
- Are there patient characteristics such as the clinical grade of the patient at presentation, age or presence of comorbidities which affect the safety or effectiveness of endovascular or other treatments?

- Are there differences in outcomes for patients who have been treated with an endovascular approach alone, compared with those who have been treated with endovascular techniques together with surgery or radiosurgery?

### 3. Endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage

The primary objective of this review is to compare the safety, effectiveness and cost-effectiveness of endovascular treatments for vasospasm with the current standard treatments (optimal medical therapy or no treatment).

There are a number of subsidiary questions which may be answered by this review:

- Are there vasospasm characteristics such as its severity or distribution which affect the safety or effectiveness of endovascular or medical treatment?
- Is there variability in the safety and effectiveness of the types of endovascular devices used (eg balloon angioplasty or intra-arterial infusion of vasodilators)?
- Are there patient characteristics such as the clinical grade of the patient at presentation, age or presence of comorbidities which affect the safety or effectiveness of endovascular or medical treatments?

### 4. Endovascular treatments for intracranial atherosclerosis

The primary objective of this review topic is to compare the safety, effectiveness and cost-effectiveness of endovascular treatments for intracranial arterial atherosclerosis with the current standard treatments (best medical therapy, no treatment or occasional surgical bypass).

There are a number of subsidiary questions which may be answered by this review:

- Are there stenosis characteristics such as location or magnitude which affect the safety or effectiveness of endovascular or medical treatment?
- Is there variability in the safety and effectiveness of the types of endovascular devices used?
- Are there patient characteristics such as the clinical grade of the patient at presentation, age or presence of comorbidities which affect the safety or effectiveness of endovascular or medical treatments?

### 5. Endovascular treatment of intracranial arteries in acute stroke

The primary objective of this review is to compare the safety, effectiveness and cost-effectiveness of endovascular treatments for acute ischaemic stroke with the current standard treatments (optimal medical therapy, intravenous thrombolytic agent or no treatment).

There are a number of subsidiary questions which may be answered by this review:

- Are there stroke characteristics such as location or size of the atherosclerotic clot which affect the safety or effectiveness of endovascular or medical treatment?
- Is there variability in the safety and effectiveness of the types of endovascular devices used?
- Are there patient characteristics such as the clinical grade of the patient at presentation, age or presence of comorbidities which affect the safety or effectiveness of endovascular or surgical treatments?
- How important is time-to-treatment following the onset of stroke, depending on whether endovascular or medical treatments are used?

## Marketing status of the technology

Endovascular devices for treating the intracranial problems covered in Reference 1093 that are listed on the Australian Register of Therapeutic Goods (ARTG) are shown in the following table. None of the devices in this table including microcatheters, coils or microballoon catheters were indicated specifically for intracranial use.

Table 1 Endovascular devices for intracranial treatment registered on ARTG.

| Description | Sponsor | ARTG number | Application (see below for key) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 |
| Microcatheters | | | • | • | • | • | • |
| Excelsior microcatheter (various) | Boston Scientific Pty Ltd | 58842 (Product ID 142216) | | | | | |
| Tracker Excel guiding microcatheter (various) | Boston Scientific Pty Ltd | 58842 (Product ID 142217) | | | | | |
| Tracker Excel infusion microcatheter (various) | Boston Scientific Pty Ltd | 72038 (Product ID 141751) | | | | | |
| Detachable Platinum coils | | | • | • | | | |
| Guglielmi Detachable Coils (various sizes) | Boston Scientific Pty Ltd | 48608 (Product ID 102803) | | | | | |
| Vortx-35 fibered platinum coil (various sizes) | Boston Scientific Pty Ltd | 48608 (Product ID 114478) | | | | | |
| GDC Trispan coils (various sizes) | Boston Scientific Pty Ltd | 48608 (Product ID 142198) | | | | | |
| Matrix SR Detachable Coils | Boston Scientific Pty Ltd | 114316 (Product ID 193870) | | | | | |
| Trufill DCS detachable coil (various models) | Johnson & Johnson Medical | 56630 (Product ID 146748) | | | | | |
| Microplex coil systems (various) | N. Stenning & Co. | 83194 (Product ID 155089) | | | | | |
| Hydrocoil system (various) | N. Stenning & Co. | 83194 (Product ID 161446) | | | | | |
| Micrus platinum microcoil delivery system (various sizes and configurations) | Medtel | 78178 (Product ID 147307) | | | | | |
| Sapphire Detachable Coil | Device Technologies Australia | 77883 (Product ID 146944) | | | | | |
| Detachable Embolisation Coils (various) | William A Cook Australia | 21823 (Product ID 144500) | | | | | |
| Liquid embolics | | | • | • | | | |
| Onyx system | Device Technologies Australia | 71300 (Product ID 136502) | | | | | |
| Histoacryl *n*-butylcyanoacrylate (NBCA) surgical tissue adhesive | B Braun Australia Pty Ltd | 10429 (Product ID 61447) | | | | | |

| Description | Sponsor | ARTG number | Application | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 |
| Microballoon catheters | | | • | • | | | |
| Occlusion Balloon Catheter (various) – Hyperform and Hyperglide | Device Technologies Australia | 71132 (Product ID 136224) | | | | | |
| Sentry Occlusion Balloon Catheter (various sizes) | Boston Scientific Pty Ltd | 58842 (Product ID 142197) | | | | | |
| Stents | | | • | • | | | |
| Neuroform 2 Stent | Boston Scientific Pty Ltd | 94705 (Product ID 165341) | | | | | |
| Particles | | | • | • | | | |
| Trufill PVA embolisation particles (various) | Johnson and Johnson Medical Pty Ltd | 56630 (Product ID 112987) | | | | | |
| PVA particles | Boston Scientific Pty Ltd | 31918 (Product ID 57844) | | | | | |
| Snare devices | | | | | | | • |
| Amplatz gooseneck microsnare kit (not indicated for intracranial use) | EV3 Australia Pty Ltd | 117105 (Product ID 197289) | | | | | |

Key:
1 = Endovascular embolisation of intracranial or spinal arteriovenous malformations
2 = Endovascular treatment of dural arteriovenous fistulae and carotid-cavernous fistulae
3 = Endovascular treatment of vasospasm caused by subarachnoid haemorrhage
4 = Endovascular treatment of intracranial arteriosclerosis
5 = Endovascular treatment of intracranial arteries in acute stroke

## Current reimbursement arrangements

There are currently no Medical Benefits Schedule (MBS) numbers specifically for intracranial endovascular treatments. However procedures such as the surgical excision of intracranial AVMs and obliteration of CCF are listed.

# Approach to assessment

## Review of literature

### Search strategy

MEDLINE, EMBASE, Current Contents, PubMed and the Cochrane Library were searched to identify relevant studies (9th January 2006). As agreed by the Advisory Panel, the searches were date restricted to 1990 to ensure that only currently available endovascular treatments were included. The York (UK) Centre for Reviews and Dissemination (CRD) databases, Clinicaltrials.gov, National Research Register, relevant online journals and the Internet were also searched. Searches were conducted without language restriction.

The search strategies used were:

#### Embolisation of intracranial or spinal arteriovenous malformations (AVMs)

Ovid MEDLINE from 1996

1. MeSH search using the term (arteriovenous fistula OR intracranial arteriovenous malformations);
2. Keyword search using the term (central nervous system vascular malformations).

Ovid EMBASE from 1980

1. MeSH search using the term (brain arteriovenous malformation) and the subheadings (complication/congenital disorder/disease management/drug therapy/epidemiology/etiology/ radiotherapy/rehabilitation/surgery/therapy);
2. Keyword search using the term (spinal dural arteriovenous fistula);
3. Keyword search using the term (dural arteriovenous fistula).

The Cochrane Library and mRCT database

1. Keyword search using the term (arteriovenous malformation);
2. Keyword search using the term (dural arteriovenous fistula).

#### Endovascular treatments for dural arteriovenous fistulae (DAVFs) and carotid-cavernous fistulae (CCF)

Ovid MEDLINE from 1996

1. Keyword search using the term (carotid-cavernous sinus fistula).

Ovid EMBASE from 1980

1. Focus search using the term (carotid-cavernous sinus fistula) and the subheadings (complication/congenital disorder/disease management/drug therapy/epidemiology/prevention/radiotherapy/side effect/surgery/therapy).

The Cochrane Library and mRCT database

1. Keyword search using the term (carotid-cavernous sinus fistula).

#### Vasospasm (SAH-induced)

Ovid MEDLINE from 1996

1. MeSH search using the term (vasospasm, intracranial) (all subject headings (a search for one Medical Subject Heading term may cover many subject headings and subheadings)).

Ovid EMBASE from 1980

1. Focus search using the term (brain vasospasm) (all subject headings).

The Cochrane Library and mRCT database

1. Keyword search using the term (vasospasm).

#### Endovascular treatments for intracranial arteriosclerosis

Ovid MEDLINE from 1996

1. MeSH search using the term (intracranial arteriosclerosis);
2. MeSH search using the term (stents);
3. MeSH search using the term (intracranial) and subheading (intracranial arteriosclerosis);
4. Terms from searches (2) and (3) combined.

Ovid EMBASE from 1980

1. Focus search using the term (intracranial arteriosclerosis) (all subject headings)
2. Re-execution of search (4) from MEDLINE

The Cochrane Library and mRCT database

1. Keyword search using the term (intracranial stenting);
2. Keyword search using the term (intracranial arteriosclerosis).

#### Endovascular treatment of intracranial arteries in acute stroke

Ovid MEDLINE from 1996

1. MeSH search using the term (thrombolytic therapy AND (intracranial stenosis OR cerebrovascular accident)).

Ovid EMBASE from 1980

1. Search using the term (blood clot lysis AND cerebrovascular accident)

The Cochrane Library and mRCT database

1. Keyword search using the term (thrombolysis).

*Note:* Where possible, searches were limited to studies in humans.

# Inclusion criteria

Table 2 Inclusion criteria for embolisation of intracranial or spinal arteriovenous malformations (AVMs)

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Participants | Human studies of patients (children and adults, including congenital connective tissue disorders) where the treatment of the AVM is the primary concern.<br>Include if AVM has an associated aneurysm | Results for patients with ruptured or unruptured intracranial aneurysms as the primary treatment |
| New intervention | Endovascular embolisation with coils, flexible stents, balloons, liquid embolic, alcohol, particles etc<br>Include if more than one endovascular intervention is used<br>Include endovascular intervention if used as retreatment after failure of initial surgery<br>Include endovascular intervention if used in combination with surgery or radiosurgery | Treatment combined with treatment for another condition (eg tumour excision)<br>Treatment not approved for use for this indication in Australia |
| Comparative intervention | Stereotactic radiosurgery (eg gamma knife)<br>Open craniotomy microsurgery (often preferable for grade 1 and 2 accessible lesions)<br>Multimodal approach popular (endovascular or radiosurgery followed by surgery)<br>Conservative / best medical treatment<br>No treatment (spontaneous regression does occur) | |
| Outcomes | Peri and postoperative morbidity and mortality<br>Efficacy and durability of treatment, including but not limited to:<br>- technical success<br>- complication (stroke) reduction<br>- postoperative imaging studies<br>- reoperation / retreatment rates<br>Patient-relevant outcomes, including but not limited to:<br>- survival<br>- functional and neurological outcomes (including symptom relief of mass effect)<br>- cognitive outcomes<br>- psychological and psychosocial outcomes<br>- quality of life<br>- return to work/normal activities<br>Complications, including but not limited to:<br>- technical (coil compaction, haemorrhage)<br>- clinical (transient or permanent neurological deficits)<br>Cost and resource use issues | Technical not clinical outcomes |
| Types of studies | Randomised and non-randomised comparative studies | Case series and case reports |
| Language | Studies in languages other than English will be included if they add substantially to the English language evidence base | |

Table 3 Inclusion criteria for endovascular occlusion of dural arteriovenous fistulae (DAVF) and carotid-cavernous fistulae (CCF)

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Participants | Human studies (adults and children) where treatment of the DAVF or CCF is the primary concern<br>CCF may be direct (high flow / traumatic (common in young adult males)) or indirect (low flow congenital (including Ehlers-Danos syndrome)), or spontaneous (older females)<br>DAVF or CCF brought about by any cause, including previous surgery or any connective tissue disease | Results for patients with ruptured or unruptured intracranial aneurysms as the primary treatment |
| New intervention | Endovascular embolisation of DAVF or CCF with:<br>Balloon, alcohol, coils, stents, glue etc.<br>Carotid / parent artery sacrifice with embolic agents<br>Any combination of different embolic agents<br>Endovascular techniques in combination with any other intervention<br>Any approach – intra-arterial, intravenous, superior ophthalmic vein (SOV) etc. | Treatment combined with treatment for another condition (eg tumour excision) |
| Comparative intervention | Stereotactic radiosurgery<br>Conservative / best medical treatment<br>No treatment (unsuitable for surgery) – dural fistulae can spontaneously resolve | |
| Outcomes | Peri- and postoperative morbidity and mortality<br>Efficacy and durability of treatment, including but not limited to:<br>- technical success<br>- reoperation/retreatment rates<br>Patient-relevant outcomes, including but not limited to:<br>- survival<br>- functional and neurological outcomes (including symptom relief of mass effect, especially vision)<br>- cognitive outcomes<br>- psychological and psychosocial outcomes<br>- quality of life<br>- return to work/normal activities<br>Complications<br>- technical (coil compaction, haemorrhage)<br>- clinical (transient or permanent neurological deficits)<br>Cost and resource use issues | Technical not clinical outcomes |
| Types of studies | Randomised and non-randomised comparative studies | Case series and case reports |
| Language | Studies in languages other than English will be included if they add substantially to the English language evidence base | |

Table 4 Inclusion criteria for endovascular treatment of vasospasm induced by subarachnoid haemorrhage

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Participants | Human studies of patients (adults and children). Vasospasm after SAH, both angiographic and symptomatic (marking the onset of ischaemic consequences) | |
| | Original aneurysm treated by surgical or endovascular approach | |
| | Include patients who have been given prophylaxis (including cisternal drainage or irrigation), optimal medical therapy, or no medical therapy | |
| New intervention | Balloon angioplasty of intracranial vessel | Intra-arterial infusion of vasodilators (no vasodilators are registered for this use in Australia) |
| Comparative intervention | Best medical treatment (HHH therapy – hypervolaemic, hypertensive & hyperdynamic therapy) | |
| | Pharmacologic regimen (eg IV nimodipine) | |
| | Both | |
| | With or without prophylaxis | |
| | No treatment | |
| Outcomes | Peri and Postoperative morbidity and mortality | Technical not clinical outcomes |
| | Efficacy and durability of treatment, including but not limited to: | |
| | - angiographic (improved vessel calibre) | |
| | - intracranial pressure (when using smooth muscle relaxants) | |
| | - technical success | |
| | - reoperation/retreatment rates | |
| | - postoperative imaging studies | |
| | Patient-relevant outcomes, including but not limited to: | |
| | - survival | |
| | - complication (stroke) reduction | |
| | - functional and neurological outcomes | |
| | - cognitive outcomes | |
| | - psychological and psychosocial outcomes | |
| | - quality of life | |
| | - return to work/normal activities | |
| | Complications | |
| | - technical (coil compaction, haemorrhage) | |
| | - clinical (transient or permanent neurological deficits) | |
| | Cost and resource use issues | |
| Types of studies | Randomised and non-randomised comparative studies | Case series and case reports |
| Language | Studies in languages other than English will be included if they add substantially to the English language evidence base | |

Table 5 Inclusion criteria for endovascular treatment of intracranial arteriosclerosis

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Participants | Human studies of patients (adults, possibly children) with intracranial atherosclerotic plaque | |
| New intervention | Endovascular approach with:<br>Balloon angioplasty with or without optimal medical treatment | Stents<br>Stent-assisted angiography<br>(Stents are not registered for use in intracranial vessels in Australia)<br>Treatment combined with treatment for another condition (eg artery protection during tumour excision) |
| Comparative intervention | Antithrombotic therapy (antiplatelet or anticoagulation)<br>Best medical treatment (warfarin or aspirin)<br>No treatment | |
| Outcomes | Peri- and postoperative morbidity and mortality<br>Efficacy and durability of treatment, including but not limited to:<br>- extent of recanalisation<br>- technical complications (distal embolisation, vessel dissection, arterial rupture)<br>- reoperation/retreatment rates<br>Patient-relevant outcomes, including but not limited to:<br>- survival<br>- functional and neurological outcomes (including symptom relief of mass effect)<br>- cognitive outcomes<br>- psychological and psychosocial outcomes<br>- quality of life<br>- return to work/normal activities<br>Cost and resource use issues | Technical not clinical outcomes |
| Types of studies | Randomised and non-randomised comparative studies | Case series and case reports |
| Language | Studies in languages other than English will be included if they add substantially to the English language evidence base | |

Table 6 Inclusion criteria for endovascular treatment of intracranial arteries in acute stroke

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Participants | Human studies of patients with acute ischaemic stroke | Patients who have suffered transient ischaemic attack, or stroke due to haemorrhage, not acute ischaemic stroke |
| New intervention | Endovascular approach with:<br>Balloon angioplasty with or without optimal medical treatment (intra-venous or oral) | Intraarterial infusion of thrombolytic agents (eg tissue plasminogen activator (human recombinant) (tPA), urokinase)<br>Snaring devices (nets, wires, Merci system etc.)<br>Clot disruption devices (jets, laser, ultrasound etc)<br>(These devices and drugs are not registered for this use in Australia)<br>Treatment combined with treatment for another condition (eg tumour excision) |
| Comparative intervention | Systemic antithrombotic therapy (antiplatelet or anticoagulation) (eg IV tPA)<br>Best medical treatment (heparin, warfarin, aspirin)<br>No treatment | |
| Outcomes | Peri- and postoperative morbidity and mortality<br><br>Efficacy and durability of treatment, including but not limited to:<br>- extent of recanalisation<br>- technical complications (distal embolisation, intracranial haemorrhage)<br>- reoperation/retreatment rates<br><br>Patient-relevant outcomes, including but not limited to:<br>- survival<br>- functional and neurological outcomes<br>- cognitive outcomes<br>- psychological and psychosocial outcomes<br>- quality of life<br>- return to work/normal activities<br><br>Cost and resource use issues | Technical not clinical outcomes |
| Types of studies | Randomised and non-randomised comparative studies | Case series and case reports |
| Language | Studies in languages other than English will be included if they add substantially to the English language evidence base | |

# Methods of the review

## Literature database

Articles were retrieved if they were judged to possibly meet the inclusion criteria. Two reviewers independently applied the inclusion criteria and any differences were resolved by discussion. Excluded studies are listed in Appendix F with reasons for exclusion. The bibliographies of all retrieved publications were handsearched for any relevant references missed in the database search (pearling).

## Data extraction

Data was extracted by one researcher and checked by a second using standardised data extraction tables developed a priori. Data was reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data was reported for a particular outcome then no value was tabulated.

## Description and methodological quality of included studies

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

These dimensions (Table 7) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two required expert clinical input as part of its determination.

Table 7 Evidence dimensions

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

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 8.

Table 8 Designations of levels of evidence

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

*Modified from NHMRC 1999.

Included studies were critically appraised for study quality according to the guidelines in Chapter 6 of the Cochrane Reviewers' Handbook (Alderson et al 2004). Included randomised controlled trials (RCTs) were examined with respect to the adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up, and any other aspect of the study design or execution that may have introduced bias. Non-randomised comparative studies were evaluated for the method of patient selection, comparability of the patient groups, completeness of follow-up, and any other feature of the study design or execution that may have introduced bias. Case series were examined with respect to the use of consecutive patient selection, losses to follow-up and reporting of outcomes. Two reviewers critically appraised each of the included studies, and any differences in interpretation were resolved through discussion. A quality score was not assigned, instead the quality of the included studies was described in a narrative fashion and any important quality issues were highlighted in the discussion of outcomes.

## Data analysis

### Meta-analysis

Where outcomes of RCTs could be sensibly combined (outcomes measured in comparable ways and no apparent heterogeneity), relative risks or weighted mean differences with 95% confidence intervals (CI) would have been calculated using RevMan 4.2 (Update Software). Relative risks or weighted mean differences would also have been calculated for some outcomes of individual RCTs as an aid in the interpretation of results. The confidence intervals represent a range within which the 'true' value of an effect size is expected to lie, with a given degree of certainty eg 95% CI.

Subgroup analyses would have been carried out for certain variables if possible.

### Handling of non-randomised data

Where statistical pooling was not possible, medians of rates (for dichotomous outcomes) or medians of means (for continuous outcomes) for all studies reporting the outcome were calculated. The data will be presented according to the comparison (eg endovascular procedure alone versus surgery alone) or endovascular intervention (for case series and case reports).

The following subgroups were also examined narratively:

- size;
- location;
- patients in poor grade (using Hunt and Hess or similar grading scheme);
- older patients;
- patients with significant comorbidities.

## Included studies

The number of studies identified as fulfilling the inclusion criteria for the review is summarised in Table 9 and listed in Appendix E.

## Expert advice

An advisory panel with expertise in neurology, neurosurgery and interventional neuroradiology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided in Appendix B.

Table 9 Summary of the included studies for endovascular neurointerventional procedures

| Study | Intervention | Level of evidence |
|---|---|---|
| 1. AVM | | |
| DeMeritt et al 1995 | Surgery; surgery and endovascular embolisation | III-3 |
| Deruty et al 1993 | Surgery alone; endovascular embolisation followed by surgery; embolisation alone; radiosurgery alone | III-3 |
| Sasaki et al 1998 | Conservatively-treated; surgery; endovascular embolisation; gamma knife radiosurgery | III-3 |
| Tomsick et al 2002 | NBCA glue embolisation; PVA particle embolisation | II |
| Nakazawa et al 2003 | Embolisation using the following glues: EVAL; eudragit-E; NBCA | III-2 |
| Total | 5 | |
| 2. DAVF and CCF | | |
| Chung et al 2002 | Conservative; embolisation; radiosurgery; surgical excision; multimodal | III-2 |
| De Paula Lucas et al 2005 | Surgery only; endovascular occlusion only; endovascular occlusion & surgery | III-2 |
| Song et al 2001 | Surgery only; embolisation only; embolisation and surgery | III-2 |
| Bavinzski et al 1996 | Endovascular; endovascular and surgery; endovascular and radiosurgery; radiosurgery | III-2 |
| Pollock et al 1999 | Radiosurgery alone; radiosurgery and embolisation | III-2 |
| Total | 5 | |
| 3. Vasospasm | | |
| Katoh et al 1999 | Therapeutic angioplasty; 'prophylactic' angioplasty; conservatively-treated controls | III-2 |
| Muizelaar et al 2001 | Prophylactic angioplasty; conservatively-treated controls | III-2 |
| Total | 2 | |
| 4. Atherosclerosis | | |
| Connors et al 1999 | Balloon angioplasty (three different techniques) | III-3 |
| Total | 1 | |
| 5. Acute stroke | | |
| Ringer et al 2001 | Balloon angioplasty following failed intra-arterial urokinase thrombolysis | III-2 |
| Ueda et al 1998 | Balloon angioplasty following failed intra-arterial urokinase thrombolysis | III-2 |
| Total | 2 | |
| TOTAL STUDIES | 15 | |

# Results of assessment

Five separate topics were investigated under the broad heading of endovascular neurointerventional procedures. These were:

1. Arteriovenous malformations
2. Dural arteriovenous fistulae and carotid-cavernous fistulae
3. Vasospasm as a result of subarachnoid haemorrhage
4. Intracranial atherosclerosis
5. Acute stroke

Search strategies were employed as described earlier, adhering to the inclusion criteria for each topic (Tables 2 - 6). The included studies were critically appraised and reported according to patient allocation and study outcomes, specifically concerning the safety and effectiveness of the techniques employed. Economic evaluation was considered where possible.

# 1. Background: Endovascular embolisation of brain and spinal arteriovenous malformations

Arteriovenous malformations (AVMs) are vascular abnormalities in the brain or spinal cord that vary greatly in their locations, sizes, shape and blood flow. The great heterogeneity in their anatomy makes prognosis and treatment choice difficult. A decision as to whether a treatment is warranted considers surgery, stereotactic radiosurgery or an endovascular approach.

Endovascular techniques have been used successfully over many years in the treatment of AVMs. This method involves the embolisation of the malformation using devices such as particles, glue and occasionally coils.

The choice of the specific technique used is dependent on the angioarchitecture of the abnormality. Large AVMs (ie more than 3cm maximum diameter or having a volume above $15cm^3$) are difficult to obliterate completely, and can require a combination of two or more treatment modalities (Henkes et al 1998).

Treatment of smaller AVMs may have an unacceptable risk/benefit ratio compared to the natural course of the disease, as smaller malformations are less likely to be symptomatic. However, most AVMs will become symptomatic during the lifetime of the patient, so will require management dependent on this risk/benefit ratio compared to the natural course of the disease (Apsimon et al 2002).

## Arteriovenous malformations

Arteriovenous malformations (AVMs) are lesions comprising a tangled mass of connected arteries and veins without an intervening capillary bed. They are highly heterogeneous in their size, shape and location. These abnormal focal arteriovenous shunts are generally thought to be congenital, although little is known about their natural history. There are very few reports of AVMs in neonates, so it is thought that they develop over time, which concurs with the age-related risk for an AVM-related symptom.

The incidence of AVMs in the adult population is:

- around 1 per 100,000 (Al-Shahi and Warlow 2001);
- most frequently revealed in people between 20-40 years of age (Soderman et al 2003), and are the most common cause of stroke in this age group;
- about 1% of all strokes (Ogilvy et al 2001).

AVMs present with:

- haemorrhage in 50% cases;
- 25% focal or generalised seizures; and
- 15% headache, local neurological deficits or other relatively mild symptoms (Brown et al 2005).

The remainder of AVMs are found incidentally (Ogilvy et al 2001). As imaging technology improves, a greater number of AVMs are being identified before haemorrhage.

The risk of developing neurological symptoms from an AVM increases with lesion size and is higher in centrally located AVMs.

After presentation, the risk of haemorrhage is:

- about 3-4% for a 30-year-old patient with AVM (Soderman et al 2003);
- approximately 2 to 3% per year (Brown et al 2005); although
- the risk of recurrent haemorrhage may be as high as 18% in the first year (Al-Shahi and Warlow 2001); and is
- even higher in the first year after the second haemorrhage (Ogilvy et al 2001). Severe vasospasm as a result of AVM-related haemorrhage is uncommon (Ogilvy et al 2001).

Of the many grading systems proposed to quantify relative risk associated with surgery on a particular AVM, the Spetzler-Martin scale (Appendix C, Table 62) is the most commonly adopted by treating neurointerventional physicians (Spetzler and Martin 1986, Ogilvy et al 2001). A score of 4 or 5 is associated with the highest risk of persistent neurological deficits after surgery.

### Pathophysiology of AVMs

AVMs are dynamic lesions which can quickly increase in size, regress or disappear spontaneously (Soderman et al 2003). Although their natural history is not fully understood, certain genetic diseases of connective tissue proteins, for example Ehlers-Danlos syndrome (EDS) type IV, can lead to an increased risk of intracranial vascular malformations.

The arteriovenous shunts seen in AVMs are caused by a tangle of arteries and veins with no intervening capillary bed, which leads to vessel wall thickening and elastic tissue destruction (Soderman et al 2003).

The central nidus may be fed by one or more arteries, with one or more veins draining the blood flow into superficial or deep venous systems. The increased blood pressure in these lesions causes vessel dilation. Stretching of the vessels may cause wall thinning which can lead to intranidal aneurysms, which are associated with between 10% and 50%

of patients with AVM (Al-Shahi and Warlow 2001). AVM histology includes clusters of normal or dilated arteries and abnormal veins with calcification and occasionally some prior haemorrhage (Brown et al 2005).

The high blood flow through the malformation can lead to cerebral hypoperfusion which may cause ischaemia in brain tissue adjacent to the lesion, known as a 'steal' phenomenon (AMSG 1999). Alternatively, the more likely mechanism for neurological deficits may be through venous hypertension and swelling.

## Endovascular procedures

Location, size, anatomy and global haemodynamics of AVMs affect the overall outcome of the disease and the choice of best treatment modality. Technical advantages in imaging have increased the detail available to the neurointerventionist regarding the abnormality, as well as improving the detection rates prior to haemorrhage. Computed tomography (CT) and magnetic resonance imaging (MRI) can be used to locate AVMs after haemorrhage, and will give some information on the lesion. Digital subtraction angiography will give more detail on the lesion and blood flow, and is the best technique for accurate diagnosis and treatment planning.

The treatment of an AVM ideally involves its complete removal from the circulatory system, as subtotal obliteration does not remove the risk of haemorrhage. It is estimated that:

- 10-40% of AVMs can be cured by embolisation alone (Berenstein et al 2005); and
- up to 70% can be successfully occluded (Willinsky et al 2001) where the intention to treat is to cure the AVM by embolisation alone.

Presurgical embolisation using endovascular approaches can reduce the size of a nidus before surgery or stereotactic radiosurgery and is common practice in many hospitals where:

- endovascular therapy alone is still considered by some as being ineffective in curing most AVMs (Doerfler et al 2004) and is often consequently used as part of a multimodal approach;
- palliative embolisation can be considered to reduce blood flow when there is no reasonable hope of obliterating the AVM completely;
- partially targeted endovascular treatment when the clinical-angioarchitectural relationship is completely understood can sometimes lead to improved natural history (Meisel et al 2002), although this is not always the case (Heros 2004); and
- may assist patients with progressive neurological deficits in which the AVM is not curable by other methods, and can lead to stablilisation and even reversal of neurological deficit (Al-Yamany et al 2000).

### Use of liquid embolic agents

Liquid embolics can be delivered through small microcatheters for injection at the site of the abnormality:

- N-butyl 2-cyanoacrylate (NBCA) is a tissue adhesive which has a low viscosity and solidifies upon contact with blood, and is made radiopaque by the addition of ethiodised oil (Lipiodol) or tantalum powder.

- A related compound, isobutyl 2-cyanoacrylate (IBCA) was one of the earliest compounds used as a liquid embolic, but its use was discontinued in the early 1990s when it was found to be a possible carcinogen (Nakstad et al 1992).

During the delivery of NBCA, care must be taken to rapidly remove the catheter after each infusion to avoid adherence of the catheter to the glue in the vessel. Due to this reason liquid embolic agents are often restricted for use in the occlusion of only high flow intracranial malformations.

- Another liquid is Onyx Liquid Embolic System (an ethyl vinyl alcohol co-polymer, dimethyl sulphoxide (DMSO) and tantalum mixture) (Arat et al 2004). It is easier to deploy than NBCA as it is cohesive but not adhesive, and precipitates due to the rapid diffusion of the DMSO solvent in the blood.

- Liquid sclerosing agents, for example absolute ethanol, can be used to cause tissue necrosis (Koebbe et al 2003).

Embolisation with liquid sclerosing agents has a more long-term effect than tissue adhesives and can be used in the treatment of larger malformations. However, absolute alcohol is a dangerous cytotoxin and great care must be taken in its use as it causes immediate and permanent vessel occlusion.

Other sclerosing agents which have been used are sodium tetradecyl sulphate, hypertonic saline, and dextrose or glucose solutions. These agents are rarely used.

Non-detachable balloons can assist with the accurate delivery of liquid embolic agents, to avoid effects beyond the nidus itself (Koebbe et al 2003).

### Particulate embolic agents

Non-absorbable polyvinyl alcohol (PVA) particles (available in a range of sizes from 150 to 1000μm) can be used within a framework comprising of silk suture or coils to remove the AVM from the circulation.

### Endovascular coil embolisation

The most common type of coil used in endovascular approaches today is the Guglielmi Detachable Coil (GDC):

- These were developed by Guglielmi and co-workers in the early 1990s (Guglielmi et al 1991a, Guglielmi et al 1991b, Guglielmi et al 1995).

- These are long, flexible platinum microcoils which can be positioned and withdrawn repeatedly, and are detached by the passage of a low voltage current through the guidewire. This current also promotes platelet aggregation and thrombosis along the coil which assists in the embolisation process.

- Previously, platinum microcoils were more rigid and came in a variety of sizes, with or without Dacron fibres.

- Coils can also be coated with hydrogel (Hydrocoils, Micro Vention Inc) which expands to nine-fold its original volume in plasma to aid in the occlusion of the nidus (Morsi et al 2004).

- Coils are used to completely fill the nidus, thus removing it from the circulation (Bavinzski et al 1997, Deol et al 2001).

- Coil displacement from the AVM can be avoided by placing a flexible stent at the mouth of the fistula (Men et al 2003).

### Transarterial-transfistula balloon embolisation

Detachable balloons have been successfully used to occlude intracerebral vessels using the endovascular route for over thirty years (Serbinenko 1974), and can be used in the treatment of AVMs (Kim et al 2004), although this use is rare.

## Existing procedures

### Surgery

Surgery, either clipping or ligation of the vessels associated with the nidus, is still the primary option for easily accessible fistulae (Heros 2004). Best results from surgery are with smaller, cortical or dural AVMs located on the surface of the brain (Soderman et al 2003). Large, deeply located AVMs have a higher rate of surgical morbidity and mortality and a lower rate of obliteration, and are normally not treated surgically.

### Radiosurgery

Stereotactic radiosurgery is most successfully used for the obliteration of small (<3cm diameter) lesions, larger AVMs that have been reduced to this size by embolisation, and abnormalities that are deep within the brain (Al-Shahi and Warlow 2005).

This procedure brings about changes in the target zone that are considered surgical. It is a non-invasive technique usually performed on an outpatient basis. The patient's head is immobilised and three-dimensional computer imaging is used to accurately direct radiation to a specific area of the brain, whilst minimising the radiation dose delivered to other parts of the head.

The radiosurgery damages the DNA of the target cells, causing blood vessels to thicken and close. The radiation may be applied in a larger single dose or in smaller, multiple-

fractionated doses. The latter technique is safer as it reduces the radiation dose to the surrounding tissue. It has been facilitated in recent years through the use of more detailed imaging technology and accurate, non-invasive fixation devices which completely immobilise the head. Fractionated stereotactic radiosurgery can be delivered over a period of days or weeks.

Stereotactic radiosurgery can be carried out in Australia using a linear accelerator (LINAC) machine which delivers high energy x-ray photons or electrons. A Gamma Knife machine (Elektra Instruments which uses gamma irradiation from multiple separate cobalt-60 sources) can also be used for the same effect, although this is unavailable in Australia. The LINAC is generally the more common machine, and can be used to treat larger volume malformations than the Gamma Knife.

## Comparator

For the treatment of AVM, the primary comparators to endovascular approaches are surgery, stereotactic radiosurgery or no treatment.

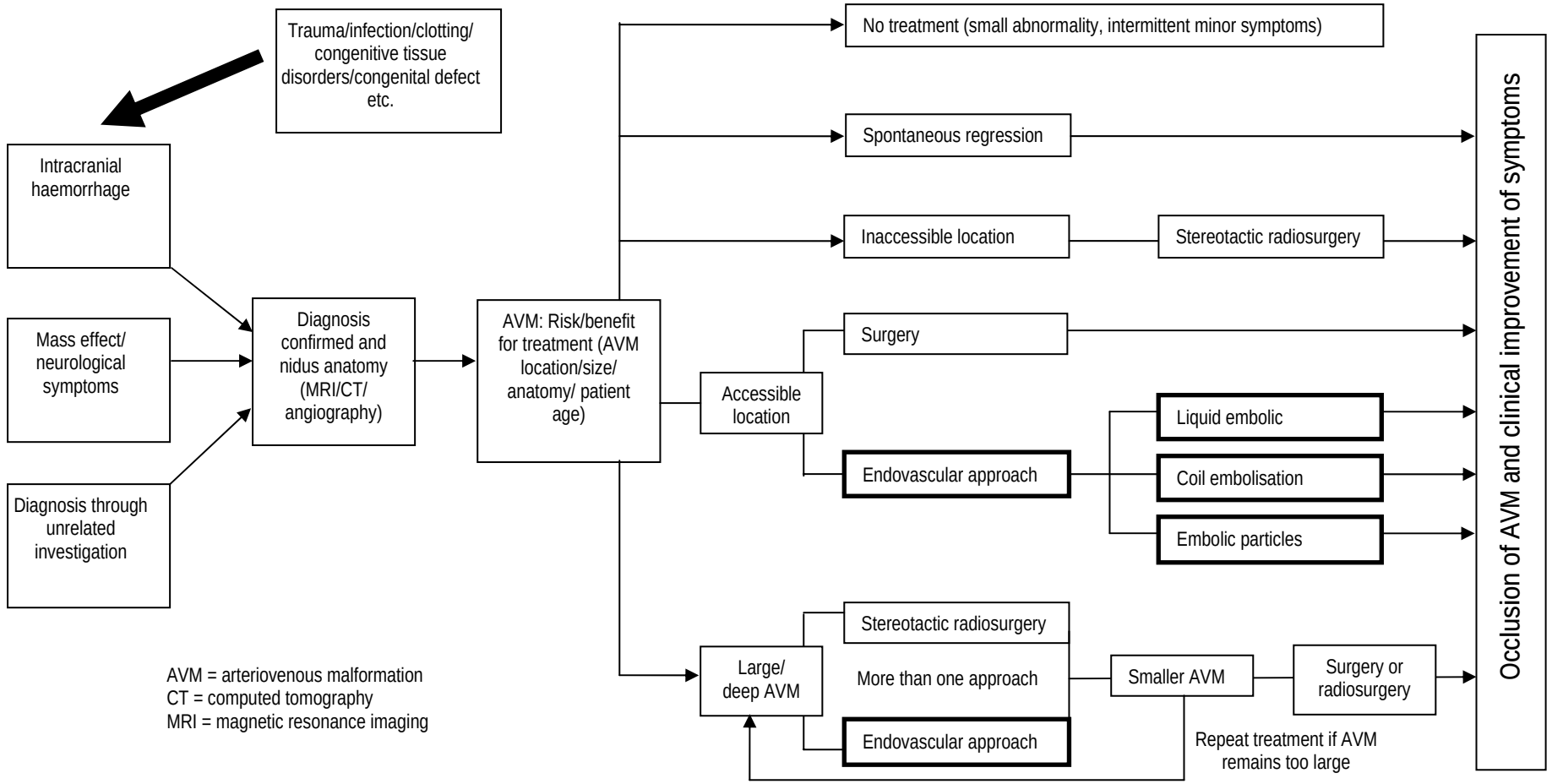
## Choosing between endovascular and surgical treatments

The decision about whether to treat a patient with an endovascular or a surgical approach is complex and takes into consideration the following:

- The size, location and haemodynamics of the abnormality. Some locations may be accessible for surgery and larger, deeper AVMs are more likely to be treated using endovascular approaches.
- Endovascular approaches are often used when surgical procedures have proved unsuccessful, so the patient may be less likely to recover fully.
- Whether the patient is symptomatic. An endovascular approach may be more likely when the patient has severe symptoms.
- The endovascular experience of the team treating the malformation.

## Clinical decision pathway

Figure 1 Clinical decision pathway, embolisation of intracranial or spinal arteriovenous malformations



## Clinical need / burden of disease

AVMs are quite rare diseases:

- the frequency of AVMs in autopsy studies range from about 0.1% (Soderman et al 2003) to 1.4% in brain tumour cases (Brown et al 2005);
- the prevalence in the adult population is probably less than 0.01% (Soderman et al 2003);
- in a population-based study in Minnesota (USA) the reported incidence of intracranial vascular malformation was 1.8 per 100,000 person-years, and the incidence of symptomatic cases and detection was 1.2 per 100,000 person-years (age- and sex-adjusted) (Brown et al 2005);
- in Glasgow (UK) the age-standardised crude detection rate is 1.12 per 100,000 adults per year for AVMs (Al-Shahi et al 2003);
- an estimate of AVM prevalence is approximately 18 per 100,000 adults per year (Al-Shahi et al 2001);
- in Western Australia, a population-based study of brain AVMs suggests a prevalence of 5 per 100,000 (ApSimon et al 2002).

Brain AVMs are responsible for:

- 1% to 2% of all strokes, 4% of strokes in young adults, 9% of subarachnoid haemorrhages and as many as one-third of all intracerebral haemorrhages in young adults (Al-Shahi and Warlow 2001); and
- 10% to 30% mortality from the first haemorrhage, with 10% to 20% of survivors having long-term disability (Ogilvy et al 2001).

ApSimon and colleagues (ApSimon et al 2002), stated that the vast majority of AVMs will eventually become symptomatic, therefore all detected AVMs should be regarded as potentially hazardous. The operating surgeon needs to decide on a case-by-case basis when to operate in order to minimise patient risk.

# Results: Endovascular embolisation of brain and spinal arteriovenous malformations

Five comparative studies (DeMeritt et al 1995, Deruty et al 1993, Sasaki et al 1998, Tomsick et al 2002 and Nakazawa et al 2003) using endovascular procedures to occlude an arteriovenous malformation (AVM) were included.

- Three authors (Deruty et al 1993, Tomsick et al 2002 and Nakazawa et al 2003) reported that endovascular procedures were performed prior to the complete excision of the nidus using surgery or radiosurgery.

- Three of the studies (DeMeritt et al 1995, Deruty et al 1993, Sasaki et al 1998) compared microsurgical excision, endovascular embolisation or radiosurgery, or a combination of both.

- Sasaki et al 1998 used a historical control group which had received conservative treatment to determine if the outcomes from any kind of intervention was better than no intervention at all.

- Two studies (Tomsick et al 2002 and Nakazawa et al 2003) used internal comparators (comparing one endovascular procedure or device with one or more other endovascular procedures or devices). Tomsick et al 2002 was a randomised controlled trial (RCT).

- These two studies, reported separately, may be able to answer the question of whether one type of endovascular occlusion material is better than another.

DeMeritt et al 1995, Tomsick et al 2002 and Nakazawa et al 2003 investigated the role of liquid adhesives (N-butyl cyanoacrylate (NBCA)) in occluding the nidus of AVMs.

Deruty et al 1993 referred to the use of occlusion using 'cyanoacrylate' and Sasaki et al 1998 described 'endovascular embolisation' but did not specify the exact type of glue used.

Nakazawa et al 2003 compared three types of liquid embolic agent, both adhesive and non-adhesive. As there was a great variety in these studies with respect to the particular endovascular techniques used and the detail in which patient data and outcomes were reported, it was difficult to compare the studies in a meaningful manner.

## Comparative studies

### Critical appraisal

DeMeritt et al 1995 investigated consecutive patients who underwent endovascular embolisation with NBCA followed by surgical resection (Table 10, Table 11). This was compared with a historical retrospective surgery-only control group which had been matched for average age. The AVM Spetzler-Martin grades were significantly higher in the embolisation and surgery group than in the surgery-only control group; however, details of control selection were not reported. DeMeritt reported the total number of patients

(n=71) was divided relatively equally between the control group and the embolisation groups (n=41 and n=30 respectively). A single interventionalist undertook all embolisation procedures of all AVMs and a single surgeon performed all resections. Members of the stroke neurology service evaluated outcomes. There was no mention of assessors being blinded to the patient grouping.

Deruty et al 1993 reported on all patients with cerebral AVM who were treated in their department over a 7-year period (Table 10, Table 11). The study patients were divided into two groups: those treated from 1985 to 1988 and those treated from 1989 to 1992. Patients were given one of four types of management:

- surgical resection;
- embolisation;
- embolisation and resection; or
- radiosurgery (alone or following surgery or embolisation). Deruty reported the radiosurgery approach (linear accelerator) was not available until after 1989 and was therefore not used on the group from the earlier time point.

Deruty et al 1993 reported the choice of treatment was determined according to the Spetzler-Martin grading of the AVM (Appendix C, Table 62). Prior to the availability of radiosurgery, the author reported that lower-grade AVMs were more commonly treated using surgery and higher grades using embolisation. After this time, the greatest difference was a reduction in the number of patients who were treated with embolisation followed by surgical resection. Consequently there was an imbalance of patient numbers between groups, with the largest number of patients being treated with embolisation followed by surgery (n=42) and the fewest number being treated with radiosurgery (n=14). No report was made regarding assessor blinding for outcome measurements.

Sasaki et al 1998 reported on patients treated over a 24-year period that had AVMs in the basal ganglia and thalamus, as identified using angiography (Table 10, Table 11). As in Deruty et al 1993, radiosurgery was used only when a gamma knife became available. All control patients (observed only, n=15) were treated in the pre-gamma knife period, and were chosen for conservative treatment as they had no history of haemorrhage, or if the nidus was too large or located in the lenticular nucleus and caused no major neurological deficits. Therefore these were selectively-chosen controls. The majority of remaining patients were treated using the gamma knife (n=66), even though this was only available for a short time over the course of the study. Few patients were treated using endovascular embolisation (n=5). The authors did not report the treatment allocation criteria or the details of the intervention technique including the type of endovascular procedure and device used. The authors reported that due to the study design, the possibility of bias in patient selection could not be excluded. No reference was made to the blinding of assessors to the patient's treatment when collecting post-treatment observations.

### Inclusion and exclusion criteria

The three included comparative studies were not randomised; the inclusion and exclusion criteria were not specific for a particular patient subset.

### Randomisation and allocation concealment

Consecutive patients were treated and reported in two studies (DeMeritt et al 1995, Deruty et al 1993). The basis of patient selection was not reported in Sasaki et al 1998, although the authors suggested that all patients treated were discussed in the study. There was no report of allocation concealment in any of the three included comparative studies.

### Losses to follow-up

Deruty et al 1993 did not specify the duration of follow-up, although there do not appear to be losses to follow-up in the data. The follow-up time reported by DeMeritt et al 1995 was 10 - 35 months for each treatment group with no losses to follow-up. Sasaki et al 1998 reported follow-up times ranging between 1.7 – 8 years, with a total of 7 patients (6.9%) lost to follow-up.

### Study populations

Deruty et al 1993 and Sasaki et al 1998 reported on four different treatment techniques with 100 and 101 patients respectively. DeMeritt et al 1995 reported on 71 patients in two groups (Table 10, Table 11).

Table 10 AVM study information

| Study | NHMRC level of evidence | Follow-up times, months (mean, (range), or [standard deviation]) | Losses to follow-up | Intervention | N |
|---|---|---|---|---|---|
| DeMeritt et al 1995 | III-3 | | | Total | 71 |
| | | 35 (4-59) | NR | Surgery alone | 41 |
| | | 10 (1-19) | NR | Surgery and endovascular embolisation | 30 |
| Deruty et al 1993 | III-3 | 88 | NR | Total | 100 |
| | | | | Surgery alone | 22 |
| | | | | Endovascular embolisation followed by surgery | 42 |
| | | | | Embolisation alone | 22 |
| | | | | Radiosurgery | 14 |
| Sasaki et al 1998 | III-3 | | 7 | Total | 101 |
| | | 79.2 [55.2] | 1 | Conservatively-treated | 15 |
| | | 96 [50.4] | 0 | Surgery | 15 |
| | | 44.4 [24] | 0 | Endovascular embolisation | 5 |
| | | 20.4 [12] | 6 | Gamma knife radiosurgery | 66 |

NOTE: NR = not reported

Table 11 Patient information

| Study | Study period | Allocation | Treatment decision | Exclusion criteria |
|---|---|---|---|---|
| DeMeritt et al 1995 | Apr 1992 – Nov 1993 | Consecutive | NR | Patients undergoing both embolisation and radiosurgery |
| Deruty et al 1993 | 1985 - 1992 | Consecutive, retrospective | NR | Patients whose AVM was diagnosed but not treated |
| Sasaki et al 1998 | 1971 – 1995 | NR | Angiographically-confirmed AVM in basal ganglia or thalamus. Conservative group had no history of haemorrhage, large nidus or no major neurological deficit | NR |

NOTE: NR = not reported

### Spetzler-Martin grade of AVM

The Spetzler-Martin (SM) grading scale ranks AVM depending on size, venous drainage and the eloquence of brain area in which the nidus is located (Table 12 and Appendix C, Table 62). The highest number on this scale (5) indicates a large AVM which drains into a deep venous system and which is located in an eloquent area of the brain, representing an AVM that is more difficult to treat. Of the studies included in this report, a greater proportion of individuals treated with endovascular approaches also presented with a high grade AVM, which adversely skewed the results for this treatment type (Table 12). The presentation symptoms of patients in each study are detailed in Table 13.

Table 12 Spetzler-Martin AVM grade

| Study | Patient group | Spetzler Martin grade of AVM | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| DeMeritt et al 1995 | Surgery only | 13/41 (32%) | | 28/41 (68%)* | | |
| | Endovascular and surgery | 3/30 (10%) | | 27/30 (90%)* | | |
| Deruty et al 1993 | All patients | 2/100 (2%) | 28/100 (28%) | 26/100 (26%) | 35/100 (35%) | 9/100 (9%) |
| Sasaki et al 1998 | Conservative | 0 | 0 | 7/15 (47%) | 2/15 (13%) | 6/15 (40%) |
| | Surgery | 0 | 0 | 13/15 (87) | 2/15 (13%) | 0 |
| | Embolisation | 0 | 0 | 2/5 (40%) | 3/5 (60%) | 0 |
| | Gamma knife | 0 | 1/66 (2%) | 55/66 (83%) | 10/66 (15%) | 0 |

NOTE: DeMeritt et al 1995: ES has significantly larger diameter and higher grade of S-M (3-5) ($p<0.05$) than S.

DeMerrit et al 1995 reported that 90% of patients treated with endovascular + surgery were SM grade 3-5 compared with 68% of those patients undergoing surgery only at the same grading of AVM. This was a statistically significant difference ($p<0.05$).

In Sasaki et al 1998, most (60%) of the patients receiving embolisation had a SM grade 4 AVM, whereas most of the patients receiving surgery or radiosurgery had an AVM of grade 3 (87% and 83% respectively). In both these studies, patients receiving an endovascular procedure had an AVM graded as being more difficult to operate on.

Table 13 Patient presentation

| Study | Patient group | Presentation |
|---|---|---|
| DeMeritt et al 1995 | All patients | NR |
| Deruty et al 1993 | All patients | Haemorrhage 41 |
| | | Epileptic seizures 39 |
| | | Others 20 |
| Sasaki et al 1998 | Conservative | Haemorrhage 10 |
| | | Seizures 4 |
| | | Headache 1 |
| | Surgery | Haemorrhage 15 (100%) |
| | Embolisation | Haemorrhage 5 (100%) |
| | Gamma knife | Haemorrhage 62 (94%) |
| | | Ischaemic neurological deficits 3 |
| | | Epileptic seizures 1 |

NOTE: NR = not reported

### Techniques and devices

DeMeritt et al 1995 used NBCA as the embolic agent (mixed with tantalum and ethiodised oil), via a femoral approach using a 7F catheter. Provocative testing was undertaken (sodium amobarbital followed by lidocaine, to check for a neurological deficit). An average of 2.4 embolisations per patient was undertaken. Information regarding the surgical technique used was not reported.

Cyanoacrylate is a broad term that may refer to N-butyl cyanoacrylate or isobutyl cyanoacrylate, and possibly others. Deruty et al 1993 reported using cyanoacrylate as the embolic agent although no further information was reported regarding the embolisation technique or devices used. Radiosurgery was undertaken using a linear accelerator; however, the exact radiosurgical technique, or surgical procedure, was not mentioned.

Sasaki et al 1998 reported the use of surgery, endovascular embolisation and radiosurgery (using a gamma knife). In each case, the technique or device used, including the type of embolic agent employed was not reported.

## Is it safe?

### Mortality

- There were no deaths in either the surgery-only group or the endovascular + surgery group in DeMeritt et al 1995 (Table 14).

- Deruty et al 1993 reported there were no deaths in the surgery-only group; however, they reported 7% (3/42) mortality for the endovascular treatments + surgery patients compared to a 14% (3/22) mortality rate in patients treated with endovascular occlusion alone.

- There was a higher proportion of patients with a higher initial Spetzler-Martin grade of AVM entered in the embolisation and surgery group (45% in SM 4-5 compared to 39% in SM 1-3) and in the embolisation alone group (41% of grade 4-5 compared to 7% of those in 1-3).

- Most of the low grade (1-3) AVMs were treated with surgery alone (38%) or embolisation followed by surgery (39%).

- Sasaki et al 1998 had the broadest range of comparators (conservative, surgery, embolisation and gamma knife).

- Patients in the conservatively-treated group had the highest mortality (43%, 6/15) compared with 20% (1/5) mortality in patients treated with endovascular embolisation.

- No patients treated with surgery and radiosurgery died.

- The majority of AVMs treated endovascularly were of a higher SM grade (60% (3/5) in grade 4 compared to 40% (2/5) in grade 3) than those treated with surgery or radiosurgery (87% (13/15) in grade 4 and 83% (55/66) in grade 3 respectively).

Table 14 Mortality

| Study | Patient group | Patient numbers | Mortality |
|---|---|---|---|
| DeMeritt et al 1995 | Surgery only | 41 | 0 |
| | Endovascular and surgery | 30 | 0 |
| Deruty et al 1993 | Surgery alone | 22 | 0 |
| | Endovascular and surgery | 42 | 3/42 (7%) |
| | Endovascular alone | 22 | 3/22 (14%) |
| | Radiosurgery | 14 | 0 |
| Sasaki et al 1998 | Conservative | 15 | 6/15 (40%) |
| | Surgery | 15 | 0 |
| | Embolisation | 5 | 1/5 (20%) |
| | Gamma knife | 66 | 0 |

### Adverse events

DeMeritt et al 1995 and Deruty et al 1993 did not report complications of their procedures.

Haemorrhagic complications recorded by Sasaki et al 1998 were as follows:

- the conservatively-treated group suffered most (80%, 12/15, five of which died); followed by the
- embolisation group (40%, 2/5, one of which died);
- surgery group (7%, 1/15); and
- gamma knife group (5%, 4/66 suffering latency-interval bleeding).

Other complications recorded by Sasaki et al 1998 included: 4/15 seizures in the observation group; 1/5 bleeding following guidewire trauma; and 2/5 cases of hemiparesis (one transient) in the embolisation group.

## Is it effective?

### Clinical outcomes

DeMeritt et al 1995 used the Glasgow Outcome Score (GOS) both as a standard measure of clinical outcome and as a description of pre-treatment patient condition (Appendix C, Table 59). Sasaki et al 1998 and Deruty et al 1993 used a 5-point ranking scale that was comparable with the GOS (Table 15, Table 16).

DeMeritt et al 1995 reported that although there was little difference between GOS scores preoperatively and 24h after surgery, there was a significant difference ($p<0.05$) between the surgery-only group and those that received embolisation and surgery at one week after the procedure (GOS 5 versus GOS < 5) in favour of embolisation and surgery. This

difference at long term (mean durations of 35 months for surgery alone, and 10 months for endovascular embolisation and surgery) approached significance (p=0.057).

Deruty et al 1993 reported that patients within each treatment group who achieved either GOS 4 or 5 (minor deterioration and no deterioration) were as follows: surgery alone 100% (22/22), embolisation and surgery 72% (30/42), embolisation alone 54% (12/22) and radiosurgery alone 100% (14/14).

Sasaki et al 1998 reported 46% (7/15) of the conservatively treated group were 'working' and 40% (6/15) of patients died. In the treatment groups, Sasaki reported patients who received surgery or radiosurgery had the best outcome (93% (14/15) or 93% (60/66) at GOS 4 or 5 respectively), whilst 60% (3/5) of the embolisation group had outcomes of GOS 4 or 5. Spetzler-Martin grades of 4 and 5 of AVM at presentation (the most difficult AVMs to treat) for each treatment group were reported as surgery 13 % (2/15), embolisation 60% (3/5) and radiosurgery alone 15% (10/66). Patients who were treated with embolisation alone had the poorest clinical outcome and they also had the poorest grade of AVM.

Table 15 Outcome scores of Deruty et al 1993 and Sasaki et al 1998

| Equivalent GOS score | Deruty et al 1993 | Sasaki et al 1998 |
|---|---|---|
| 5 | No deterioration | Excellent |
| 4 | Minor deterioration | Good |
| 3 | Long-lasting deficit | Moderately disabled |
| 2 | Major aggravation | Severe disability |
| 1 | Death | Death |

Table 16 Glasgow outcome scores

| Study | Patient group | Glasgow outcome score | | | | | Patient numbers |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | |
| DeMeritt et al 1995 | Pre-op | | | | | | |
| | Surgery only | 0 | 0 | 2% (1/41) | 22% (9/41) | 76% (31/41) | 41 |
| | Endovascular and surgery | 0 | 0 | 0 | 13% (4/30) | 87% (26/30) | 30 |
| | 24h after surgery | | | | | | |
| | Surgery only | 0 | 5% (2/41) | 7% (3/41) | 51% (21/41) | 37% (15/41) | 41 |
| | Endovascular and surgery | 0 | 0 | 7% (2/30) | 50% (15/30) | 43% (13/30) | 30 |
| | 1 week after (a) | | | | | | |
| | Surgery only | 0 | 2% (1/41) | 5% (2/41) | 52% (21/41) | 41% (17/41) | 41 |
| | Endovascular and surgery | 0 | 0 | 3% (1/30) | 27% (8/30) | 70% (21/30) | 30 |
| | Long term (a) | | | | | | |
| | Surgery only (mean 35 months) | 0 | 0 | 2%(1/41) | 32% (13/41) | 66% (27/41) | 41 |
| | Endovascular and surgery (mean 10 months) | 0 | 0 | 0 | 13% (4/30) | 87% (26/30) | 30 |
| Deruty et al 1993 | Surgery alone | 0 | 0 | 0 | 18% (4) | 82% (18) | 22 |
| | Embolisation and surgery | 7% (3) | 10% (4) | 12% (5) | 24% (10) | 48% (20) | 42 |
| | Embolisation alone | 14% (3) | 14% (3) | 18% (4) | 9% (2) | 45% (10) | 22 |
| | Radiosurgery alone | 0 | 0 | 0 | 14% (2) | 86% (12) | 14 |
| Sasaki et al 1998 | Conservative | 43% (6/15) | 7%(1/15) | 0 | 0 | 46% (7/15) | 15 |
| | Surgery | 0 | 7% (1/15) | 0 | 27% (4/15) | 67% (10/15) | 15 |
| | Embolisation | 20% (1/5) | 0 | 20% (1/5) | 20% (1/5) | 40% (2/5) | 5 |
| | Gamma knife | 0 | 0 | 7% (4/66) | 20% (16/66) | 73% (44/66) | 66 |

NOTE: DeMeritt: (a) SE significantly better than SO (GOS 5 v GOS <5 p<0.05 1 week after surgery, p=0.057 long-term).

## Angiographic outcomes

Deruty et al 1993 reported that the angiographic outcome in the embolisation group revealed complete eradication of 5% (1/22) of AVMs; however, complete eradication of AVMs after surgery occurred in 95% (61/64) of patients.

## Internal comparative studies

### Critical appraisal

Tomsick et al 2002 evenly randomised patients prior to treatment into two groups (n=52 each) receiving either NBCA or PVA occlusion. However, the method of randomisation was not reported. An unbiased practitioner was involved in reporting all observations of the study, both pre- and post-embolisation, although the exact method of blinding was not reported. There was no significant difference reported between patient groups for mean Spetzler-Martin grade of AVM (Table 17). The mean values for pre-treatment Glasgow outcome score (GOS), volume of AVM, deep venous drainage, age and gender distribution reported was also similar between each group. The authors detailed the pre-interventional status of both groups of patients and treatment parameters. GOS scores were recorded as grades of 5, or below 5, and were not separated into individual scores.

Nakazawa et al 2003 did not report patient pre-intervention condition, the duration of follow-up, the study period or patient allocation, other than that they included only concurrent patients with AVM of greater than 3cm in diameter. Patient allocation criteria were not reported. Most patients received eudragit-E as the embolic agent (n=33), whilst very few were given NBCA (n=4). It appears that no blinding was undertaken for post-interventional observations.

Table 17 Internal comparison Spetzler-Martin grade of AVM

| Study | Patient group | Spetzler-Martin grade of AVM | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| Tomsick et al 2002 | NBCA group (mean 2.9) | 5/52 (10%) | 13/52 (25%) | 20/52 (39%) | 11/52 (21%) | 3/52 (6%) |
| | PVA group (mean 2.9) | 5/50 (10%) | 14/50 (28%) | 17/50 (34%) | 10/50 (20%) | 3/50 (6%) |
| Nakazawa et al 2003 | All patients | NR | | | | |

NOTE: NBCA = n-butylcyanoacrylate; PVA = polyvinyl alcohol; NR = not reported.

### Inclusion and exclusion criteria

Tomsick et al 2002 included patients with an AVM Spetzler-Martin grade 1 or 2 only if the feeding pedicle was located in an area difficult to access surgically or the anticipated benefit of embolisation exceeded the risk. Nakazawa et al 2003 included patients who had AVM with a diameter larger than 3 cm.

### Randomisation and allocation concealment

The exact process of randomisation was not reported for the two groups investigated by Tomsick et al 2002. The basis of patient selection was not reported in Nakazawa et al 2003, although the author suggested that all patients treated were discussed in the study. Patient presentation was reported by Tomsick but not by Nakazawa (Table 20).

## Losses to follow-up

Tomsick et al 2002 and Nakazawa et al 2003 did not specify the duration of follow-up although they did report that no patients were lost to follow-up (Table 18).

## Sample size

Tomsick et al 2002 had the largest cohort size of 104 individuals, split into two equal groups. Nakazawa et al 2003 had three groups of varying sizes comprising of 50 patients (Table 18).

Table 18 Internal comparison study details

| Study | Level of evidence | Follow-up | Losses to follow-up | Intervention | N |
|---|---|---|---|---|---|
| Tomsick et al 2002 | II | NR | 0 | Total | 104 |
| | | | | Occlusion using NBCA | 54 (a) |
| | | | | Occlusion using PVA particles | 50 |
| Nakazawa et al 2003 | III-2 | NR | 0 | Total | 50 |
| | | | | EVAL | 13 |
| | | | | Eudragit-E | 33 |
| | | | | NBCA | 4 |

NOTE: (a) 2 patients had failed PVA occlusion and were transferred to the NBCA group. NR = not reported

Table 19 Internal comparison patient information

| Study | Study period | Allocation | Treatment decision | Exclusion criteria |
|---|---|---|---|---|
| Tomsick et al 2002 | Oct 1996 – Mar 1999 | Randomised | NR | AVM with Spetzler-Martin grade of 1 or 2, unless located in an area difficult to access surgically |
| Nakazawa et al 2003 | NR | NR | NR | AVM < 3 cm in diameter |

NOTE: NR = not reported

Table 20 Internal comparison patient presentation

| Study | Patient group | Presentation |
|---|---|---|
| Tomsick et al 2002 | NBCA group | Intracerebral haemorrhage 14 |
| | | Subarachnoid haemorrhage 7 |
| | | Seizures 24 |
| | | Altered mental status 6 |
| | | Headache 14 |
| | | Vision deficits 7 |
| | PVA group | Intracerebral haemorrhage 12 |
| | | Subarachnoid haemorrhage 3 |
| | | Seizures 21 |
| | | Altered mental status 6 |
| | | Headache 14 |
| | | Vision deficits 7 |
| Nakazawa et al 2003 | All patients | NR |

NOTE: NR = not reported

## Techniques and devices

Tomsick et al 2002 compared NBCA (with ethiodised oil and tantalum powder) with PVA particles (of sizes varying between <500 μm and 1400 μm in size) as the main occluding agents. Both these agents were often used in association with microcoils (a mean of 14.4 coils per patient with NBCA and 10 per patient with PVA). A variety of infusion catheters (3F and flow-directed) and guidewires (0.010 – 0.018 inch) were used, larger ones being used mainly for the deposition of PVA particles. A similar number of vessels embolised per patient were similar for each group (2.2 for NBCA and 2.1 in the PVA group). The endovascular approach used (eg transfemoral) was not reported; however, after randomisation the devices used were chosen following the assessment of the angioarchitecture of each AVM. Each AVM was surgically resected after embolisation, although the surgical technique employed was not reported.

Nakazawa et al 2003 reported on the use of three different types of liquid embolic agent. Two were non-adhesive, an ethylene vinyl alcohol co-polymer (EVAL, dissolved in DMSO) and Eudragit-E (a mixture of methyl and butyl methacrylate, plus diethylaminoethyl methacrylate copolymer, dissolved in ethanol) which were produced 'in house'. The third device, NBCA, was used at a low concentration diluted in ethiodol. Various flow- and wire-guided microcatheters were used to deliver the liquids, although the specific sizes and routes of access were not reported.

## Patient crossover

Tomsick et al 2002 reported two patients who were randomised to the PVA embolisation group also received NBCA, because the original PVA treatment was not fully successful.

# Is it safe?

## Mortality

Nakazawa et al 2003 reported the mortality in total for all patients in the study as 3/50 (6%). Tomsick et al 2002 reported that 1/54 (2%) patients treated with NBCA died, compared to 3/50 (6%) of those treated with PVA particles (Table 21).

Table 21 Internal comparison mortality rates

| Study | Patient group | Mortality |
|---|---|---|
| Tomsick et al 2002 | NBCA group | 1/54 (2%) |
| | PVA group | 3/50 (6%) |
| Nakazawa et al 2003 | All | 3/50 (6%) |

## Adverse events

Tomsick et al 2002 reported at least one adverse event was experienced by 50% of the NBCA group compared with 53.8% in the PVA group. Total haemorrhage (including vessel perforation and all post-procedural haemorrhages) was also less in the NBCA group (13% compared with 28.9% in the PVA group). Nakazawa et al 2003 reported haemorrhagic complications for the three liquid embolics used in the study (Table 22). The eudragit-E group had the most haemorrhages during and after the embolisation procedure (18%), followed by EVAL. The NBCA patients suffered no complications.

Table 22 Internal comparison haemorrhagic complications

| Complication | Tomsick et al 2002 | | Nakazawa et al 2003 | | |
|---|---|---|---|---|---|
| | NBCA group | PVA group | EVAL | Eudragit-E | NBCA |
| Vessel P (OTW) | 1/54 (2%) | 3/52 (6%) | 0 | 2/33 (6%) | 0 |
| Vessel P (flow) | 0 | 1/52 (2%) | 0 | 0 | 0 |
| Post-embolisation | 4/54 (5%) | 3/52 (6%) | 1/13 (8%) | 4/33 (12%) | 0 |
| Post-operative (a) | 2/54 (4%) (b) | 8/52 (15%) (b) | 0 | 1/33 (3%) | 0 |
| Total | 7/54 (13%) | 15/52 (29%) | 1/13 (8%) | 7/33 (21%) | 0/4 (0%) |

NOTE: P = perforation, OTW = over-the-wire catheter, Flow = flow-guided catheter,
(a) Tomsick 2002, post-surgery; Nakazawa 2003, post-radiosurgery
(b) $p<0.05$ [in intent-to-treat analysis]

# Is it effective?

## Clinical outcomes

Tomsick et al 2002 measured outcomes in terms of GOS before and after treatment, but Nakazawa et al 2003 did not use the GOS scoring system but used a comparable 5-point ranking scale (Table 23). Nakazawa did not report clinical outcomes separately for the

different patient groups, but states that 66% of all patients were ranked as excellent at discharge.

Table 23 Outcome scores of Nakazawa et al 2003

| Equivalent Glasgow outcome score | Nakazawa et al 2003 |
|---|---|
| 5 | Working |
| 4 | Independent |
| 3 | Dependent |
| 2 | Bedridden |
| 1 | Dead |

Tomsick et al 2002 reported patients from the two treatment groups had a similar clinical outcome at discharge (Table 24). Slightly less patients in the NBCA group (14/54, 26.3%) were reported with GOS <5 compared to the PVA-treated patients (17/50, 33.3%), suggesting a slight advantage for NBCA. Long-term outcomes were not reported. Both these groups had the AVM surgically resected following endovascular embolisation.

Table 24 Clinical outcomes

| Study | Patient group | Glasgow outcome score | | | | | Patient numbers |
|---|---|---|---|---|---|---|---|
| | | 1 Dead | 2 Bedridden | 3 Dependent | 4 Independent | 5 Working | |
| Tomsick et al 2002 | Before treatment | | | | | | |
| | NBCA group | | | 3 (7%) | | 49 (94%) | 52 |
| | PVA group | | | 6 13% | | 44 (88%) | 50 |
| | Before discharge | | | | | | |
| | NBCA group | | | 14 (26%) | | 40 (74%) | 54 |
| | PVA group | | | 17 (33%) | | 33 (67%) | 50 |
| Nakazawa et al 2003 | All patients | 3 (6%) | 1 (2%) | 9 (18%) | 4 (8%) | 33 (66%) | 50 |

NOTE: Tomsick et al 2002 reported Glasgow outcome score 1-4 together, not separately.

### Angiographic outcomes

Tomsick et al 2002 reported a mean reduction in AVM volume of 75% after NBCA occlusion and 87% after PVA occlusion.

## Discussion

This review included 5 studies – 3 level III studies comparing endovascular treatments with non-endovascular treatments and 2 studies which compared different types of endovascular treatments (one RCT and one level III study).

A recent Cochrane review on treatments for brain AVMs found no RCTs that compared endovascular with non-endovascular treatments (Al-Shahi and Warlow 2006).

### Non-randomised comparative studies

The study populations of Deruty et al 1993 & Sasaki et al 1998 were similar (100 & 101 respectively) with DeMerritt et al 1995 being slightly smaller (n=71). All authors reported on treatments of AVMs involving surgery alone and endovascular embolisation either alone or followed by surgery. Additionally, Deruty reported on radiosurgery and Sasaki also reported on radiosurgery (gamma knife) but also included a conservatively treated group in the study cohort.

Reporting of study design such as exclusion criteria, treatment allocation, follow-up and losses to follow-up were dissimilar across the studies such that comparisons were difficult to make.

In terms of safety:

- There were no deaths reported for any of the intervention groups in DeMeritt et al 1995.
- For the other two studies (Deruty et al 1993 and Sasaki et al 1998), there were no deaths in patients treated with either surgery or radiosurgery alone.
- Mortality in patient groups treated with endovascular embolisation alone was 14% and 20% in each study. Mortality was reduced when endovascular embolisation was used in conjunction with surgery (from 14% to 7% in Deruty et al 1993).
- Most mortality was seen in the conservatively-treated group (43% in Sasaki et al 1998).

For effectiveness:

- DeMeritt et al 1995 reported that there was a significant increase in patients at GOS 5 who were treated with endovascular occlusion followed by surgery, over patients treated with surgery alone ($p<0.05$), at one week after surgery. This difference neared significance at long term ($p=0.057$).
- Deruty et al 1993 and Sasaki et al 1998 patients' treated with embolisation alone had poor outcomes compared to either surgery, radiosurgery, or surgery + embolisation.
- Deruty also reported that complete eradication of the AVM occurred in only 5% of the embolisation group; however, in the surgery group the AVM was completely eradicated in most (95%) of patients.
- Both studies in which the Spetzler-Martin grade of AVM was recorded for the different treatment groups (DeMeritt and Sasaki), endovascular embolisation was used to treat patients with higher grades of AVM, that is malformations which were more difficult to treat due to their size, drainage and location in the brain.
- In DeMeritt et al 1995 the AVMs treated by embolisation and surgery were significantly larger and of higher grade than those treated with surgery alone.

The outcomes for patients treated with embolisation techniques appeared poor when compared to outcomes of other techniques; however, patients were often treated endovascularly when there was no other treatment option available, with AVMs which were difficult to treat. Endovascular procedures may be most effective when used in combination with surgical excision of the nidus, to reduce the size of the malformation to facilitate successful surgery.

### Internal comparative studies

The remaining two studies investigating endovascular embolisation of AVMs were internal comparisons which compared:

- NBCA and PVA occlusion followed by surgical excision (Tomsick et al 2002); and
- three different types of adhesive (EVAL, eudragit-E and NBCA) (Nakazawa et al 2003).

In Tomsick et al 2002, with regards to safety NBCA had marginally fewer deaths than PVA, and there were fewer complications in NBCA compared with PVA. Also, at discharge, a slightly greater proportion of patients were rated as being at GOS 5 in the NBCA group compared with the PVA group, although there was a greater mean reduction in AVM volume after PVA treatment than after NBCA.

Nakazawa et al 2003 did not report many of the pre-interventional details and outcomes separately for each endovascular technique used. Haemorrhagic adverse events were reported separately; eudragit-E had the greatest number of adverse events, which the authors suggested was due to the ethanol used as a solvent for the glue.

There were very few studies which compared the use of different embolic materials in the treatment of brain or spinal AVMs. The data presented here was gathered from two studies with relatively small patient populations and does not show any notable differences in the types of endovascular occlusion material used to treat AVMs. The use of a liquid adhesive (NBCA) might improve haemorrhage rates compared with particle occlusion agents (PVA), possibly from the narrower catheters which can be used to deliver liquid embolic agents (Tomsick et al 2002).

The Cochrane review (Al-Shahi and Warlow 2006) mentioned an unpublished RCT which compared the use of the liquid non-adhesive embolic, Onyx, as an occlusion material, compared with NBCA. The preliminary report was mentioned on the FDA website. It is also important to note that there were many case series which dealt with endovascular treatment of AVMs, which were excluded from this report due to the lack of comparative data.

Two of these case series include large numbers of consecutive cases.

Lasjaunias et al 1995 reported the endovascular treatment using glue (bucrylate):

- 179 consecutive cases of AVMs in children, which are very rare conditions. Of the individuals treated with embolisation, some received partial staged resection and some received surgery or radiosurgery.

- For patients in whom embolisation was completed, 34/56 had no neurological abnormality and 8/56 died.

- 31 patients did not undergo endovascular embolisation as they were considered unsuitable for this procedure. This group included patients who were operated on surgically or treated conservatively. Postoperatively, almost half of these patients died (15/31), while very few (5/31) were considered normal with no neurological abnormality.

Meisel et al 2002 discussed the treatment of 662 patients who were managed for brain AVM:

- 450 were treated with complete or partial endovascular embolisation;

- a small proportion of these had also been previously treated with surgery, embolisation or radiosurgery.

It was not possible to determine outcomes for these different patient subsets. Outcomes were not reported for patients who did not receive treatment but were only given for patients who had received embolisation. Of the patients who received an embolisation, a total of 15/450 died, five of these within the first 24h after embolisation.

## Summary

The published evidence for the treatment of intracranial AVMs by an endovascular approach is unclear. Due to the small number of studies, it is difficult to draw a meaningful conclusion with respect to relative safety, effectiveness and cost-effectiveness.

## What are the economic considerations?

None of these studies discussed costs for the use of endovascular procedures in the treatment of AVMs. Therefore it was not possible to undertake a detailed specific economic evaluation. Many parameters are likely to be similar to the costs for treating ruptured cerebral aneurysms (see MSAC Reference 33). Using the calculations from MSAC Reference 33 and adjusting for a slightly shorter hospital stay (3 less days' rehabilitation – based on MSAC assessment 1028 on 'Gamma knife radiosurgery', October 2000):

- The costs of surgical excision of an AVM are of the order of $19,400.

- The costs of endovascular treatment of an AVM are up to $23,400 (assuming that coils are the most expensive set of consumable items and are more expensive than other endovascular agents such as glues and angioplasty balloons).

- The costs of combined endovascular treatment/surgery are up to $25,200 (additional costs incurred for imaging, catheter lab and endovascular consumables).

According to the MSAC assessment 1028 on 'Gamma knife radiosurgery', October 2000 the costs of gamma knife radiosurgery for AVM treatment range from $7,700 to $13,000 (for the private system). These calculations have been made using Australian national

diagnosis related groups (AN-DRGs) and are likely to be somewhat lower than calculations using the methodology adopted in MSAC Reference 33.

While it was not possible to make any determinations about the effectiveness of endovascular treatments for AVMs, the unit costs of treating AVM with surgery, radiosurgery or combined endovascular and radiosurgery, or combined endovascular and surgery may be roughly similar, particularly if less costly endovascular agents are used.

# 2. Background: Endovascular embolisation of dural arteriovenous fistulae and carotid-cavernous fistulae

Dural arteriovenous fistulae (DAVF) are abnormal communications between an artery and a draining sinus vein. Carotid-cavernous fistulae (CCF) are a subtype of DAVF which exist between the carotid artery (CA) and the cavernous sinus (CS). Both DAVF and especially CCF (due to their location) are unsuitable for surgery, and so have long been treated using endovascular techniques including detachable balloons, coils, stents and liquid embolic agents. These techniques are often used in combination, depending on the size and location of the fistula. Balloons are often used to aid in the deployment of other embolic agents, for example with stents, to limit the spread of a liquid embolic agent, or aid in the localisation of a second detachable balloon. Stents can also be used in association with other devices, to reduce the risk of coil relocation. Patients suffering from Ehlers-Danlos syndrome (EDS) type IV are at greater risk of developing a CCF, but endovascular procedures are used less frequently in their treatment due to the delicate nature of the vasculature (Desal et al 2005).

## Dural arteriovenous fistulae

Dural arteriovenous fistulae (DAVF), also called dural AVMs, involve a vascular malformation of the wall of one of the major venous sinuses (Brown et al 2005). DAVF are distinguished from AVMs by the presence of a direct, high flow fistula between a single artery and vein (Al-Shahi and Warlow 2001). DAVF are direct shunts within the dura mater, the blood vessels and sinuses which surround the brain (Fukai et al 2001). They are less common than AVMs, with an age-standardised crude detection rate of approximately 0.1 per 100,000 adults per year (Al-Shahi et al 2003).

Venous drainage patterns allow DAVF to be classified into five types according to the Cognard Scale (Appendix C, Table 56): type I, located in the main sinus, with anterograde flow; type II, located in the main sinus, with reflux into the sinus (IIa), cortical veins (IIb) or both (IIa+b); type III, with direct cortical venous drainage without venous ectasia; type IV, with direct cortical venous drainage with venous ectasia; and type V, with spinal venous drainage (Klisch et al 2004, Cognard et al 1995).

## Carotid-cavernous fistulae

Carotid-cavernous fistulae (CCF) are abnormal connections between the internal (ICA) and external (ECA) carotid artery (or its branch) and the cavernous sinus (CS), a large vein behind the eye which receives blood from the orbit (via the ophthalmic veins), pituitary gland and the brain. CCF result in an abnormally high blood pressure in the cavernous sinus, and may be divided into two main categories – direct or indirect (Ringer et al 2005).

They have also been classified by Barrow and colleagues into four types, A, B, C or D, based on arterial supply (Barrow et al 1985, see Appendix C, Table 55).

Direct (type A), or high blood flow, CCF occur where drainage into the CS arises directly from the internal carotid artery (ICA). They are commonly caused as a result of craniomaxillofacial trauma and are mostly seen in young men (Brosnahan et al 1992). Indirect, or low flow, CCF result from drainage supplied by ECA and ICA branches and occur more commonly in elderly women. Type B CCF are supplied by dural branches of the cavernous ICA and are relatively uncommon (Ringer et al 2005). Type C is supplied by dural branches of the ECA. Type D has both dural supply from the ICA and ECA. The causes of indirect CCF are unknown, but are thought to be multifactorial and they can appear spontaneously. They are also observed as a result of connective tissue disorders, and may arise from clot formation, or be associated with aneurysms.

In the presence of arteriovenous shunt in the CS, blood flow becomes reversed in the ophthalmic veins, and the increase in localised blood pressure results in many of the symptoms associated with CCF. These commonly include ocular manifestations including swelling of the eyelid, proptosis, glaucoma, ocular redness, double vision or loss of vision. Headache or neurological deficits may be seen, although the latter is unusual in CCF, and a bruit is usually heard over the globe. Cerebral oedema, ischaemia or haemorrhage may also occur. The clinical presentation depends on the anatomy of the CCF, specifically its size, location and venous drainage (Baldauf et al 2004). Clinical diagnosis can be confirmed through imaging of the dilated ophthalmic veins using CT or MRI scanning, but should be confirmed using angiography.

### Pathophysiology of carotid-cavernous fistulae

The ICA is firmly held by the dura at the entrance and exit of the cavernous sinus. Between these two points of fixation it is vulnerable to tears due to penetrating injury or shearing stresses. CCF occur due to traumatic or spontaneous tears in the wall of the ICA (direct CCF) or one of its branches (indirect CCF) and leads to a short-circuiting of the blood flow directly to the dural sinuses. CCF are most commonly of the direct variety, arising from closed head injury in which the ICA has been ruptured or has sheared from its dural attachment. These head injuries may be mild or severe, and include knife and bullet trauma (Liebman et al 1996); they may develop immediately, or days or weeks later (Gratz et al 1991). Direct CCF usually have a high blood flow.

Indirect, or dural, CCF usually occur spontaneously, possibly as a result of a congenital malformation, or due to atherosclerosis or systemic hypertension. Dural CCF spontaneously resolve from 5% up to 50% of all cases, even after confirmation by angiography (Sasaki et al 1988, Meyers et al 2002). And, as they often have a benign natural history and are rarely life-threatening, a 'wait and see' strategy is often applied, unless there is a risk of blindness.

Dural CCF are most common in middle-aged women. They are also seen in individuals suffering from hereditary collagen diseases such as Marfan syndrome and Ehlers-Danlos syndrome (EDS) type IV (Ng et al 2003, Desal et al 2005, Forlodou et al 1996). In patients with EDS type IV, a mutation in collagen type III (COL3A1 gene) causes numerous vascular disorders. Vessels have reduced total collagen content and thin walls with irregular elastic fibres (Mitsuhashi et al 2004), and are at greater risk of damage (Halbach et al 1990).

High-risk CCF occur when there is insufficient venous drainage from the cavernous sinus, causing a build up of blood pressure in the fragile cerebral cortical veins (Meyers et

al 2002). Long-term ocular damage may occur due to increased blood pressure in the superior ophthalmic vein (SOV), or the CCF may haemorrhage.

## Endovascular procedures

Treatment of DAVF and CCF involves obliteration of the fistula by occluding it with various devices. Endovascular embolisation is beneficial not only due to the difficulty in access for surgical intervention, but also as this prevents the bleeding associated with open surgery. Commonly, endovascular procedures are carried out through the femoral artery at the groin. Transarterial embolisation with detachable balloons is considered the best initial treatment for direct CCF (Lewis et al 1995, Miller et al 1995). Dural CCF access can be more complicated and a variety of endovascular approaches have been used. Transvenous approaches may be used for indirect or direct CCF that cannot be treated by transarterial routes, usually through the internal jugular vein and inferior petrosal sinus (Biondi et al 2003, Cheng et al 2003, Halbach et al 1988). The superior ophthalmic vein (SOV) can also be used to approach the CCF if no other route is possible, although this must be surgically exposed via the upper eyelid (Quinones et al 1997, Baldauf et al 2004, Hanneken et al 1989, Miller et al 1995).

The choice of embolic agent to be used is dependent on the location and size of the fistula, and on the common practice of the centre at which the treatment is carried out. Detachable balloons have been the most widely used device (Ahn et al 2003), although recent advances in endovascular technology have provided a greater choice of procedures for the neuroradiologist, including the development of liquids, coils and stents. These techniques are frequently used in combination with one another, depending on the anatomy of the fistula.

If possible, parent artery blood flow is preserved. If the fistula is too large for successful occlusion, the feeding artery itself can be blocked using a detachable balloon.

### Transarterial-transfistula balloon embolisation

Detachable balloons have been successfully used to occlude intracerebral vessels using the endovascular route for over thirty years (Serbinenko 1974), and are effective in the treatment of direct CCF and some DAVF (Lewis et al 1995, Phadke et al 1998). Balloons are available in various sizes and materials, including latex and silicone, and long-term closure is thought to be good (Lewis et al 1996, Yang et al 2004). Both latex and silicone balloons may be filled with water-soluble contrast medium, while silicone balloons may also be filled with a polymerising substance such as hydroxyethylmethacrylate (Lewis et al 1996). Silicone balloons provide improved performance with decreased thrombogenicity, and increased manoeuvrability and functional reliability (Lewis et al 1995). A second, fixed, balloon, may be used to facilitate placement of the detachable embolisation balloon (Teng et al 2000). Balloon embolisation is normally carried out via the arterial route, as placement is dependent on the direction of blood flow (Kobayashi et al 2003).

If the CCF is sufficiently large and cannot be successfully occluded, ICA sacrifice may be considered if other adequate intracranial blood supply exists. A test balloon occlusion is carried out to confirm that this will be tolerated prior to the permanent deployment of a detachable balloon in the parent artery.

In cases of a fistula in patients suffering EDS type IV it has been suggested that balloons should not be used in its occlusion, due to the inherent risk of dissection of the weaker vessels (Kanner et al 2000). Other potential complications with the use of balloons include balloon puncture, premature deflation or migration.

### Endovascular coil embolisation

The use of detachable coils is a common technique for the endovascular occlusion of DAVF and CCF. This technique is described in greater detail in the previous section on AVMs.

### Stent embolisation

Depending on the nature of the DAVF or CCF, a flexible stent may be placed across the orifice of the fistula to obstruct it (Felber et al 2004, Kocer et al 2002, Weber et al 2001). This procedure effectively removes the fistula from the circulation if it cannot be fully embolised. A stent is a stainless steel mesh, occasionally covered with a biocompatible membrane (for example, Dacron, silicone or polytetrafluoroethylene), which can be fixed in size or flexible, and is sometimes located with the assistance of a balloon (stent-assisted balloon angioplasty). Flexible stents are more commonly used intracranially as they are easier to navigate through tortuous blood vessels and are less likely to damage the delicate vasculature. Currently available stents can be too rigid for use in this location, especially in more distal regions of the intracranial vasculature.

### Use of liquid embolic agents

The placement of balloons, coils or stents may not be feasible in tortuous or narrow vessels. In this case, liquid embolics may be used as they can be delivered through smaller microcatheters for injection at the site of the fistula. This technique is described in greater detail in the previous section on AVMs.

### Particulate embolic agents

Other embolic agents which have been used are non-absorbable polyvinyl alcohol (PVA) particles (available in a range of sizes from 150 to 1000μm), which can be used within a framework comprising of silk suture or coils.

## Existing procedures

Due to their location in the cavernous sinus, CCF are unsuitable for surgery to directly close the fistula. In the past, surgery normally involved the sacrifice of the carotid artery (Phadke et al 1998). Emergency surgical ligation of the ICA for instance is associated with an unacceptable incidence of major complications (Kocer et al 2002).

Conservative therapy of common carotid or jugular artery manual self compression can be used in the treatment of mild, indirect CCF, and is successful in about one-third of patients (Annesley-Williams et al 2001).

### Radiosurgery

Stereotactic radiosurgery is not commonly used in the treatment of CCF, but can be used to treat large or deeply located DAVF.

## Comparator

As there is no traditional surgical intervention or medical regimen for treating CCF, the primary comparators to endovascular approaches are stereotactic radiosurgery or no treatment. The comparators for endovascular approaches to DAVF are surgery, stereotactic radiosurgery or no treatment.

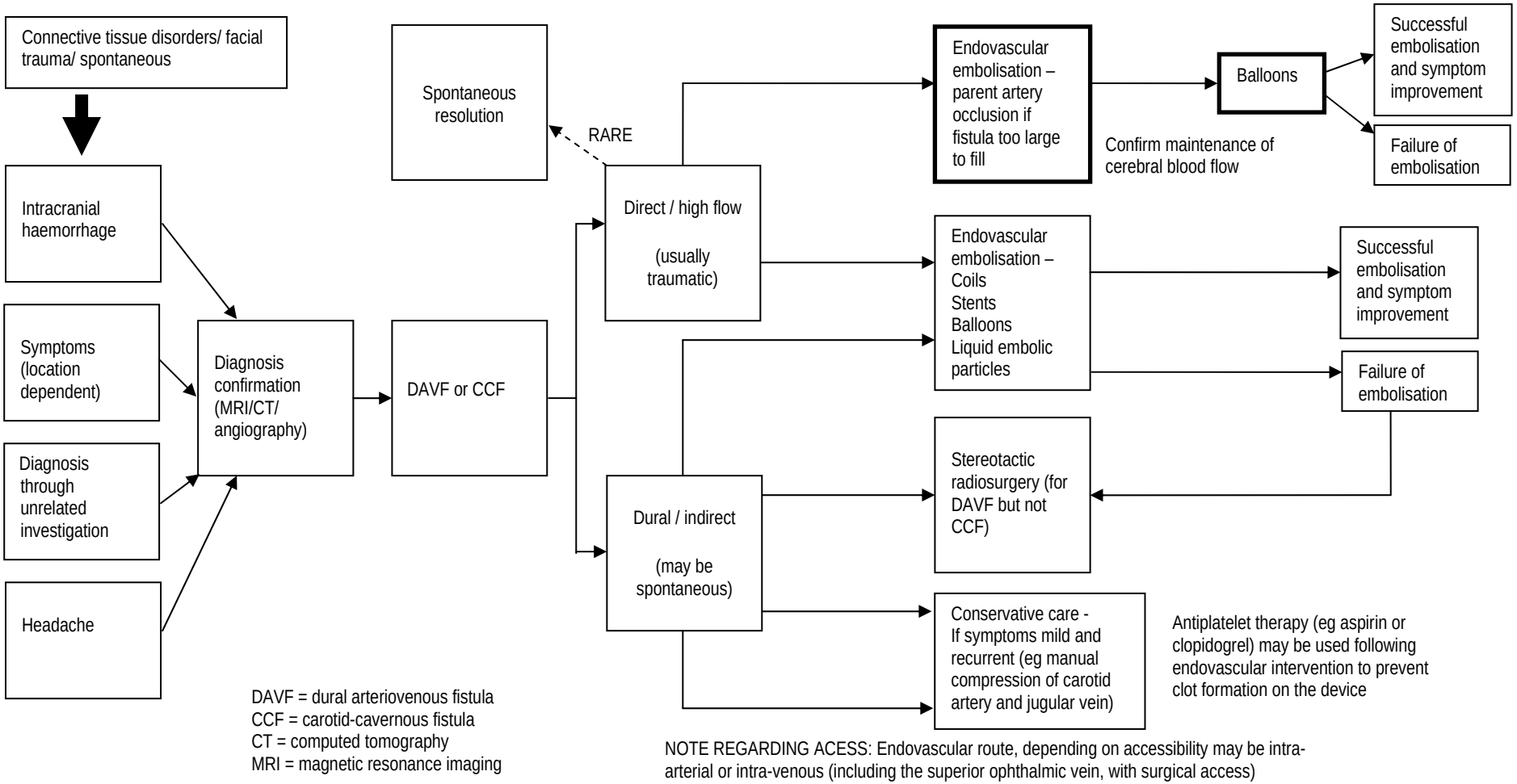
## Choosing between endovascular and medical treatments

The decision about whether to treat a patient with an endovascular or a surgical approach is complex and takes into consideration the following:

- Whether the patient is symptomatic. An endovascular approach may be more likely when the patient has severe symptoms.
- The location of the fistula. Peripheral locations are accessible for balloon angioplasty, however distal locations are more easily treated using infusion of a liquid agent.
- The morphology of the fistula.
- Endovascular procedures can be used to reduce the size of a DAVF prior to surgery or radiosurgery, although this is unlikely for a CCF.
- The endovascular experience of the team treating the fistula.

## Clinical decision pathway

Figure 2 Clinical decision pathway, embolisation of dural arteriovenous fistulae and carotid-cavernous fistulae



## Clinical need / burden of disease

DAVF and CCF are infrequently observed brain vascular abnormalities. Dural CCF are a subset of DAVFs which account for 10-15% of all intracranial malformations (Annesey-Williams et al 2001, Klisch et al 2004). Put in figures, in Glasgow (UK) the age-standardised crude detection rate for AVMs was 1.12 per 100,000 adults per year, compared with 0.16 for DAVFs (Al-Shahi et al 2003). Most CCF are direct, which are caused by trauma to the skull base (Coley et al 2003). Direct CCF occur in about 1% - 2% of patients with traumatic head injuries (Ringer et al 2005). Both types of CCF are very rare in children, especially in the absence of trauma or underlying connective tissue disorders (Albayram et al 2004, Rai et al 2004).

# Results: Endovascular embolisation of dural arteriovenous fistulae and carotid-cavernous fistulae

## Dural arteriovenous fistulae

Two studies were identified which assessed endovascular treatments for dural arteriovenous fistulae (DAVFs): Chung et al 2002 and De Paula Lucas et al 2005. Both studies were non-randomised and made concurrent comparisons (level III-2) (Table 25).

### Critical appraisal

In Chung et al 2002, 60 consecutive patients were treated for dural arteriovenous fistulae (DAVF), as diagnosed using angiography. Of these, 34 were dural fistulae of the cavernous sinus (CCF) and shall be discussed later in the document. The remaining 26 patients are discussed in this section on DAVF. Patients were treated with one or a number of surgical techniques, including conservative treatment, embolisation, radiosurgery, surgical excision or multimodal treatment. The last of the surgical techniques, multimodal, refers to a combination of embolisation and at least one other surgical technique. Chung et al 2002 reported how patients were allocated into the treatment groups and patient numbers in each groups. The Cognard scale was used to grade the DAVF for each patient (Appendix C, Table 56). Although patients were not allocated treatment based on this grading, there were similarities in the distribution of patients with Cognard scale grades between each treatment technique. The conservative treatment technique was used as a control in order to judge the efficacy of the other techniques. Patients were chosen to receive conservative treatment if they had either mild symptoms or severe symptoms that were unlikely to benefit from any treatment modality. No blinding was reported in assessing the efficacy of the outcomes achieved by each treatment technique.

De Paula Lucas et al 2005 reported on the outcomes of a 3-month study involving a total of 93 patients from four different centres. Patients were treated for DAVFs by either surgery only, endovascular occlusion only, or by endovascular occlusion followed by surgery. Patients received endovascular occlusion followed by surgery when the endovascular treatment method failed. No explanation was given as to the allocation of patients to either of the other two treatment groups. The aim of this study was to assess which amongst these most commonly used treatment techniques had the better patient outcomes. Successful outcomes were judged by De Paula Lucas et al 2005 as those which achieved both a clinical and therapeutic cure. This study had a pronounced bias in the distribution of patients between treatment techniques. The majority of patients received endovascular embolisation alone. The authors did not provide any clinical grading of patient DAVFs upon presentation, nor were there any information describing any blinding procedures used to judge patient outcomes.

De Paula Lucas et al 2005 reported clinical outcomes (success and failure) for CCF separately from other DAVFs. This shall be included in the CCF section. As all other information was not separated with regard to fistula type, the data included in this section shall include that for DAVFs and CCFs together.

Table 25 DAVF study information

| Study | NHMRC level of evidence | Intervention | Patient numbers | Treatment decision | Follow–up, months (mean, range) | Losses to follow-up | Allocation |
|---|---|---|---|---|---|---|---|
| Chung et al 2002 | III-2 | Total | 26 | Presented with mild symptoms that did not deteriorate, and presented with severe neurological symptoms | Total 15 (0 – 65) | NR | Consecutive, retrospective |
| | | Conservative | 9 | NR | 12.75 (0-53) | | |
| | | Embolisation | 8 | NR | 16 (1-60) | | |
| | | Radiosurgery | 1 | NR | 4 (4) | | |
| | | Surgical excision | 5 | NR | 6.2 (2-10) | | |
| | | Multimodal | 3 | NR | 42.3 (14-65) | | |
| De Paula Lucas et al 2005 | III-2 | Total | 93 | NR | 3 | NR | Consecutive, retrospective |
| | | Surgery only | 5 | NR | | | |
| | | Endovascular occlusion only | 75 | NR | | | |
| | | Endovascular occlusion & surgery | 13 | If endovascular approach failed then surgery was attempted | | | |

NOTE: NR: Not reported

## Inclusion and exclusion criteria

Chung et al 2002 did not report inclusion criteria, however patients with a direct fistula between the carotid artery and the cavernous sinus were excluded from the study.

De Paula Lucas et al 2005 did not report inclusion criteria. Patients were excluded from this study if they presented with either a dural AVM associated with pial AVM; vein of Galen malformation; scalp arteriovenous fistulae (AVF); direct CCF; and AVF of the foramen magnum with medullary drainage, medullary AVM and arteritis.

## Sample size and distribution

Study sample sizes and the distribution of patients amongst treatment groups differed considerably between each of the studies. The largest study population was recruited for the De Paula Lucas et al 2005 study. In total 93 consecutive patients were retrospectively investigated, and divided into the Groups A, B, and C according to their type of treatment. Patients in Group A (surgery only, n=5), only received surgical treatment, patients in Group B (endovascular occlusion only, n=75) only received endovascular treatment, and patients in Group C (endovascular occlusion & surgery, n=13) received both endovascular

and surgical treatment. The study completed by Chung et al 2002 investigating DAVF had a sample population of 26 patients. These patients received either conservative treatment (n=8), embolisation (n=9), radiosurgery (n=1), surgical excision (n=5) or multimodal treatments (n=3). The multimodal treatment group was designated by the authors of this review and represented only a very small number of individuals who received endovascular embolisation together with another type of treatment (surgery and/or radiosurgery). Some of the information from the Chung et al 2002 study was derived from one large table summarising DAVF location, treatment and outcome for each individual patient.

### Outcome analysis

None of the studies reported any pre- or postoperative blinding of assessments.

### Study design

Each of the included studies retrospectively investigated the safety and efficacy of outcomes on concurrent patients.

There was a large variation in study duration as illustrated in Table 25. De Paula Lucas et al 2005 had the shortest study duration time at 7 months, but also had the largest study population (n=93). This may have been the result of the use of four different sampling locations and the diversity of treatments investigated. The longest study duration time was achieved by Chung et al 2002 at 120 months in which the entire cohort population was taken from one medical centre. This study also included the largest number of treatment techniques, including control treatment, embolisation, radiosurgery and multimodal.

### Follow-up

The duration of the follow-up period was reported in both studies. Chung et al 2002 used a follow-up period of between 0 and 65 months (mean=15), while De Paula Lucas et al 2005 followed their patients for 3 months.

### Technique

Four mutually exclusive treatment options were analysed by Chung et al 2002; conservative treatment, embolisation, radiosurgery, and an additional treatment group, multimodal, which was incorporated by the reviewers to account for patients who received embolisation followed by another form of treatment (Table 26). The exact treatment incorporated into this group included embolisation and gamma knife surgery (GKS) (n=1), embolisation and surgical excision (n=1), and embolisation and GKS and surgical excision (n=1). Chung et al 2002 did not describe the nature of conservative treatment. Embolisation was performed on patients either via a transvenous (n=11) or transarterial approach (n=17), with both of these approaches used in the treatment of five patients. All transvenous embolisations used coils (tungsten, platinum or Guglielmi Detachable coils) placed via the femoral vein. All transarterial embolisations were achieved using polyvinyl alcohol (PVA) or n-butyl 2-cyanoacrylate (NBCA). Radiosurgery (gamma knife surgery, GKS) was performed using the Leksell Gamma Plan system, where the median marginal radiation dose was 20Gy with range of 15 – 25Gy (mean 20.8). The exact surgical excision technique was not described by Chung et al 2002.

Patients in the study completed by De Paula Lucas et al 2005 were grouped according to the type of treatment they received. 'Surgery only' patients underwent either of two procedures: coagulation and resection of the affected vein, or skeletonization of the compromised venous sinus. 'Endovascular occlusion only' patients received particle embolisation using PVA, a mixture of NBCA and lipiodol, as well as free microcoils or Guglielmi detachable coils. 'Endovascular occlusion & surgery' patients first received the endovascular treatment as described for 'Endovascular occlusion only' followed by a neurosurgical procedure. Details of this neurosurgical procedure were not described.

As both of these studies reported on various types of occlusion devices, often mixed with others, it was not possible to report outcomes for each device separately from others. Therefore 'endovascular techniques' in general were reported, in comparison with other techniques (surgery, radiosurgery or conservative treatment).

## Allocation

Consecutive patients were investigated in both the Chung et al 2002 and De Paula Lucas et al 2005.

### Initial type / grade of dural arteriovenous fistulae

Table 26 Cognard grade of dural arteriovenous fistulae (Chung et al 2002)

| | Patient numbers | | | | | | |
|---|---|---|---|---|---|---|---|
| Treatment | I | IIa | IIb | IIa+b | III | IV | Total |
| Control | 1 | 1 | 0 | 2 | 1 | 3 | 8 |
| Embolisation | 1 | 0 | 1 | 1 | 2 | 4 | 9 |
| Radiosurgery | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Surgical excision | 1 | 0 | 0 | 0 | 2 | 2 | 5 |
| Embolisation & other | 0 | 1 | 0 | 0 | 1 | 1 | 3 |
| Total | 3 | 2 | 1 | 3 | 6 | 11 | 26 |

The Chung et al 2002 study used the Cognard scale as a pre-treatment grade to assess each patient's type of DAVF (Appendix C, Table 56). Table 26 reports the number of patients and type of Cognard scale DAVFs analysed by Chung et al 2002. This shows that more patients presented with Cognard grade IV DAVFs for all the different techniques used.

De Paula Lucas et al 2005 did not report on the presentation of symptoms for patients enrolled in their study.

## Is it safe?

### Mortality

Two deaths were reported by Chung et al 2002 for the treatment of DAVFs, both treated with conservative treatment techniques (n=8). No deaths were reported by De Paula Lucas et al 2005.

### Adverse events

No adverse events were recorded by De Paula Lucas et al 2005 in the treatment of DAVFs. Three patients displayed adverse events in the study completed by Chung et al 2002. Two patients developed transient facial numbness after transarterial embolisation which resolved within a few days. Treatment of another patient with radiosurgery resulted in decreased visual acuity. The authors did not note whether this occurred in patients treated for CCF or other DAVF.

# Is it effective?

## Clinical outcomes

Table 27 Clinical outcomes

| Study | Treatment | Outcome | Patient number (%) | P values |
|---|---|---|---|---|
| De Paula Lucas et al 2005 (a) | Surgery | Success | 4/5 (80%) | pns |
| (All DAVF) | Endovascular | Success | 43/75 (57%) | P=0.001 (versus endovascular alone) |
| | Endovascular & surgery | Success | 13/13 (100%) | |
| Chung et al 2002 | Embolisation | Cured | 3/9 (33%) | NR |
| | N=9 | Improved | 2/9 (22%) | NR |
| | | No response | 2/9 (22%) | NR |
| | | Aggravated | 2/9 (22%) | NR |
| | Radiosurgery | Cured | 0/1 (0%) | NR |
| | N=1 | Improved | 1/1 (100%) | NR |
| | | No response | 0/1 (0%) | NR |
| | | Aggravated | 0/1 (0%) | NR |
| | Conservative | Cured | 0/8 (0%) | NR |
| | N=8 | Improved | 0/8 (0%) | NR |
| | | No response | 4/8 (50%) | NR |
| | | Aggravated | 4/8 (50%) | NR |
| | Embolisation & other | Cured | 0/3 (0%) | NR |
| | N=3 | Improved | 2/3 (66%) | NR |
| | | No response | 0/3 (0%) | NR |
| | | Aggravated | 1/3 (33%) | NR |
| | Surgical excision | Cured | 2/5 (40%) | NR |
| | N=5 | Improved | 2/5 (40%) | NR |
| | | No response | 0/5 (0%) | NR |
| | | Aggravated | 1/5 (20%) | NR |

NOTE: (a) These clinical outcomes include 43 CCFs and of these 25 (58%) were successfully treated
pns = p value not significant; NR = not reported

De Paula Lucas et al 2005 described clinical outcomes in terms of either success or failure (Table 27). In this regard, the most successful type of intervention was that of endovascular embolisation and surgery, with all patients being successfully treated. Surgery alone had an 80% success rate (4/5) and endovascular embolisation alone had a 57% (43/75) success rate. De Paula Lucas et al 2005 used a two by two Fisher exact test to compare the outcomes for each of the techniques used in each respective group. The results from this analysis demonstrated that the combined interventional technique (endovascular occlusion and surgery) was significantly better than the endovascular treatment only technique used for ($p=0.001$). There was no statistically significant difference between 'surgery only' and 'endovascular occlusion only', or between 'surgery only' and 'endovascular & surgery'.

In the Chung study, the most successful treatment option was surgical excision, with an 80% improvement (4/5) in patient outcome. Multimodal techniques had a 66% improvement (2/3), embolisation had a 55% improvement (5/9), and no patients improved in the conservatively-treated group (0/8). Radiosurgery was used to treat one patient, who improved.

### Retreatment / recurrence

Chung et al 2002 and De Paula Lucas et al 2005 did not report on any retreatment or recurrences in either of their studies.

## Other studies for dural arteriovenous fistulae

### Song et al 2001

Song et al 2001 appeared to be a comparative study which reported on consecutive patients (n=30) who underwent different procedures (surgery (n=7), glue embolisation (n=16), or embolisation following surgery (n=7)) to treat spinal DAVF. The mean age of all patients was 65 years; 27 men and 5 females were originally included. They did not separate the data according to the technique used, but presented most pre-treatment information and outcomes for all patients regardless of treatment technique used. The authors did report gait and micturition outcomes for patients treated with surgery only, embolisation only, or embolisation and surgery, as seen in Table 28. Gait and micturition disabilities were graded according to the Aminoff-Logue Scale (see Appendix C, Table 54).

The most successful treatment for gait improvement was embolisation and surgery, with 86% (6/7) improved, compared to 57% (4/7) and 44% (7/19) improved for surgery only and embolisation only, respectively. Embolisation and surgery was also the best treatment for improvement of micturition.

Table 28 Treatment outcomes (Song et al 2001)

| Study | Group | | Disability | | |
|---|---|---|---|---|---|
| | | | Patient number (%) | | |
| | | | Improved | Same | Worse |
| Song et al 2001 | Gait | Surgery only | 4/7 (57%) | 3/7 (43%) | 0/7 (0%) |
| | | Embolisation only | 7/16 (44%) | 9/16 (57%) | 0/16 (0%) |
| | | Embolisation & surgery | 6/7 (86%) | 0/7 (0%) | 1/7 (14%) |
| | Micturition | Surgery only | 1/7 (14%) | 5/7 (72%) | 1/7 (14%) |
| | | Embolisation only | 5/16 (31%) | 9/16 (56%) | 2/16 (13%) |
| | | Embolisation & surgery | 5/7 (71%) | 1/7 (14%) | 1/7 (14%) |

### Bavinzski et al 1996

Bavinzski et al 1996 reported on consecutive patients with cranial DAVF who had been treated with endovascular, radiosurgical and surgical approaches (Table 29). Although this should be considered a case series (level IV), all the information for each patient was tabulated and data could be separated for each technique. Twenty-two patients were treated with endovascular embolisation alone. The endovascular technique used was performed using a 7F guidewire through the carotid or femoral artery, and using a 0.014-0.016 inch microcatheter to deposit PVA particles, glue or microcoils. There was an uneven distribution of patients between procedures. Most (n=22) received endovascular embolisation, whilst fewer had combination treatment (n=5 for endovascular and surgery, n=2 for endovascular and radiography), and only one patient had radiography. The reasoning for procedural choice was not given. A good or excellent outcome for each procedure was stated as being 72% (16/22) of those treated endovascularly, 75% (3/4) for those who received endovascular and surgery, 50% (1/2) for those who received endovascular and radiography, whilst the single patient who was treated using radiosurgery alone made an excellent recovery.

Table 29 Summary of Bavinzski et al 1996

| Study | Approach | Follow-up (mean) months | Losses to follow-up | Outcome |
|---|---|---|---|---|
| | | | | Good-excellent |
| Bavinzski et al 1996 | Endovascular | 47 | 0 | 16/22 (72%) |
| | Endovascular & surgery | 57.5 | 1 | 3/4 (75%) |
| | Endovascular & radiosurgery | 18 | 0 | 1/2 (50%) |
| | Radiosurgery | 10 | 0 | 1/1 (100%) |

## Discussion

The primary interest of this report was to investigate the endovascular treatment of dural arteriovenous fistulae (DAVF). Each of the studies compared the safety and efficacy of

various types of interventional techniques for the treatment of DAVFs. Unfortunately there were few commonalities in these treatments between the studies. Although the two main studies used glue to perform embolisations, De Paula Lucas et al 2005 occasionally used glue in combination with coils; the study does not specify which patients received these two materials. There is therefore no separated data regarding patient outcomes for those who were treated with glue embolisation alone, and no specific comparison can be made between the two studies and their respective embolisations. Within each study there was an unequal distribution of patients between each interventional technique which may have biased the reported outcomes. There were some promising results reported by each study; however, more work needs to be completed in this area with larger randomised control trials before a more definitive answer regarding the validity of these techniques can be made.

Both studies reported that techniques other than endovascular embolisation alone provided the best clinical outcome. In De Paula Lucas et al 2005 the most successful technique used was endovascular + surgery, followed by surgery alone, with an endovascular approach alone being least effective in terms of outcome. There were much greater numbers of patients treated using endovascular embolisation alone (n=75 compared with 13 and 5 for the other groups).

In Chung et al 2002 the most successful treatment for DAVFs, in terms of clinical outcome, was surgical excision. Multimodal techniques was the next favourable, then embolisation alone, with conservative treatments being least effective with no patients having a favourable outcome (improved or cured).

Endovascular embolisation alone was therefore not successful in the treatment of DAVF. It seemed that an endovascular approach may have been used in both these studies where another approach (mainly surgical excision) was not possible, due to location or angioarchitecture of the fistula. It also seemed that endovascular approaches, when used as part of a multimodal treatment scheme, were more successful than endovascular embolisation alone.

## Expert opinion

It is important to note that in Australia and worldwide an endovascular approach is the most frequently used procedure to occlude dural AVF or CCF. Only a small number of patients are treated for these conditions. Thus information comparing endovascular treatments to other procedures, such as surgery or radiosurgery, will not be available. Also, there is a large variation in the type of occlusion devices used to treat DAVFs, which are dependent on the location, size, and access of the fistula, as well as differences between centres.

## Summary

Overall the evidence base for endovascular embolisation of DAVFs was poor (there were no randomised controlled studies), small (there were only a few studies with relatively low patient numbers) and varied (the studies employed a variety of devices and treatment combinations). Therefore the safety and effectiveness of endovascular procedures in the treatment of brain or spinal DAVF cannot be determined.

## What are the economic considerations?

No costing information for endovascular treatments of DAVFs was available from the literature. However, assuming that hospital stay is similar after surgery, radiosurgery, endovascular treatment or combined treatments, costs per treatment may be roughly similar (as was outlined for AVMs above). Again it was not possible to make any determination about the effectiveness of endovascular treatments for DAVFs and so a cost-effectiveness analysis could not be done.

## Carotid-cavernous fistulae

Two studies on carotid-cavernous fistulae (CCF) were included: Pollock et al 1999 (level III-3) and Chung et al 2002 (level III-2). The Pollock et al 1999 study was graded at the NHMRC level III-3, and the Chung et al 2002 study at the III-2 NHMRC level. The Chung et al 2002 study is the same study mentioned previously reporting on DAVFs and is able to be included here because information on CCFs has been reported separately.

### Critical appraisal

The Chung et al 2002 study is critically appraised in the section on DAVF.

Pollock et al 1999 reported on a small study of 20 patients with CCFs. Neither inclusion nor exclusion criteria were detailed in this study. The distribution of patients between both treatment techniques was relatively equal (radiosurgery alone (n=7) and embolisation and radiosurgery (n=13)). Treatment decision was not randomised but was made following reviewing images of the fistulae. Pollock et al 1999 used both the Cognard and Barrow scales to assess patients CCFs (Appendix C, Table 55 and 56). There was a reasonable similarity in the distribution of patients with regard to Cognard and Barrow type CCFs between both treatment techniques. No clinical scales were used to judge patient outcomes, nor was any information provided describing any blinding procedures for outcome analysis.

De Paula Lucas was reported and critically appraised in the above section on DAVFs. Although most of the patient details and outcomes were reported with regard to DAVFs including CCFs, clinical outcomes (reported as success or failure) were reported separately for CCF alone. Therefore these data will be included in this section concerning CCF. All other information regarding this study has been reported in the above DAVF section.

### Inclusion and exclusion criteria

Chung et al 2002 did not include patients presenting with a direct fistulae between the carotid artery and the cavernous sinus.

### Sample size & distribution

Thirty four patients with CCF were treated in Chung et al 2002. Of these the majority were treated using endovascular embolisation (24/34). The remaining patients were treated using radiosurgery (4/34), embolisation and radiosurgery (1/34), or were treated using conservative treatment (5/34). None of the CCF were surgically excised. In the study conducted by Pollock et al 1999 the total patient population was smaller, n=20. This patient pool was divided in two, where one group received radiosurgery alone (n=7), and the other received radiosurgery and embolisation (n=13).

Table 30 CCF study information

| Study | NHMRC level of evidence | Intervention | Patient number | Treatment decision | Follow–up (months, range) | Losses to follow-up | Allocation |
|---|---|---|---|---|---|---|---|
| Chung et al 2002 | III-2 | Total | 34 | Presenting with mild symptoms that did not deteriorate, and presented with severe neurological symptoms | 14.7 (0-57) | NR | Consecutive, retrospective |
| | | Conservative | 5 | NR | 6 (0-18) | | |
| | | Embolisation | 24 | NR | 15.9 (1-57) | | |
| | | Radiosurgery | 4 | NR | 17.8 (12-28) | | |
| | | Surgical excision | 0 | NR | NA | | |
| | | Embolisation & radiosurgery | 1 | NR | 0 (0) | | |
| Pollock et al 1999 | III-2 | Total | 20 | Based on angiographic analysis | Median=36 (4-59) | NR | Prospective |
| | | Radiosurgery alone | 7 | | | | |
| | | Radiosurgery & embolisation | 13 | | | | |

NOTE: NR – not reported

## Study design

The study design used by Chung et al 2002 to investigate CCFs was the same design used in the authors' investigation of DAVF, and is described in the previous section.

Pollock et al 1999 had a shorter study duration period and the least amount of participants (n=20), however this study used one location, and only compared two different treatment techniques (radiosurgery alone, versus radiosurgery and embolisation).

## Follow-up

The follow-up period for patients treated for CCF in the Chung et al 2002 study ranged between 0 to 57 months (mean=13). Pollock et al 1999 had a longer follow-up period of 4 to 59 months (mean=36). No losses to follow-up were reported by either study.

## Technique

In Chung et al 2002, the treatment techniques, conservative treatment, embolisation and radiosurgery, were performed in the same manner as described above in the treatment of DAVF.

Two treatment groups, radiosurgery alone, and embolisation followed by radiosurgery, were analysed by Pollock et al 1999. Patients who also received embolisation were initially treated with polyvinyl alcohol particles (PVA); however, in some cases additional materials were required such as silk sutures, gelfoam or microcoils.

The median marginal dosage used in the radiosurgery techniques used by both Chung et al 2002 and Pollock et al 1999 are identical. Both studies report on the outcomes of a median marginal dosage of 20Gy, with similar dosage ranges of 15 – 25Gy in Chung et al 2002 and 18 – 20Gy in Pollock et al 1999.

## Allocation

The allocation of treatment for patients with CCF by Chung et al 2002 was the same as described for the allocation of patients with DAVF.

Pollock et al 1999 carried out a retrospective analysis of 93 patients with CCF.

Table 31 Presentation

| Pollock et al 1999<br>Symptom (a) | n/N | % |
|---|---|---|
| Radiosurgery alone | | |
| Chemosis/proptosis | 6/7 | 86% |
| Diplopia | 4/7 | 57% |
| Decrease vision | 2/7 | 29% |
| Tinnitus | 2/7 | 29% |
| Headache | 2/7 | 29% |
| Prior embolisation | 0/7 | 0% |
| Radiosurgery & embolisation | | |
| Chemosis/proptosis | 12/13 | 92% |
| Diplopia | 9/13 | 69% |
| Decrease vision | 6/13 | 46% |
| Tinnitus | 5/13 | 38% |
| Headache | 4/13 | 4% |
| Prior embolisation | 2/13 | 15% |

NOTE: (a) patients may have presented with multiple symptoms.

## Initial type / grade of DAVF

Pollock used both the Barrow and the Cognard scales, whereas Chung used the Cognard scale, to grade the fistulae (Table 32 and 33).

Table 32 Barrow DAVF type

| Pollock et al 1999 Grade | n/N | % |
|---|---|---|
| Radiosurgery alone | | |
| A | 0/7 | 0 |
| B | 1/7 | 14 |
| C | 1/7 | 14 |
| D | 5/7 | 71 |
| Radiosurgery & embolisation | | |
| A | 0/13 | 0 |
| B | 0/13 | 0 |
| C | 2/13 | 15 |
| D | 11/13 | 85 |

Because Barrow Grade A arteriovenous fistulae are direct, not dural flow fistulae they were not included by Pollock et al 1999. In comparing the radiosurgery alone with the radiosurgery and embolisation treatment groups, the arrangement of patients was quite similar for Barrow type of DAVF. The majority of patients in each treatment group were diagnosed as having DAVFs within Barrow type C and D (n=85% in the radiosurgery alone group and n=100% in the radiosurgery and embolisation group). This commonality strengthens any comparisons which can be drawn regarding the safety and efficacy of these two techniques.

Table 33 Cognard DAVF scale / treatment group

| Patient number | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chung et al 2002 | | | | | | | |
| Treatment | I | IIa | IIb | IIa+b | III | IV | Total |
| Control | 4 | 0 | 0 | 1 | 0 | 0 | 5 |
| Embolisation | 15 | 1 | 0 | 4 | 4 | 0 | 24 |
| Radiosurgery | 1 | 0 | 1 | 0 | 2 | 0 | 4 |
| Multimodal | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Total | 20 | 1 | 2 | 5 | 6 | 0 | 34 |
| Pollock et al 1999 | | | | | | | |
| Treatment | I | IIa | IIb | IIa+b | III | IV | Total |
| Radiosurgery alone | 1 | 6 | 0 | 0 | 0 | 0 | 7 |
| Radiosurgery and Embolisation | 0 | 9 | 0 | 3 | 1 | 0 | 13 |
| Total | 1 | 15 | 0 | 3 | 1 | 0 | 20 |

The Cognard scale was used by Chung et al 2002 and Pollock et al 1999.

For both Chung et al 2002 and Pollock et al 1999 the Cognard type of CCF treated was reasonably similar between each treatment type. In Chung, most of the patients treated had type I DAVF, but in Pollock most of the patients had type IIa DAVFs.

For Pollock et al 1999, for patients treated with either radiosurgery or radiosurgery and embolisation, most DAVFs were of Barrow Type D and are Cognard Type IIa.

## Is it safe?

### Mortality

No deaths were reported by either Chung et al 2002 or Pollock et al 1999 for the treatment of CCF.

### Adverse events

Three patients displayed adverse events in the study completed by Chung et al 2002. Two patients developed transient facial numbness after transarterial embolisation which resolved within a few days. Treatment of another patient with radiosurgery resulted in decreased visual acuity. The authors did not note whether this occurred in patients treated for CCF or other DAVF.

Table 34 Adverse effects

| Study | Treatment | Adverse Effects |
|---|---|---|
| Pollock et al 1999 | Radiosurgery | Left side hemiparesis |
| | Radiosurgery & embolisation | Nerve palsy |
| | Radiosurgery & embolisation | Transient aphasia |

Pollock et al 1999 reported 3 adverse events (Table 34); stereotactic radiosurgery causing effects in one patient and two patients suffering after receiving endovascular embolisation.

Stereotactic radiosurgery left one patient feeling lethargic with left side hemiparesis after treatment, resulting from an occlusion of the M1 segment of the middle cerebral artery (MCA). Intra-arterial thrombolytic therapy was used to return the patient to their nominal status.

Treatment with the embolisation procedure resulted in nerve palsy developing in one pre-radiosurgical embolisation patient. This complication was left to resolve and 54 months later the diplopia had improved. A second patient developed a venous infarction during a postradiosurgical embolisation which resulted in transient aphasia. This complication was also left to resolve itself, improving in the months after the procedure.

## Is it effective?

### Clinical outcomes

Pollock et al 1999 reported effectiveness solely in relation to symptom improvement. 'Radiosurgery alone' group and 'radiosurgery and transarterial embolisation' achieved success rates of 100% and 92% respectively. There was no significant difference in these outcome values ($p=1.0$, students t test). There was a statistically significant difference between the two groups with regard to 'time to patient improvement' ($p<0.001$). The duration to patient improvement was shorter for patients who received both 'radiosurgery and transarterial embolisation' (2 weeks) as compared to patients receiving 'radiosurgery alone' (6 months).

The most successful treatments used in Chung et al 2002 were embolisation and radiosurgery, with all patients having an improved or cured outcome in both groups (24 and 4 patients respectively). Twenty percent (1/5) of those patients treated with conservative techniques had an improved outcome, whilst the patient treated with embolisation and radiosurgery had no response upon treatment.

The same radiosurgery mean dosage was successfully used by Chung et al 2002 and Pollock et al 1999, with patients from both studies achieving clinical outcomes which were graded as either 'cured' or 'improved'. These positive outcomes were achieved in spite of the variation in Cognard scale grades of patients.

All the CCFs reported in De Paula Lucas et al 2005 were treated using endovascular occlusion, by both arterial and venous access. Clinical outcome was the sole measure reported separately for CCF in this study. The transvenous approach appeared best, and all of the transarterial approaches were failures. In total, 17/32 (53%) of CCF were successfully treated.

Table 35 Clinical outcomes

| Study | Treatment | Outcome | Patient numbers |
|---|---|---|---|
| Pollock et al 1999 | Radiosurgery N=7 | Symptom improvement | 7/7 (100%) |
| | Radiosurgery & embolisation N=13 | Symptom improvement | 12/13 (92%) |
| Chung et al 2002 | Embolisation | Cured | 13/24 (54%) |
| | N=24 | Improved | 11/24 (46%) |
| | | No response | 0/24 (0%) |
| | | Aggravated | 0/24 (0%) |
| | Radiosurgery | Cured | 1/4 (25%) |
| | N=4 | Improved | 3/4 (75%) |
| | | No response | 0/4 (0%) |
| | | Aggravated | 0/4 (0%) |
| | Conservative | Cured | 0/5 (0%) |
| | N=5 | Improved | 1/5(20%) |
| | | No response | 3/5 (60%) |
| | | Aggravated | 1/5 (20%) |
| | Embolisation & radiosurgery | Cured | 0/1 (0%) |
| | N=1 | Improved | 0/1 (0%) |
| | | No response | 1/1 (100%) |
| | | Aggravated | 0/1 (0%) |
| De Paula Lucas et al 2005 | Transarterial embolisation N=4 | Success | 0/4 (0%) |
| | Transvenous embolisation N=28 | Success | 17/28 (61%) |

## Retreatment / recurrence

Chung et al 2002 did not report any retreatment recurrence.

Recurrent symptoms were found in four patients in the Pollock et al 1999 study. These patients were from the radiosurgery and transarterial embolisation group. Three of these patients demonstrated a postoperative improvement after radiosurgery and transarterial embolisation only to later deteriorate. These patients received repeat transarterial particulate embolisation, with this repeat procedure achieving a complete obliteration of the fistulae. The third patient presented with intraocular pressure and a worsening of vision, and was treated with a coil occlusion of the cavernous sinus. Following this procedure the patient had a quick improvement in their level of chemosis and intraocular pressure. The fourth patient presented with persistent diplopia which was surgically treated (the outcome was not recorded).

## Discussion

It is important to note that due to the location of fistulae within the cavernous sinus the use of surgical practices is almost impossible. Consequently interventions other than microsurgery, including endovascular procedures, provide a more practical means of treating patients with these conditions. Endovascular embolisation (alone or in combination with radiosurgery) comprised most, if not all of the procedures undertaken in the three included studies. The remaining procedures were radiosurgical or conservative management. Surgical excision of the CCF was not undertaken in any study.

Within two of the studies reported here (Chung et al 2002 and Pollock et al 1999) the distribution of patients and their respective Cognard AVF type was relatively similar with regard to each treatment technique. The treatment outcomes achieved through the use of radiosurgery alone proved to be the most successful. Both studies performed radiosurgery in the same way and achieved outcomes of improved or cured in all patients. The use of radiosurgery together with other interventional techniques produced outcomes that were not as beneficial as those achieved by radiosurgery alone. The only recorded complications found in these studies arose in patients receiving radiosurgery together with embolisation.

Embolisation alone also provided a good outcome for treatment of CCF, with all patients treated in this manner cured or improved in the Chung et al 2002 study. Embolisation when used in combination with radiosurgery was also successful in terms of clinical outcome with 12/13 patients achieving symptom improvement in the Pollock et al 1999 study. Chung et al 2002 also used this multimodal approach, but only for one patient who did not respond to treatment. In De Paula Lucas et al 2005 endovascular embolisation was less successful, with about half of all treatments regarded as a success.

## Expert opinion

In Australia and worldwide, an endovascular approach is the most frequently used procedure to occlude dural CCF. The numbers of patients being treated for this condition are small. Thus information comparing endovascular treatments to other procedures, such as surgery or radiosurgery, generally will not be available. There is a large variation in the type of occlusion devices used to treat CCF, which are dependent on the location, size and access of the fistula, as well as differences between centres. Another variation in the treatment of dural fistulae is to sacrifice the parent artery, either through surgery or endovascular approaches, when occlusion of the fistulae itself is not feasible due to its size or location. Expert opinion suggests that in the treatment of CCF, carotid artery blood flow needs to be preserved at all costs.

All the studies discussed above with regard to CCF reported dural fistulae of the cavernous sinus. Direct CCF are traumatic ruptures of the draining vein in the cavernous sinus, and the numbers of people treated for direct CCF have dropped dramatically following the introduction of seat belts and airbags in motor vehicles.

## Summary

In summary, for CCF it seems that radiosurgery alone may be the best mode of treatment, although endovascular embolisation, either alone or in combination with radiosurgery, is also successful in providing a good clinical outcome. As neither of the

studies reported above are RCTs, and both have reasonably low number of patients, there was not sufficient evidence to comment on the safety and efficacy of endovascular embolisation on the treatment of CCF.

## What are the economic considerations?

No costing information for endovascular treatments of CCFs was available from the literature. Assuming that hospital stay is similar after surgery, radiosurgery, endovascular treatment or combined treatments, costs per treatment may be roughly similar (as was outlined for AVMs above). Again it was not possible to make any determination about the effectiveness of endovascular treatments for CCFs and so a cost-effectiveness analysis could not be done.

# 3. Background: Endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage

Expert opinion of the Advisory Panel suggested that subarachnoid haemorrhage (SAH) is most commonly caused by trauma. The second most common cause is the rupture of an intracranial aneurysm, which affects approximately 10 in 100,000 individuals annually (Pluta 2005). Even after surviving the SAH and successful surgery, subsequent vasospasm may lead to ischaemic symptoms which may result in permanent neurological dysfunction or death. Endovascular treatments for vasospasm include balloon angioplasty and the intra-arterial delivery of smooth muscle relaxants. There is no direct surgical procedure for the treatment of vasospasm. Cisternal irrigation with or without thrombolytic therapy for the removal of blood in the subarachnoid space may be performed following the clipping of a ruptured aneurysm to reduce the risk of subsequent vasospasm (Usui et al 1994). Medical treatments include hypervolaemic, hypertensive and hyperdynamic therapy (Sen et al 2003, Treggiari et al 2003); the use of systemic vasodilators (including calcium channel blockers); and injection of fibrinolytic agents into the subarachnoid space, with or without induced hypothermia (Wu et al 2004). These medical therapies are frequently administered as prophylaxis immediately after the treatment of the aneurysm, in order to reduce the risk of vasospasm. The ultimate goal of these treatments is to increase blood flow to the brain and reduce the risk of delayed ischaemic neurological deficit (DIND), and to protect the neural tissue from irreversible ischaemic damage. Endovascular therapies have the advantage over other treatments in that they can be localised to the required vessels if the vasospasm is focal, and are often used when aggressive medical therapies fail to result in a reduction of symptoms.

## Cerebral vasospasm

Cerebral vasospasm is a narrowing of the lumen of an artery in the subarachnoid space, and is the most common complication of SAH (Smith and Enterline 2000). Vasospasm may occur in the absence of clinical signs and can be identified using angiography or the non-invasive transcranial Doppler ultrasonography (TCD). This is often termed as angiographic, or radiological, vasospasm. Symptomatic vasospasm is when the ischaemic consequences of the vasospasm are clinically observed due to changes in the neurological status of the patient.

Vasospasm is normally diagnosed with the onset of neurological deterioration. It is the most common complication following SAH as earlier intervention has greatly reduced the incidence of re-bleeding. It occurs as detected by angiography in up to 70% of patients and is clinically symptomatic in around 30% all of patients following SAH (Smith and Enterline 2000, Wu et al 2004). The vasospasm itself may be localised to only one artery, or can be more diffuse and cause more generalised vasospasm through larger areas of the brain, which is often most clinically problematic. When symptomatic, the DIND caused by vasospasm may be a small localised event, or cause a stroke, or death. Five to ten per cent of hospitalised SAH patients die from cerebral vasospasm (Nishizawa and Laher 2005).

Chronologically, symptomatic cerebral vasospasm occurs from day 3 or 4 following the incidence of SAH, has maximal incidence at days 6 to 8, and rarely occurs after day 17 (Sen et al 2005). Vasospasm can be seen on angiography between 4 to 12 days after SAH. Left untreated, mild vasospasm will slowly resolve over a period of 2 to 4 weeks (Harrod et al 2005).

### Pathophysiology of intracranial vasospasm

Normal artery structure has a lining comprised of a single endothelial cell layer, surrounded by the tunica intima (collagen and proteoglycan connective tissue). Next is a layer of smooth muscle cells, called the tunica media. The outer layer is the adventitia, or tunica externa, composed of loose fibrous connective tissue. In normal arteries, vasoconstriction is brought about through intracellular calcium signalling, where an increased concentration of free calcium ions activates myosin light chain kinase which causes vascular contraction. Conversely, nitric oxide is a potent vasodilator (Pluta 2005), and activates potassium ion channels which inhibit the calcium signalling.

The exact pathophysiology of arterial vasospasm is unknown, although it is thought to be a prolonged arterial contraction leading to structural changes and fibrosis of the arterial wall, exacerbated by constituents of the inflammatory response due to SAH, and the aggregation of platelets and white blood cells in the lumen (Harrod et al 2005). Histological changes of arteries during vasospasm include oedema and thickening of the tunica intima and tunica media, necrosis and proliferation of the tunica media, and adventitial inflammation resulting in luminal narrowing and rigidity of the vessel wall.

The development and severity of SAH-induced vasospasm is generally accepted to be proportional to the amount of blood in the subarachnoid space and the duration of exposure of the intracranial vessels to it. The time period during which erythrocytes break down and blood disappears from the cerebrospinal fluid (CSF) (through lysis and phagocytosis) closely mirrors the onset and resolution of clinical vasospasm (Smith and Enterline 2000). Some of the blood factors thought to be involved in the onset of vasospasm ('spasmogens') include haemoglobin, serotonins, prostaglandins, catecholamines, histamine, angiotensin, proteins of the complement system, adhesion molecules and endothelin (Armstead 2004, Lin et al 2004, Weir et al 1999, Sercombe et al 2002, Pluta 2005, Dumont et al 2003). Oxyhaemoglobin, diffusing from lysed erythrocytes, also fulfils the criteria for a spasmogenic agent and is widely thought to be a main contributory agent (Nishizawa and Laher 2005). Inflammatory responses are also thought to play a role (Sercombe et al 2002), with the presence of blood products in the subarachnoid space eliciting a robust cascade of events.

## Endovascular procedures

Various imaging techniques can be used to investigate vasospasm. Transcranial Doppler ultrasonography (TCD) is non-invasive and although it lacks detail, is the most useful and simple method of assessing cranial blood flow in patients at risk of vasospasm. Magnetic resonance imaging (MRI) and computed tomography (CT) can be useful in identifying areas of localised ischaemia. Conventional angiography is required for the definitive diagnosis and specific localisation of cerebral vasospasm (Smith and Enterline 2000), although it is invasive with a 0.1% risk of neurological deficit.

### Transluminal balloon angioplasty

After catheterisation, a compliant angioplasty balloon is placed into the artery, in conjunction with intravenous heparin as an anticoagulant, which is carefully monitored to maintain an activated clotting time of twice baseline. The balloon used may be of two types: flow directed, or over-the-wire. The latter is more easily placed as it does not depend on flow for its localisation. During balloon angioplasty the vessel wall is mechanically stretched which causes morphological changes to the artery. Animal models suggest that these resolve within 3 weeks (Smith and Enterline 2000), although there are still concerns regarding long-term injury. Patients are usually selected for balloon angioplasty when they have not responded to other treatment, as there is a risk of vessel dissection using this procedure. The results of a successful procedure are long lasting.

### Infusion of a smooth muscle relaxant

Certain drugs may be delivered directly into the artery at the location of the constriction using microcatheters. This enables smaller amounts of vasodilator to be used at higher concentrations in the direct vicinity of the vasospasm, although systemic hypotension is a common complication of this treatment. Detailed angiography is required for the correct placement of the catheter. Smooth muscle relaxants such as nimodipine, nicardipine and papaverine are calcium channel blockers, and act upon the voltage-dependent calcium channels present in the cell membrane of cerebral artery cells (Nishizawa and Laher 2005). Papaverine is popular as a topical neurosurgical vasodilator, and when it is used in this manner the side effects of systemic administration can be avoided, although re-treatment of the spastic vessel is often required. Fasudil hydrochloride is also a calcium antagonist vasodilator which brings about its action through the inhibition of the protein kinase, Rho kinase. This procedure is considered less invasive than balloon angioplasty with a reduced risk of vessel perforation, and can be used for more distal vasospasm (Smith and Enterline 2000), although both techniques are often used in conjunction with each other. It is common for patients to require reinfusion of the drug due to the recurrence of symptoms.

Although these drugs have been used for many years in this manner (intra-arterially) in other countries, at the moment the use of intra-arterial vasodilators is not approved for this indication in Australia, so will not be included in the final report.

## Existing procedures

### Hypervolaemic, hypertensive, hyperdynamic therapy

Hypervolaemic, hypertensive, hyperdynamic therapy (triple-H therapy) involves a combination of hypervolaemia (an increase in the volume of the circulating plasma), induced arterial hypertension and haemodilution. It has been used commonly for the treatment of vasospasm since the 1970s, and increases cerebral blood flow through the narrowed vessels. Fluids used intravenously to increase volume are a combination of crystalloids (eg 0.9% saline) and colloids (high molecular molecules such as albumin or dextran) (Sen et al 2003). Used prophylactically, triple-H therapy can prevent delayed ischaemia and improve clinical outcome after treatment of SAH, although a randomised controlled trial has never been undertaken (Sen et al 2003). There are contradictory

reports concerning the efficacy of triple-H therapy, and dangerous side effects are possible, including repeat SAH from an untreated aneurysm (Dorsch 2002).

### Irrigation of subarachnoid space

A number of Japanese groups have advocated clearing blood from the subarachnoid space by cisternal irrigation with inflow and outflow catheters (Sasaki et al 2000, Usui et al 1994, Kinouchi et al 2004) as a prophylactic to reduce the risk of vasospasm. This is often coupled with fibrinolytic therapy to disrupt the clot (using tPA or urokinase) and has been shown to be effective in reducing the incidence of post-SAH vasospasm. This procedure is not an approved use of these agents in Australia.

### Systemic pharmacological regimen

Fasudil is an inhibitor of the Rho kinase pathway which has been shown to play a role in sustained cerebral vasospasm. It has been used in Japan since 1995 to treat vasospasm (Nishizawa and Laher 2005). Its effects are short-term. Nicardipine and nimodipine are calcium channel blockers and have been used systemically as prophylactic vasodilators following SAH (Rinkel et al 2005). Nimodipine is more selective toward the cerebral vasculature and has less risk for systemic hypotension. Sodium ozagrel has been used in Japan and inhibits vasoconstriction brought about from thromboxane $A_2$, and is additionally beneficial as it also reduces platelet aggregation (Nakashima et al 1998). Currently, only nimodipine is approved for this indication in Australia.

### Subarachnoid injection of fibrinolytic agents and smooth muscle relaxants

Here the drug is administered to the vessels within the subarachnoid space around the thrombus which remains in the brain following SAH. Care must be taken regarding the location of the injection and also to avoid complications such as infection. Drugs that can be administered in this way are tissue plasminogen activator (tPA) and urokinase (Sasaki et al 2000, Usui et al 1994) for prophylactic thrombolysis of the clot, or papaverine for vasodilation of the affected arteries. The fibrinolytic agent may be applied as a single intraoperative bolus (Findlay et al 1991, Ohman et al 1991), followed by irrigation of the subarachnoid space with saline (Findlay 1995) or as a postoperative injection, often repeated until the thrombus is cleared on imaging (Mizoi et al 1993). Results so far suggest that intracisternal thrombolysis has a clinical benefit in reducing vasospasm after SAH (Amin-Hanjani et al 2004 and Pluta 2005). None of these agents are approved for this use in Australia.

### Hypothermia

Cerebral protection with mild hypothermia (32 - 34ºC) may be beneficial when conventional treatments are ineffective, although there are serious side effects that limit its use in some patients (Boulos et al 2004).

### Lumbar cerebrospinal fluid drainage

Draining the CSF has recently shown to be effective at removing spasmogens from the subarachnoid space (Pluta 2005, Klimo et al 2004, Hirashima et al 2005). Lumbar CSF drainage not only promotes the removal of blood products and potential spasmogens but also encourages the formation of new CSF. It is not clear yet whether this technique is effective alone (Klimo et al 2004) or only when used in combination with fibrinolytic therapy (Hirashima et al 2005).

## Comparator

As there is no surgical intervention for treating vasospasm, the primary comparators to endovascular treatments are pharmaceutical treatments, triple-H therapy or no treatment.

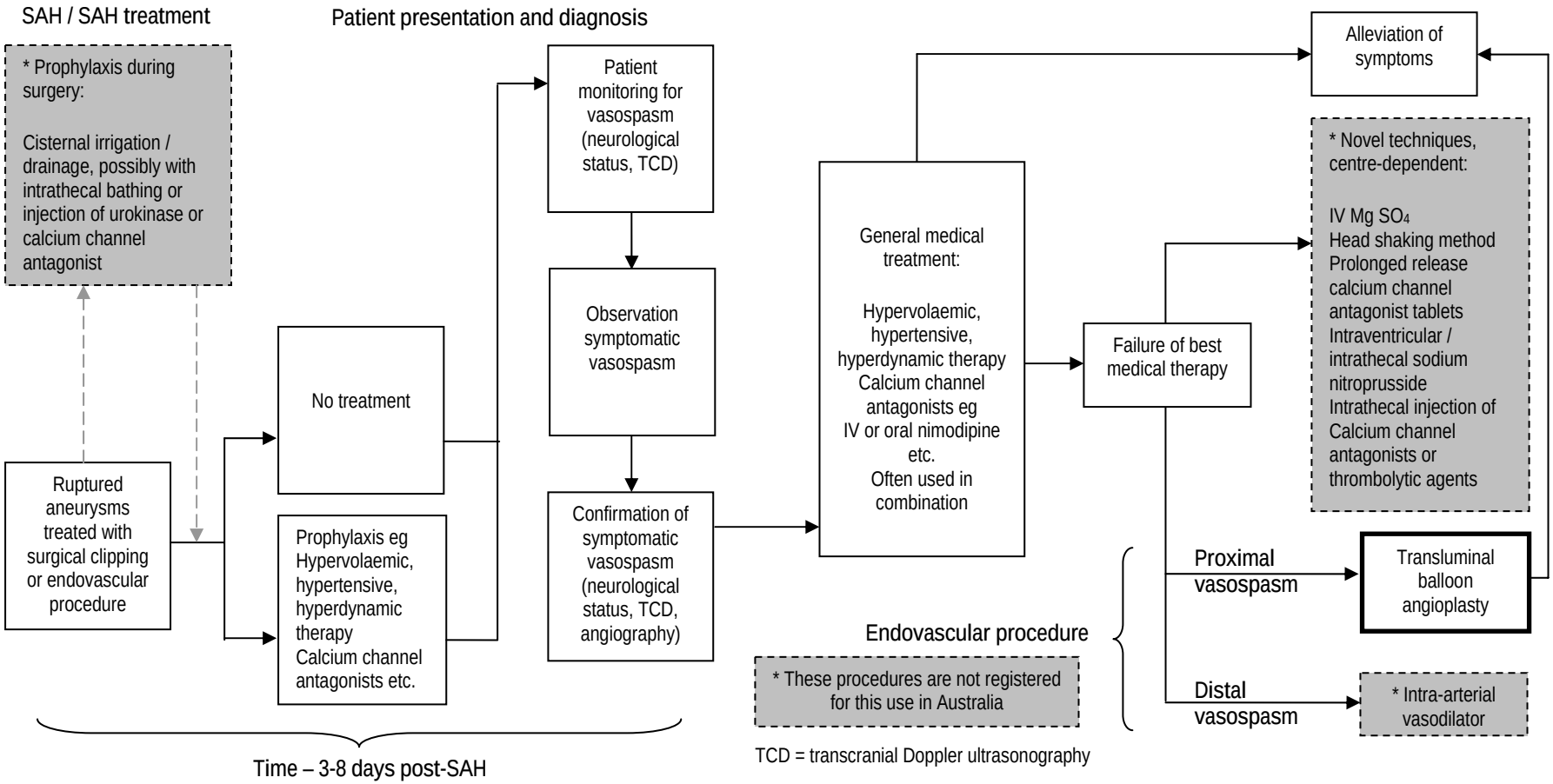
## Choosing between endovascular and medical treatments

The decision about whether to treat a patient with an endovascular or a medical approach is complex and takes into consideration the following:

- Endovascular approaches are often used when medical procedures have proved unsuccessful.
- Whether the patient is symptomatic. An endovascular approach may be more likely when the patient has severe symptoms.
- The location of the vasospasm. Proximal locations involving few arteries may be accessible for balloon angiography, other locations may be more easily treated using vasodilator infusion, although more generalised vasospasm may be more successfully treated with systemic medication.
- The endovascular experience of the team treating the vasospasm.

## Clinical decision pathway

Figure 3 Clinical decision pathway, vasospasm



## Clinical need / burden of disease

The management of patients after treatment for SAH essentially involves minimising the risk of and treating vasospasm, which is the main cause of morbidity and mortality for patients who survive an aneurysmal SAH. Vasospasm is detected with angiography in around 70% of untreated patients at the time of maximum vasospasm, seven days after SAH (Dorsch 2002). Up to 30% of all patients have symptomatic vasospasm, which without specific treatment leads to death or permanent disability in two-thirds of these patients (Dorsch 2002).

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

### Australian data

In Australia there have been a number of epidemiological studies focused on either stroke or SAH. The Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS Group 2000) studied the incidence of SAH in Australia and New Zealand from data in four population-based registers between 1995 and 1998. The age and sex-adjusted annual incidence rate for first ever SAH (1996-1998) was 6.5 (95% CI, 5.8 to 7.2) per 100,000 but was higher in New Zealand (9.9 per 100,000 95% CI 7.9 to 12.4) reflecting higher rates of SAH in the Maori and Pacific populations (ACROSS Group 2000). Of the 436 patients with SAH, 76% (330/436) were found to have a ruptured aneurysm.

A study of stroke survival in Western Australia between 1995 and 1998 found SAH responsible for 807/7784 (4%) of hospital admissions for stroke. The mean age of these patients was 54.3 years (range 52.3 to 56.3) and 57.5% female (Lee et al 2003).

The North East Melbourne Stroke Incidence Study (NEMESIS) reported incidence of stroke among a population of 133 816 residents of one area of Melbourne between 1996 and 1997. The age adjusted annual incidence of first ever stroke was 100 (95% CI, 80 to 119) per 100,000 (Thrift et al 2001). Assuming that around 4% of these strokes were SAH the estimated incidence are 4 in 100,000 which is consistent with the ACROSS data.

From this data, and assuming that symptomatic vasospasm is seen in 30% of patients who have suffered SAH, this equates to between 1.2 and 2 cases of vasospasm per 100,000 of the population.

There is scant data showing the effectiveness of current medical treatments of vasospasm, and it is accepted that these treatments may have major side effects. As the actual cause of cerebral vasospasm is still poorly understood it is likely that more topical approaches, such as is possible using endovascular approaches, are safer and more successful.

# Results: Endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage

Two comparative studies were identified which examined the impact of endovascular techniques on patients who suffered aneurysmal subarachnoid haemorrhage (SAH) (Table 36). Katoh et al 1999 reported on the outcomes of four different interventional techniques that were used once the patient exhibited symptoms of vasospasm, compared with conservatively treated control treatments. Muizelaar et al 2001 initiated treatment as a prophylactic measure in 'at risk' patients who were yet to present with symptoms of vasospasm. Due to the pre- and post-vasospasm focus of each of these studies it was difficult to directly compare their outcomes.

Patients reported in Katoh et al 1999 were treated in five groups:

- patients who developed clinical deterioration due to vasospasm who underwent percutaneous transluminal angioplasty (PTA) (therapeutic PTA group);
- patients with angiographic vasospasm without clinical deterioration who underwent PTA ('prophylactic' PTA group);
- patients with clinical vasospasm who were treated with intra-arterial (IA) papaverine infusion (therapeutic PPV group);
- patients with angiographic vasospasm who received IA (intra-arterial) PPV ('prophylactic' PPV group);
- patients who underwent standard medical therapy including HHH (conservative treatment group).

No further detail was given regarding the techniques or devices used. The exclusion criteria set for this Report precludes the analysis of any study groups in which the intra-arterial infusion of papaverine was used. As papaverine was administered in two groups for therapeutic and prophylactic uses, data from these two groups will be excluded from any analysis in this study. Only therapeutic PTA, 'prophylactic' PTA and the control group fit the inclusion criteria for analysis in this study, therefore analysis will focus on the safety and efficacy outcomes achieved within these groups. The patient number for included treatments in Katoh et al 1999 was therefore 70, from a total number of 84.

As expected, the timing of treatment differed between the three groups. Therapeutic PTA was undertaken at a mean of 11 days (5 – 15 days) and 'prophylactic' PTA at a mean of 9.1 days (5 – 13 days). No values were provided for the control group as these did not undergo an interventional procedure.

In the Muizelaar study, the patients remained intubated following surgery or coiling of the ruptured aneurysms. Femoral access was used. Diagnostic angiography was undertaken initially to check for vasospasm, followed by a 4mm x 10mm, 0.1ml occlusion balloon-type angioplasty balloon catheter with systemic heparinisation. Balloons were inflated to less than 6 atmospheres for 5 seconds, to a diameter no larger than the native diameter of the

artery. Arteries treated were the A1 segment of the middle cerebral artery (MCA), the internal carotid artery (ICA), the P1 segment of the posterior cerebral artery (PCA), the basilar artery (BA) and the vertebral artery (VA).

### Critical appraisal

Neither of the two studies used randomised allocation of patients. However, Muizelaar et al 2001 did have well-defined inclusion criteria, including a specific Fisher grade of SAH, the possibility of treatment within three days of the bleed, as well as the inclusion of patients who did not have any evidence of vasospasm as confirmed using angiography. This would mean that, as far possible, the patients were at a similar clinical level at the beginning of the study, and had not yet begun to deteriorate as a result of vasospasm. Although clinically significant vasospasm would not be expected to occur in all patients following SAH, their use of a control group allows some estimation of how many patients might have been expected to develop vasospasm without other intervention. Twice as many patients received the endovascular treatment than were in the control group (n=18 versus n=9). Seven of the nine controls were excluded from PTA treatment for various reasons. Four had severe atherosclerosis or vascular abnormalities which did not allow passage of the balloon (two of these received PTA, but in only one part of the intracranial circulation). Three were excluded as they were admitted to hospital several days after SAH (one of these had early vasospasm). Outcomes were well-defined. Transcranial Doppler (TCD) ultrasonography was used to grade cerebral blood flow velocities for 10-14 days following SAH. Delayed ischaemic neurological deficit (DIND) was attributed to vasospasm if it occurred within days 3-14 after SAH and could not be attributed to another cause, and was confirmed using angiography. Final Glasgow Outcome Score (GOS) was evaluated by an experienced, blinded assessor, minimising bias in outcome assessment, although the technique for blinding was not mentioned.

Katoh et al 1999 reported on all the patients admitted to their site for treatment for cerebral aneurysm during a defined period, but excluded patients who had to undergo surgery for the removal of a large blood clot. The patients were divided into five groups, although the rationale for their allocation was not described. These patients underwent balloon angioplasty or papaverine infusion, either on development of angiographically- or clinically-significant vasospasm (named the prophylactic group and therapeutic group respectively). These were compared to standard medical therapy. Clinical outcome was reported using GOS. The authors did not report any blinding of the assessors.

### Inclusion and exclusion criteria

Katoh et al 1999 excluded patients who underwent surgery for evacuation of massive haematoma, but included those considered to be candidates for early surgical intervention within 72h after SAH. Muizelaar et al 2001 included patients who had Fisher grade 3 SAH (see Appendix C Table 58). These patients were considered to be at greatest risk of developing vasospasm after aneurysm rupture. These patients received treatment for their ruptured aneurysm (surgical or neurointerventional), and were able to receive balloon angioplasty within 3 days of the bleed. In addition, (contrary to Katoh et al 1999) patients were only included if they had no angiographic evidence of vasospasm prior to the balloon angioplasty.

Table 36 Vasospasm study information

| Author | Level of evidence | Study period | Study design | Treatment | Number of patients | Timing of treatment, days (mean and range) | Age (mean and range) |
|---|---|---|---|---|---|---|---|
| Katoh et al 1999 | III–2 | 1990 – 1993 | Comparative study with multiple comparative concurrent groups with control | Therapeutic PTA | 12 | 11 (5-15) | 56 (26 – 72) |
| | | | | Prophylactic PTA | 18 | 8.5 (5-13) | 52 (19 – 74) |
| | | | | Therapeutic papaverine (a) | 4 | 8 (7-10) | 57 (51 – 68) |
| | | | | Prophylactic papaverine (a) | 10 | 8 (7-12) | 52.9 (35 – 63) |
| | | | | Control (conservative treatment) | 40 | NA | 56 (29 – 77) |
| Muizelaar et al 2001 | III-2 | June 1997 – May 1998 & April 2000 – August 2000 | Matched concurrent comparative study | Prophylactic PTA | 18 | Within 3 days of rupture | 48 (29 – 75) |
| | | | | Control (conservative treatment) | 9 | NA | 61 (37 – 78) |

NOTE: (a) = study arms not able to be analysed in this review as they did not meet the inclusion criteria ; NA = not applicable

## Follow-up and losses to follow-up

Katoh et al 1999 did not specify the duration of the follow-up, although no patients were lost to follow-up. In the Muizelaar et al 2001 study, outcomes were assessed at around 3 months with no patients reported as lost to follow-up during that time.

## Pre-procedural grade of patient

The Hunt and Hess or the similar Hunt and Kosnik scale was used in each study to grade the pre-interventional clinical grade of each patient (Table 37). On this scale, an increasing score represents a worsening grade of stroke (Appendix C, Table 60). In the Katoh study, each patient's pre-intervention Hunt and Kosnik grade was recorded and is illustrated in Table 37. There were no significant differences between age, gender, Hunt and Kosnik grade or the location of ruptured aneurysms between groups.

Table 37 Pre-intervention Hunt and Hess or Hunt and Kosnik grade

| Study | Group | Pre-intervention H&H or H&K grade | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| Katoh et al 1999 (Hunt and Kosnik) | Therapeutic PTA | 3/12 (25%) | 5/12 (41%) | 3/12 (25%) | 1/12 (8%) | 0 |
| | Prophylactic PTA | 6/18 (33%) | 6/18 (33%) | 4/18 (22%) | 2/18 (11%) | 0 |
| | Control | 8/40 (20%) | 18/40 (45%) | 9/40 (22%) | 5/40 (13%) | 0 |
| Muizelaar et al 2001 (Hunt and Hess) | At admission | | | | | |
| | Prophylactic PTA | 1/18 (6%) | 4/18 (22%) | 7/18 (39%) | 5/18 (28%) | 1/18 (6%) |
| | Control | 0 | 2/9 (22%) | 3/9 (33%) | 1/9 (11%) | 3/9 (33%) |
| | Pre-op | | | | | |
| | Prophylactic PTA | 1/18 (5.6%) | 4/18 (22%) | 9/18 (50%) | 3/18 (17%) | 1/18 (6%) |
| | Control | 0 | 2/9 (22%) | 4/9 (44%) | 2/9 (22%) | 1/9 (11%) |

Muizelaar et al 2001 recorded patient Hunt and Hess grade on admission and pre-operative. Although there was a slight difference in distribution at both times for the two groups, there was no reported statistical difference between the two treatment groups with regard to Hunt and Hess grade.

In the Katoh et al 1999 study, the ruptured aneurysms were located in similar areas between the three treatment groups, all in the anterior circulation (Table 38). Muizelaar et al 2001 also had a similar distribution between the two treatment groups, although a minority of patients had aneurysms in posterior locations (17% of patients on the prophylactic PTA group and 22% in the conservative group, all of these in the basilar artery).

Table 38 Location of the ruptured aneurysms

| | Katoh et al 1999 | | | Muizelaar et al 2001 | |
|---|---|---|---|---|---|
| Location | Therapeutic PTA | Prophylactic PTA | Conservative | Prophylactic PTA | Conservative |
| Anterior circulation | | | | | |
| MCA | 4/12 (33%) | 6/18 (33%) | 18/40 (45%) | 1/18 (6%) | |
| ACA | 1/12 (8%) | 3/18 (17%) | 8/40 (20%) | | |
| IC/PCA | 3/12 (25%) | 4/18 (22%) | 10/40 (25%) | | |
| ACoA | 3/12 (25%) | 5/18 (27%) | 2/40 (5%) | 11/18 (61%) | 4/9 (44%) |
| IC bifurcating | 1/12 (8%) | | | | |
| PCoA | | | | 3/18 (17%) | 3/9 (33%) |
| Other locations | | | 2/40 (5%) | | |
| Posterior circulation | | | | | |
| BA | | | | 3/18 (17%) | 2/9 (22%) |

NOTE: MCA, middle cerebral artery; ACA, anterior cerebral artery; IC/PCA, internal carotid-posterior communicating artery (PcoA); ACoA, anterior communicating artery; IC bifurcating, internal carotid-bifurcating; PCoA, posterior communicating artery; BA, basilar artery.

# Is it safe?

## Mortality

In Muizelaar et al 2001, one patient (6%) in the balloon angioplasty group died of a rupture of the posterior inferior cerebellar artery (PICA) during angioplasty, and two (11%) died of pulmonary complications after recovery (Table 39). Four patients (44%) died in the control group. Two of these deaths were from vasospasm, and the other two were from respiratory failure unrelated to aneurysm rupture. In the Katoh study, no patients died in the PTA groups (therapeutic and prophylactic), and there were 5 deaths (13%) in the control, conservatively-treated, group, all seemingly as a result of the vasospasm.

## Adverse events

In Katoh et al 1999, adverse events were not reported for the PTA groups. Muizelaar et al 2001 did not report adverse events beyond those which resulted in patient mortality (Table 38).

Table 39 Mortality and adverse events

| Study | Group | Mortality | Adverse Events |
|---|---|---|---|
| Katoh et al 1999 | Therapeutic PTA | 0/12 | 0/12 |
| | Prophylactic PTA | 0/18 | 0/18 |
| | Control | 5/40 (13%) – seemingly due to vasospasm | NR |
| Muizelaar et al 2001 | Prophylactic PTA | 3/18 (17%) – 1 PICA rupture, 2 pulmonary complications | 1/18 (8%) |
| | Control | 4/9 (44%)- 2 vasospasm, 2 respiratory failure | NR |

NOTE: PICA = posterior inferior cerebellar artery; NR = not reported

## Recurrence

No recurrence of vasospasm and subsequent re-treatment of patients who underwent PTA was reported by either Katoh et al 1999 or Muizelaar et al 2001.

# Is it effective?

## Clinical outcomes

Katoh et al 1999 reported that outcomes for patients treated with PTA prophylaxis was significantly better than those experienced by the control patients ($p=0.01$) using the GOS scale (Table 40). Additionally, the combined results from both prophylactic and therapeutic PTA groups demonstrated a better outcome than the control group, although this did not reach statistical significance ($p=0.09$). The specific GOS scores compared were not reported. Vasospasm occurred in 17/40 (42%) of the control patients, and in only

1/18 (6%) of the prophylactic PTA patients. Clinical symptoms were improved in 7/12 (58%) patients treated with therapeutic PTA, and vasospasm occurred in 2/12 (17%) of this group following PTA treatment.

Muizelaar et al 2001 reported improved outcomes for patients who had received prophylactic PTA compared to control patients, with a higher number receiving a GOS score of 4 or 5 (Table 40). In addition, as previously reported, there were fewer patient deaths in the PTA-treated group, though the statistical significance was not reported. Most importantly, none of the patients treated with prophylactic PTA suffered from vasospasm, whilst 6/9 (66%) of the patients treated medically suffered clinical vasospasm (Table 41). Muizelaar is currently heading an ongoing, larger scale, multi-centre randomised controlled trial of this technique where balloon angioplasty is used as prophylaxis for patients at high risk of vasospasm after SAH, compared to conventional medical management. Five sites in three different countries are involved and, as of December 2004, 152 patients had been recruited for the study. Enrolment in this study ceased on 1st February 2006 (personal communication); therefore, results were not available. For further information, see http://www.strokecenter.org/trials/TrialDetail.aspx?tid=199.

Table 40 Glasgow outcome scale scores after treatment

| Study | Group | Glasgow Outcome Score | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| Katoh et al 1999 | Therapeutic PTA | 0 | 0 | 4/12 (33%) | 2/12 (17%) | 6/12 (50%) |
| | Prophylactic PTA | 0 | 0 | 0 | 3/18 (17%) | 15/18 (83%) |
| | Control | 5/40 (13%) | 1/40 (3%) | 4/40 (10%) | 9/40 (23%) | 21/40 (52%) |
| Muizelaar et al 2001 | Prophylactic PTA | 3/18 (17%) | 0 | 0 | 5/18 (28%) | 10/18 (56%) |
| | Control | 4/9 (44%) | 0 | 0 | 1/9 (11%) | 3/9 (33%) |

NOTE: PTA = percutaneous transluminal angioplasty

Table 41 Vasospasm outcomes

| Study | Group | Outcomes | | |
|---|---|---|---|---|
| | | Clinical symptoms improved | Occurrence of vasospasm | Absence of post-operative focal deficit |
| Katoh et al 1999 | Therapeutic PTA | 7/12 (58%) | 2/12 (17%) | 6/12 (50%) |
| | Prophylactic PTA | NA | 1/18 (7%) | 13/18 (72%) |
| | Control | NA | 17/40 (43%) | 34/40 (85%) |
| Muizelaar et al 2001 | Prophylactic PTA | NA | 0/18 | NR |
| | Control | NA | 6/9 (66%) | NR |

NOTE: PTA = percutaneous transluminal angioplasty; NA = not applicable; NR = not reported

## Discussion

Although the two studies investigated in this review with regard to vasospasm may seem reasonably comparable, it is important to note the different use of the term prophylactic in

each. Muizelaar et al 2001 used the term 'prophylactic treatment' to describe balloon angioplasty when it is used in the absence of any vasospasm, as determined using angiography. In Katoh et al 1999, the therapeutic PTA group was treated for clinically symptomatic vasospasm, whilst the 'prophylactic' PTA group was treated in the absence of clinically symptomatic vasospasm, but in the presence of angiographic vasospasm. Therefore, the patients in the Katoh et al 1999 'prophylactic' PTA group may be expected to have been associated with a poorer clinical condition than the Muizelaar et al 2001 'prophylactic' PTA patients.

Both studies recorded the pre-interventional status of their treatment groups and noted that there was no significant difference between the groups at this stage. Both studies included control patients who were not treated with balloon angioplasty, however, the Muizelaar et al 2001 control patients were not included in the treatment group for various reasons, including atherosclerotic changes and vascular abnormalities. Katoh et al 1999 did not report the method of allocation of patients in the control group who were selected to have conservative treatment over intra-arterial intervention.

Mortality rates were lower in both studies with PTA therapy whether used prophylactically or therapeutically, compared with conservatively treated patients. Katoh et al 1999 did not report any adverse events in either of the two PTA groups; Muizelaar et al 2001 reported the fatal rupture of an artery in one patient. There were no adverse events in either of the studies' conservatively treated groups, which may be reasonably expected, as they did not undergo any procedure. In both studies, clinical improvement was advanced in the prophylaxis group compared to the control group. This improvement was statistically significant in the Katoh study, whilst there was no significant improvement over conservative treatment when PTA was used to treat clinically symptomatic vasospasm (therapeutic PTA).

Vasospasm outcomes were improved in patients reported in both studies following PTA treatment. Katoh et al 1999 suggested that PTA treatment in patients who were suffering clinically significant vasospasm improved their symptoms. The appearance of vasospasm was reduced in patients who had received PTA treatment either therapeutically or 'prophylactically', compared with patients who did not receive PTA. Of the patients who received prophylaxis PTA in the Muizelaar et al 2001 study, none suffered vasospasm, whilst more than half of the patients who did not receive PTA suffered vasospasm.

## Expert opinion

Expert opinion from the Advisory Panel suggested that balloon angioplasty is rarely used in Australia for the treatment of vasospasm. Futhermore, balloon angioplasty would almost never be used as a prophylactic measure as the risk of intervention would far outweigh the possible benefits, considering that the patient would not necessarily develop symptomatic vasospasm following SAH. In the case of medically-refractory, symptomatic vasospasm, it is more likely that the primary treatment in Australia would be the intra-arterial infusion of a vasodilator. The use of these drugs in this manner is not presently endorsed by the TGA. This procedure would normally be undertaken in a large facility, by experienced neurointerventionalists with access to the technology required. Ethical approval is arranged locally to allow this procedure to be undertaken.

## Summary

These results suggest that PTA is most efficacious in treating vasospasm before the appearance of clinically significant vasospasm, either when vasospasm is not detectable on angiography, or when spastic arteries are angiographically visible, but before vasospasm is clinically apparent. PTA does not appear to be effective in treating vasospasm after it has become clinically symptomatic. It should be noted that these results were taken from only two studies which made valid comparisons of like groups neither of which are RCTs, and involve relatively small numbers of patients. Muizelaar is in the process of completing a larger randomised trial investigating the use of balloon prophylaxis in the treatment of vasospasm.

## What are the economic considerations?

No information is available concerning costing of PTA as a treatment of SAH-induced vasospasm. Therefore specific economic evaluation data on this treatment could not be given.

# 4. Background: Endovascular treatments for intracranial atherosclerosis

Treatment of intracranial vascular stenosis using endovascular techniques has become more common over the past few years due to the improvement of microcatheters, balloons and stents, and the improvement in use of these techniques in treating coronary atherosclerosis. There is still some controversy regarding the use of these methods in the delicate intracranial vasculature as there were very few trials and evidence regarding their effectiveness (Chimowitz et al 2001). Endovascular procedures provide an alternative to the use of warfarin or aspirin, although they are technically demanding with potentially serious procedural side effects including stroke and vessel rupture, and are most commonly used following the failure of medical regimens.

## Atherosclerotic disease

Atherosclerosis is a chronic, systemic, disease that causes various cardiovascular complications. It is the process in which the deposits of fatty substances, cholesterol, cells, cellular waste products, calcium and other substances build up on the inner lining of an artery, forming a solid substance which reduces the diameter of the vessel lumen. This main pathological component of atherosclerosis is termed an atheromatous plaque. These plaques occur most often in large arteries such as the coronary artery, the superficial femoral artery, the subrenal aorta and the carotid arteries (Rollo et al 2001). The plaques can increase in size and cause an occlusion *in situ*, or if unstable can break off and cause an occlusion in another part of the vasculature. Multiple factors can contribute to atherosclerosis, including diabetes, hyperlipidemia, smoking, hypertension, immune and genetic factors (Ohashi et al 2004).

Intracranial vascular stenosis reduces blood flow leading to ischaemia in the brain, and accounts for 5-29% of all ischaemic strokes (Chimowitz et al 1995, Schumacher et al 2004), and is one of the most high risk vascular conditions encountered by neurointerventionists. Intracranial atherosclerotic plaques are associated with a higher risk of stroke or death than any other intracranial disorder (such as unruptured aneurysms, unruptured AVM, DAVF, spinal AVM or vertebral AVF) (American Society of Interventional and Therapeutic Neuroradiology (ASITN) 2001).

### Pathophysiology of intracranial atherosclerosis

Most intracranial stenoses are identified when they become symptomatic, at which time the disease has a very poor prognosis (Levy et al 2002). The most dangerous stenoses, both for patient prognosis and ease of operation, are long (> 10mm), eccentric, stenoses which take up a considerable proportion of vessel diameter (Levy et al 2002). Significant occlusions occupy > 70% of the vessel calibre and are often referred to as high-grade stenoses. The recent onset of symptoms may indicate an unstable plaque. The most vulnerable plaques at a high risk of rupture have a soft core, possibly infiltrated by white blood cells, covered by a thin, unstable fibrous cap (Rollo et al 2001).

Although most commonly identified when symptomatic, the presence of a plaque can be recognised through investigation of intracranial blood flow dynamics using transcranial

Doppler ultrasonography (TCD). Cerebral blood vessels can be examined in greater detail using CT angiography, in which vessels are imaged using iodine-based contrast material detected with X-rays, or magnetic resonance angiography, which can provide images of vessels without the need for contrast material. MRI techniques use strong magnets and radiowaves to align the protons of hydrogen atoms in human tissue, and are intrinsically three-dimensional. The gold standard for detailed vessel imaging is cerebral angiography, an invasive technique which requires the placement of a catheter through the femoral artery, and the use of contrast material. Initially, blood perfusion may increase through the area of the plaque due to increased blood jet velocity through the stenosis (Schumacher et al 2004). Blood flow will eventually be reduced as the plaque grows. Studies have shown that larger, echolucent, plaques can generate a higher number of embolic particles following endovascular intervention (Biasi et al 2004). The echolucency of the plaque can therefore be a parameter which indicates the risks of particular treatments.

### Risk factors for intracranial atherosclerosis

Risk factors for intracranial atherosclerosis are the same as for general atherosclerosis, and include hyperlipidaemia, cigarette smoking, hypertension and insulin-dependent diabetes (Knuiman and Vu 1996). Higher numbers of cases are seen in people of African, Hispanic or Asian descent (Cloud and Marcus 2003).

## Endovascular procedures

The success of coronary angioplasty and stenting, and the development of improved balloon, microcatheter and stent technology over the past 10 years has driven the use of these techniques in the treatment of intracranial atherosclerosis (Chimowitz et al 2001). Both these procedures are technically demanding at many levels and carry substantial risk, including haemorrhage due to vessel dissection or rupture, vessel occlusion or ischaemic stroke (Schumacher et al 2004). The risk of vessel dissection and rupture are greater in cerebral vessels, which have delicate surrounding tissue and a thinner adventitia than in coronary vessels, which have a thicker adventitia and supporting myocardium (Boulos et al 2004). Due to these hazards, patients undergoing endovascular revascularisation have typically undergone and failed best medical therapy as a primary treatment. The risk of undergoing endovascular procedures must be identified for each individual patient as this depends on the location of the stenosis, its length and its morphological features, together with the presentation of the patient. Reported rates of procedural morbidity and mortality range from 10-20% (Schumacher et al 2004) and may be even higher for neurologically unstable patients.

The endovascular procedure itself must be performed under general anaesthesia, using a standard transfemoral approach (Schumacher et al 2004). Heparin infusion is used throughout the procedures to achieve an activated clotting time of twice baseline. Antiplatelet agents (eg aspirin and clopidogrel) are used pre-, peri- and post-procedurally to reduce the risk of platelet aggregation as a side effect. Procedural technical success is measured as degree of vessel recanalisation, and clinical success is based on the absence of stroke or transient ischaemic attack (TIA) 30 days or more after the intervention.

### Transluminal / percutaneous balloon angioplasty

The risks involved with using this technique include distal embolisation of plaque material causing ischaemic stroke, and haemorrhagic stroke due to vessel dissection or arterial rupture.

### Arterial stents

Balloon-mounted stents are put into position with the aid of angioplasty. Stents provide the potential advantage over simple balloon angioplasty of improved long-term patency rates by avoiding recoil. They also reduce the risk of distal embolisation by trapping plaque material against the artery wall. They are therefore frequently used with high-grade stenoses that are considered unsuitable for angioplasty alone. Stents may also be used following initial angioplasty (stent-assisted angioplasty), especially for high-grade stenoses (Levy et al 2003). The main problems with the use of stents have been with their placement and deployment, as it is often difficult and dangerous to locate rigid, balloon-mounted stents through and within some of the tortuous intracranial vessels. The recent development of more flexible stents, for example the Wing-span stent (Boston Scientific) and Neurolink system (Guidant Corporation, The SSYLVIA Study Investigators 2004), has improved this situation, and has enabled stents to be used in more distal areas of atherosclerosis (Al-Mubarak et al 1998). These are easier to guide through the delicate cerebral vasculature and the exact sizing of the stent is less important. This has enabled stent use to be slightly less technically demanding with less risk of vessel dissection or arterial rupture. Stents have also been developed with various coatings to help reduce the formation of thrombi on the stent itself. These include polytetrafluoroethylene (PTFE), titanium-nitric oxide, heparin, sirolimus and paclitaxel (drug-eluting stents) (Boulos et al 2004).

Although the use of stents for this indication is common in some countries, none of the stents currently listed on the TGA are registered for use in treating intracranial atherosclerosis; therefore, the use of stents will not be discussed in the final report.

## Existing procedures

There are no comparable surgical procedures for the treatment of intracranial atherosclerosis due to the difficulty of surgical approach compared to that for cervical carotid bifurcation stenosis (ASITN 2001). Surgical approaches of intracranial arterial bypass have been attempted in the past but these did not provide clinical benefit over best medical therapy (EC/IC Bypass Study Group 1985).

### Existing medical treatments

Currently, there is no consensus as to what constitutes 'best medical therapy' for the treatment of intracranial atherosclerosis. Treatment of patients with intracranial arterial stenosis has traditionally consisted of antithrombotic therapy (antiplatelet or anticoagulation agents such as aspirin or warfarin) together with the management of vascular risk factors. Statins (HMG-CoA reductase inhibitors) (Bedi and Flaker 2002) and angiotensin-converting enzyme inhibitors have also been used (Schumacher et al 2004).

Antiplatelet agents (aspirin, dipyridamole and clopidogrel) and warfarin (an anticoagulant) have been used widely in the treatment of symptomatic intracranial stenosis for many years. Patients on aspirin therapy may have a stroke risk of up to 20%, whilst early studies suggested that warfarin treatment could reduce this to approximately 10% per year (Chimowitz et al 1995). A recent multi-centre randomised trial has shown warfarin to be associated with significantly higher rates of adverse events whilst providing no benefit over aspirin for atherosclerotic intracranial arterial stenosis (Chimowitz 2005). Also, neither antiplatelet agents nor warfarin completely halt the progression of atherosclerosis (Chimowitz et al 1995, Straube et al 2005).

## Comparator

As there is no surgical intervention for treating intracranial atherosclerosis, the primary comparators to endovascular approaches are pharmaceutical treatments (eg antiplatelet agents or warfarin) or no treatment.

## Choosing between endovascular and medical treatments

The decision about whether to treat a patient with an endovascular or a medical approach is complex and takes into consideration the following:

- Endovascular approaches are used when medical procedures have proved unsuccessful, so the patient may be less likely to recover fully.
- Medical therapy failures must be recognised early.
- Whether the patient is symptomatic. An endovascular approach may be more likely when the patient has symptoms from a high grade stenosis.
- The location of the plaque. Proximal locations are more accessible for endovascular procedures. Peripheral locations are much more difficult to access for intracranial endovascular procedures.
- Stents are often used for the treatment of severely stenotic (> 70%) lesions.
- The endovascular experience of the team treating the stenosis.

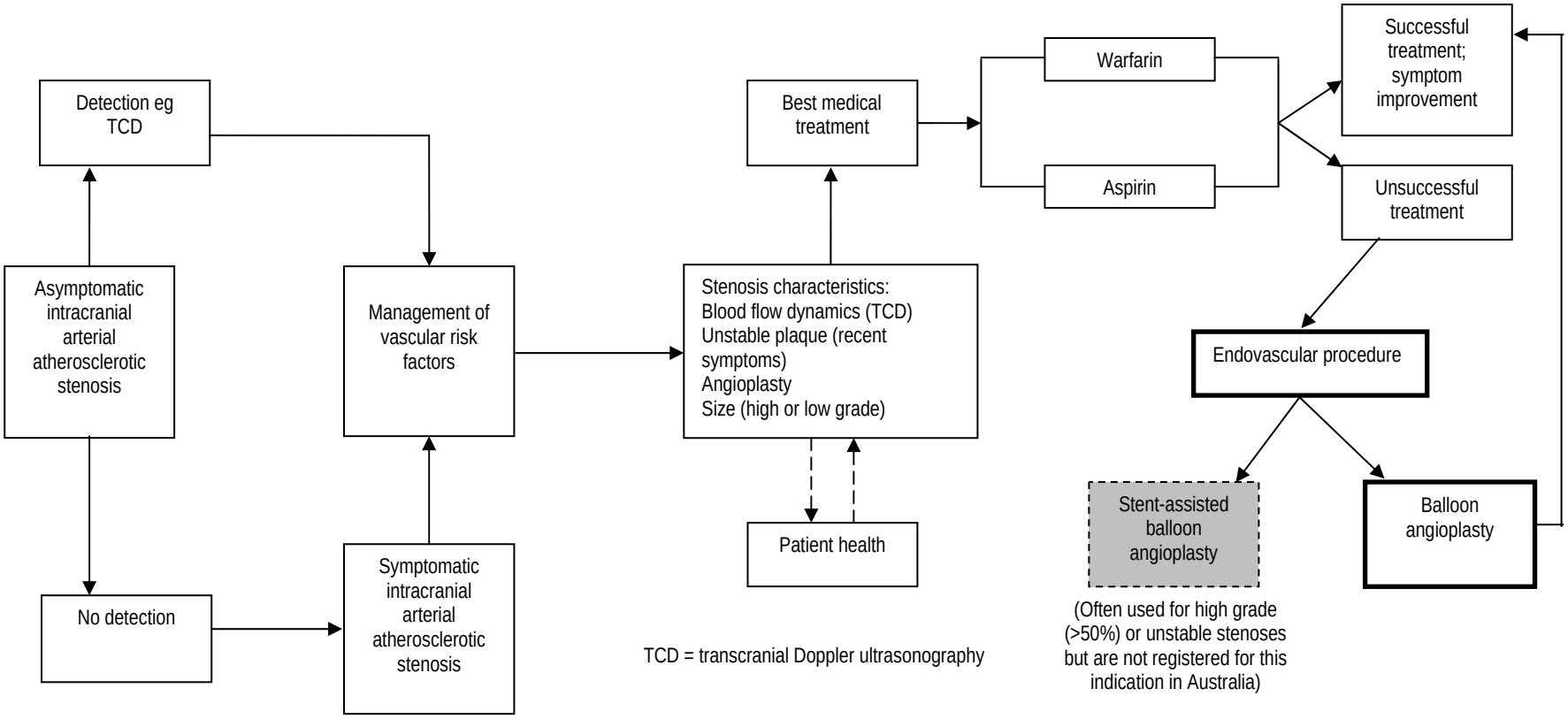
## Clinical need / burden of disease

Intracranial atherosclerosis accounts for about 5-29% of all ischaemic strokes depending on the population examined (Chimowitz et al 1995, Schumacher et al 2004). In the USA, there are approximately 750,000 strokes per year (Smith et al 2005), of which about 40,000 are caused by intracranial stenosis (Schumacher et al 2004).

In Australia, stroke is the third most common cause of death and is a major cause of disability (Hankey 2000). According to the Australian Institute of Health and Welfare (AIHW), nearly 50,000 Australians have a stroke annually. This subject is covered in greater detail in the following section on acute stroke.

## Clinical decision pathway

Figure 4 Clinical decision pathway, treatments for intracranial arterial atherosclerosis




Other medical therapy commonly used before and after intervention include aspirin, clopidogrel, abciximab, urokinase, also starins and angiotensin-converting enzymes

# Results: Endovascular treatments for intracranial atherosclerosis

## Critical appraisal

Only one comparative study of endovascular balloon angioplasty could be included (Connors et al 1999, Table 42). This was a non-randomised historical comparison (III-3) which compared three different techniques for balloon angioplasty carried out over discrete periods within a single site (Table 42 and 43). There were a total of 70 patients, however these were unevenly distributed between the three different techniques, with the majority (50 patients) treated using the latest procedure (Table 44). The authors retrospectively examined all patient details and outcomes for each technique used.

The presentation of the patients, and the severity of the initial stenosis, was not discussed by the authors. Patients were referred to the study by either a neurologist or a neurointerventionist, and the stenosis was confirmed by angiography. Symptoms had to be related to the target lesions.

Table 42 Intracranial atherosclerosis study information

| Study | NHMRC level of evidence | Study period | Intervention | Study design |
|---|---|---|---|---|
| Connors et al 1999 | III-3 | 1989-1999 | Balloon angioplasty | Three different techniques historically compared, varying size of balloon and method of inflation (early, middle, later) |

Table 43 Patient information

| Study | Patient Nx | Patient age (years) | Allocation | Treatment decision | Exclusion criteria | Follow-up (months) | Losses to follow-up |
|---|---|---|---|---|---|---|---|
| Connors et al 1999 | 70 | NR | Consecutive | Referral by neurologist or neurointerventionist | NR | 12 months | 0 |

NOTE: NR = not reported

Table 44 Patient allocation

| Study | | | | | |
|---|---|---|---|---|---|
| Connors et al 1999 | Technique/period | Early | Middle | Late | Total |
| | Dates undertaken | 1989-1992 | 1992-1993 | 1994-1999 | 1989-1999 |
| | Patient numbers | 8 | 12 | 50 | 70 |

### Techniques used

The techniques of transluminal balloon angioplasty were described with respect to each time period in which the particular procedure was used. In the early period (1989 – 1992), the balloon chosen was slightly smaller in diameter than the vessel which it was chosen to dilate. A moderate balloon inflation rate was achieved in 15 to 30 seconds. In the middle period (1992 – 1993) the balloon was chosen to be as close to the size of the vessel as possible, and was then oversized by 0.25 mm. Each balloon was inflated as fast as possible. In the later period (1994 – 1999), the balloon was undersized by 0.2mm or 0.7mm, and inflated at an extremely slow rate for between 2 - 5 minutes. Heparin (5000U) was administered intravenously, followed by a further infusion of 1000U per hour. From 1996, patients also received abciximab (0.25 mg/kg) during the procedure, with continuous infusion at a rate of 10 μg/minute for 12 hours post-operatively.

The devices used were similar throughout, with the STEALTH or FasSTEALTH balloon angioplasty catheter used for all procedures.

### Follow-up and losses to follow-up

Follow-up times were not stated for both the early and middle time-periods. Patient details and outcomes were retrospectively collected from patient files. In the later time period, follow-up was conducted at 3, 6 and 12 month intervals. There were no losses to follow-up.

Table 45 Lesion location

| Study | Location | Early period | Middle period | Later period |
|---|---|---|---|---|
| Connors et al 1999 | ICA | 2/8 | 4/12 | 17/50 |
| | MCA | 3/8 | 2/12 | 15/50 |
| | Distal VA | 2/8 | 2/12 | 11/50 |
| | VBJ | 0 | 1/12 | 0 |
| | BA | 1/8 | 3/12 | 5/50 |
| | PCA | 0 | 0 | 2/50 |

NOTE: ICA, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; VBJ, vertebrobasilar junction; BA, basilar artery; PCA, posterior cerebral artery.

The distribution of the stenosis was similar between all treatment periods in this study. Most lesions (43/70) were in the anterior circulation (Table 45).

## Is it safe?

### Mortality

In the early phase there was one patient death (13%) from restenosis and in the middle phase there was also only one patient death (8%) due to abrupt occlusion. In the later period there were five deaths (10%): one patient (2%) died due to a technical complication of vessel perforation with the occlusion wire, and four patients (8%) died from restenosis.

### Re-treatment

One patient from the early period had symptomatic restenosis and was re-treated in the middle period. In the middle period one patient demonstrated rebound stenosis and was re-treated. In the later period there were four (8%) instances of restenosis, all of which were successfully treated with repeat angiography.

### Adverse events

There were no neurological adverse events reported for any patient treated. Four patients had uncomplicated mild dissection in the early period, as identified from post-operative angiography, although there was no flow restriction. In the middle period, only one patient had a completely uneventful course and one patient (8%) suffered a stroke due to vessel occlusion caused by a thrombus. In the later period, there were two cases of intra-procedural transient ischaemic attack, both of which resolved completely within 24 hours, and two instances of stroke which had no long-term effect.

## Is it effective?

### Clinical outcomes

Good outcomes were reported as the patient being stabilised or improved. Seven out of eight patients (88%) in the early group had a good outcome, compared with 10/12 (83%) and 49/50 (98%) in the middle and later period respectively (Table 46).

### Angiographic outcomes

In the early period, 38% of patients had residual stenosis greater than 50%, whilst no patient had residual stenosis in the middle period and 16% had residual stenosis in the later period.

Table 46 Outcomes for the three different techniques

| Connors et al 1999 | Number of patients/period | | | |
|---|---|---|---|---|
| Result | Early (n = 8) | Middle (n = 12) | Late (n = 50) | Total (n = 70) |
| Good outcomes (stable or improved) | 7 (88%) | 10 (83%) | 49 (98%) | 66 (94%) |
| Residual stenosis > 50% | 3 (38%) | 0 | 8 (16%) | 11 (16%) |
| Restenosis | 1 (13%) | 0 | 4 (8%) | 5 (7%) |
| Dissection | | | | |
| Uncomplicated, mild | 4 (50%) | 3 (25%) | 5 (10%) | 12 (17%) |
| Associated with thrombus | 0 | 5 (42%) | 2 (4%) | 7 (10%) |
| Associated with occlusion | 0 | 1 (8%) | 0 | 1 (1%) |
| Due to recrossing site | 0 | 1 (8%) | 0 | 1 (1%) |
| TOTAL DISSECTION | 4/8 (50%) | 10/12 (83%) | 9/50 (18%) | 24/70 (34%) |
| Rebound stenosis | 0 | 1 (8%) | 0 | 1 (1%) |
| Intra-procedural transient ischaemic attack | 0 | 0 | 2 (4%) | 2 (3%) |
| Stroke | | | | |
| Due to dissection/ occlusion | 0 | 1 (8%) | 0 | 1 (1%) |
| Hemorrhagic conversion | 0 | 0 | 1 (2%) | 1 (1%) |
| Intraparenchymal hematoma | 0 | 0 | 1 (2%) | 1 (1%) |
| Death | | | | |
| Due to abrupt occlusion | 0 | 1 (8%) | 0 | 1 (1%) |
| Due to vessel perforation | 0 | 0 | 1 (2%) | 1 (1%) |
| TOTAL DEATHS | 0/8 | 1/12 | 1/50 | 2/70 |

## Discussion

It is difficult to comment with confidence on the use of balloon angioplasty to treat intracranial atherosclerosis as only one relatively small comparative study met the inclusion criteria. The level of evidence was further reduced as the study was a historical comparison, comparing three techniques for balloon angioplasty which had been adopted over certain periods of time, with no control group with which to fully judge safety and effectiveness. In making the assumption that the reported techniques have evolved to improve overall patient outcomes, the technique used in the latest period should be safer and more effective than earlier methods. With the great majority of all patients being treated in the later period (n=50), and significantly fewer treated in the early (n=8) and middle (n=12) periods, increased skill was also likely to favourably influence the outcomes from the later period.

With this very limited data, the outcomes seemed slightly better in the later period, although all study periods achieved a favourable outcome in over 80% of patients. There appeared to be a high proportion of dissections in the middle period; however, the authors did not specifically address potential reasons for this anomaly.

In reviewing this single study, the safest and most effective treatment for intracranial atherosclerosis appeared to be the method adopted in the later period. The higher number

of patients in this group and the accrual of skill in the learning curve may have also influenced this result. Given the lack of other comparative studies with which to compare these results, it was not possible to comment on overall safety and effectiveness of this endovascular procedure compared with any other current medical or surgical technique; nor was it possible to comment on whether the outcomes reported in this study were similar to data from other centres.

## Summary

It is not possible to draw any meaningful conclusions with regard to the safety and effectiveness of endovascular treatment of intracranial atherosclerosis, as there were no properly randomised controlled trials and few comparative studies on this in the national and international literature. More primary research must be undertaken before the safety and effectiveness of these procedures can be commented upon with confidence.

## What are the economic considerations?

It is not possible to locate any studies which discussed costs for these types of treatments, either nationally or internationally. Therefore an economic evaluation on the endovascular treatments for intracranial atherosclerosis cannot be provided.

# 5. Background: Endovascular treatment of intracranial arteries in acute stroke

Over the past few years there has been an intense growth in endovascular devices for the removal of the embolus during acute ischaemic stroke. The treatments can broadly be categorised into two groups. The first is the use of microcatheters to deliver thrombolytic agents (eg tissue plasminogen activator (tPA) or urokinase) near the site of the clot in the intracerebral arteries. The second group includes various mechanical thrombectomy devices (laser, ultrasonography, fluid jet, snare or retrieval devices) (Nesbit et al 2004). Many of these developments are recent advances and are still in the process of gaining approval. The goal of all acute stroke treatments is artery recanalisation and the restoration of blood flow, which must be carried out as quickly as possible after stroke onset. Endovascular techniques allow interventional radiologists to successfully treat blockages at a later time-point (up to 8 hours) compared to medical treatments (up to 3 hours). The most common and serious potential complication of endovascular stroke treatment is intracerebral haemorrhage, whether through the use of intra-arterial devices or thrombolytic drugs.

## Acute stroke

Please refer to 4, Endovascular treatments for intracranial atherosclerosis (page 96), for a more general introduction to atherosclerosis.

Following heart disease and cancer, stroke is the third largest cause of mortality and the leading cause of morbidity in the western world. In the US alone, 750,000 people suffer stroke each year (Benchenane et al 2004). More than one-third of patients who have suffered stroke will subsequently die from its consequences. There are two major types of stroke. Haemorrhagic strokes account for approximately 20% of all strokes. These strokes occur when a vessel ruptures within the brain (intracerebral haemorrhage), or into the space surrounding the brain (subarachnoid haemorrhage). This process, and the subsequent clot, may lead to brain damage. The second type of stroke is the ischaemic stroke and is the more common, accounting for approximately 80% of all strokes. It can occur spontaneously in a narrowed artery, or when a thrombus or embolism formed in another part of the vasculature travels to the brain. The resultant occlusion can interrupt blood supply to the brain, and lead to cerebral ischaemia and tissue damage. Atherosclerosis can lead to vessel narrowing and increase the risk of ischaemic stroke. A transient ischaemic attack (TIA) can be a precursor to a stroke and results from the temporary blocking of a vessel. Risk factors include hypertension, cigarette smoking, diabetes, atrial fibrillation and carotid stenosis (Hankey 2000, Knuiman and Vu 1996). The clinical effect of a stroke depends on the duration and degree of flow impairment and the location and volume of brain tissue affected, therefore acute stroke management requires early intervention to restore adequate perfusion to prevent or limit cerebral ischaemia. Full recovery of the patient is dependent on the speed and extent of clot lysis following the initial onset of stroke.

### Pathophysiology of stroke

Acute ischaemic stroke is caused by intra- or extra-cerebral artery obstruction which reduces blood flow and induces irreversible neuronal damage. The blockage is usually caused by a thrombus from elsewhere in the vasculature that becomes wedged in the narrow cerebral vessels, or at the position of an atherosclerotic stenosis. Cerebral ischaemia progresses towards irreversible brain damage within minutes or hours of vessel occlusion (Higashida 2003).

At the location of the occlusion a core zone supplied by the occluded artery experiences profound ischaemia and rapidly progresses to irreversible damage. The surrounding area (the penumbral zone) experiences slower damage which may be reversible for several hours after stroke onset (Leary et al 2003). Improved imaging technology can potentially give more information regarding the size and location of the thrombus, together with the nature and magnitude of ischaemic damage to the brain tissue, and if it is reversible. Even though these protocols take valuable time to implement, they may be useful in selecting patients who are most likely to benefit from endovascular approaches. The information may also importantly detect stroke which has occurred as a result of haemorrhage.

The risk factors and progression of the disease in stroke is similar to that in systemic atherosclerosis, which often involves multiple vascular beds. Expert opinion suggests that hypertension is the main factor related to stroke development, conferring a 6-fold risk. Smoking is another important modifiable risk factor that increases both the risk of development and progression of the disease, conferring a 2- to 3-fold risk. Other factors include diabetes and hyperlipidaemia (Hankey 2000, Knuiman and Vu 1996).

## Endovascular procedures

The key to successful stroke therapy is a quick time-to-treatment, often referred to as stroke onset to treatment time (OTTT), following the ischaemic attack. Depending on the treatment used, its application must be within the first few hours, possibly up to 8 hours or more, after stroke onset. The development of soft, atraumatic microcatheters and steerable microguidewires has enabled safe access of the larger intracranial vessels. Endovascular techniques can provide a longer window for successful thrombolysis than common medical therapies as the treatment or device is delivered proximal to the clot giving it the potential to be more effective than a systemic regimen.

Imaging of the brain to determine ischaemic damage is essential to the correct use of these techniques. MRI is highly sensitive to ischaemic changes in brain tissue, while CT, although more readily available and quicker to use, is less sensitive to early ischaemic changes. Diffusion-weighted MRI and perfusion-weighed MRI are often used together to determine ischaemic areas of brain by observing loss of cell membrane integrity (DWMRI) and blood flow (PWMRI) (Fisher and Schaebitz 2000, Fisher and Brott 2003, Ringer and Tomsick 2002). Other techniques which measure intracranial blood perfusion are single-photon emission computed tomography (SPECT), positron emission tomography (PET) and Xenon-CT. CT perfusion can also be used to quantify blood flow using a normal CT scanner, which provides a colour map of ischaemic areas. These three techniques require the use of tracers or contrast agents. As with the other topics covered in this report, cerebral angiography is the gold standard to give most vessel detail

on intracranial blood flow abnormalities. All these procedures may assist the physician to determine which patients would derive the most benefit from thrombolytic therapy.

### Intra-arterial infusion of thrombolytic agents

A carotid artery was successfully recanalised using intra-arterial injection of plasmin in 1958 (Sussman and Fitch 1958), and intra-arterial cerebral fibrinolytic therapy for acute stroke was first described in 1983 (Zeumer et al 1983). More recently, the PROACT randomised controlled trial has investigated the direct arterial delivery of the thrombolytic agent pro-urokinase (del Zoppo et al 1998).

This endovascular technique allows the delivery of smaller dosages of the drug with greater concentrations at the required site whilst minimising systemic exposure, thus lowering the risk of haemorrhage. Disadvantages of this treatment include increased cost, possible delay to treatment, the requirement of angiography and a skilled endovascular team, and the risk and discomfort associated with neuroendovascular procedures (Ringer and Tomsick 2002).

The thrombolytics, or 'clot-busters' that have been used in this way include recombinant tissue plasminogen activator (tPA), urokinase and the modified forms of tPA that have been developed by pharmaceutical companies (for example saruplase, alteplase and reteplase) (Qureshi 2004). A standard catheterisation technique is used. A 6-French guide catheter is deployed into the femoral artery whilst the patient is under either local anaesthesia with a mild sedative or general anaesthesia (required for about half of all patients (Harrigan and Guterman 2005)). A loading bolus of intravenous heparin is given to achieve a clotting time of twice baseline and an angiogram is performed. A microguide wire is used to position an infusion microcatheter, along which the thrombolytic agent is infused, in some cases for up to an hour. This intra-arterial therapy can be combined with intravenous drug treatment (eg heparin, tPA or platelet glycoprotein IIb-IIIa antagonists).

Although the intra-arterial infusion of drugs in this manner is common in many countries, the use of thrombolytic agents is not approved for this application in Australia, so will not be included in the final report.

### Mechanical endovascular treatments

The potential advantages of mechanical thrombolysis are rapid vessel recanalisation and the minimal use of thrombolytic agents which thus lowers the risk of haemorrhage. They can be used either to completely remove the occlusion or to increase the surface area of the clot exposed to thrombolysis. Care must be taken that the mechanical energy used to break up and/or remove the thrombus does not damage the vessel wall, especially considering that these devices are often relatively bulky. Their uses may be of greatest benefit in patients who have come to medical attention over 3 hours after stroke onset (Leary et al 2003).

Over the past decade, a great variety of endovascular devices have been developed to remove clots during the treatment of stroke (Nesbit et al 2004). These devices have frequently been used firstly for clot removal from coronary intervention and have then been modified to be suited to the more delicate intracranial vasculature. As these devices

are novel, there are many questions remaining regarding their effectiveness and safety. Accordingly, these devices have not been registered on the TGA for use in Australia, so will not be included in the final report.

### Clot removal

The thrombus is removed through a catheter, providing rapid recanalisation and reducing the risk of distal embolisation that can be seen with mechanical clot disruption. This technique minimises the use of thrombolytic agents. There are many different types of devices which can be used for the removal of clots (Nesbit et al 2004, Leary et al 2003):

a) Snare devices eg Microsnare (Microvena, Minneapolis MN), Neuronet (Guidant, Temecula, CA), Amplatz gooseneck microsnare (EV3 Australia Pty Ltd). These are wire nets that can be deployed around the thrombus to capture and remove it, or to break up the clot (Leary et al 2003). The In-Time retrieval device (Boston Scientific) is an expandable wire mesh that can be used in a similar way.

b) Suction devices eg NeuroJet (Possis Medical, Minneapolis MN). A local vortex suction is used in combination with mechanical thrombectomy. Multiple high-pressure fluid jets create a vortex which fragments the thrombus while simultaneously evacuating the small particles. The NeuroJet is similar to the larger AngioJet device which has been used successfully in the treatment of coronary vessel thrombi (Boulos et al 2004).

c) The Merci Retriever System (a development of the Concentric Retriever System) (Concentric Medical, Mountain View, CA), is a nitinol wire helix, similar to a corkscrew, the loops of which can ensnare the thrombus, which is then withdrawn into the catheter for removal from the body (Smith et al 2005, Gobin et al 2004).

Of these devices, only the Amplatz gooseneck microsnare is registered for use in Australia (Table 1). This is not indicated for use in the cerebral vasculature.

### Clot disruption

These devices destroy the clot within the artery. In the process they produce small fragments which have the potential to cause distal emboli. The risk of this must be considered for each patient. In its simplest form, this device may be a simple microguide wire which can be passed over the thrombus to disrupt it, or simply increase the surface area available to thrombolytics. Balloons may also be used in a similar manner, although great care must be taken in both instances to avoid vessel dissection. Even if it does not result in full vessel recanalisation, clot disruption can increase the surface area of a thrombus exposed to a thrombolytic agent, enhancing the effectiveness of the drug. Again, there is a significant risk of causing damage to the vessel wall. The two main classes of devices which bring about clot disruption are:

a) Laser thrombolysis devices include the Endovascular Photoacoustic Recanalisation (EPAR), Endovasix Inc., Belmont, CA (Berlis et al 2004) and LaTIS, LaTIS Inc (Minneapolis, MN). The photo energy is converted into acoustic energy which causes thrombus emulsification and creates subcapillary-sized particles (Leary 2003).

b) Ultrasonography or augmented fibrinolysis devices, including the EKOS MicroLysUS infusion catheter, EKOS Corporation (Bothell WA). Ultrasonography in conjunction with the simultaneous intra-arterial infusion of a thrombolytic agent has been shown to accentuate enzymatic fibrolysis. This therapy may be used for up to one hour. Ultrasound loosens the plaque, allowing greater penetration of the thrombolytic agent.

None of the above clot disruption devices are indicated in Australia for use in intracranial arteries.

## Existing procedures

Antiplatelet agents (eg aspirin, clopidogrel or combination aspirin and dipyridamole) and anticoagulants (warfarin) are the main medical treatments for the treatment of ischaemic stroke, and are used to reduce the risk of cardiovascular disease. All are associated with a small risk of bleeding complications (Algra et al 2001). Other medical treatments for stroke include antihypertensive agents (such as the ACE inhibitors), or statins which reduce the levels of cholesterol in the blood and therefore reduce the risk of cardiovascular and cerebrovascular disease. Aspirin is the most widely used drug to prevent stroke and other serious vascular events among high risk patients (Hankey 2000), and has been shown to reduce the risk of subsequent serious vascular events by about a quarter (Antiplatelet Triallists' Collaboration 1994). Aspirin inhibits platelet cyclooxygenase and thromboxane production. The structurally-related drugs ticlodipine and clopidogrel are thienopyridines and act to block platelet ADP receptors.

The thienopyridine derivatives (eg clopidogrel) and combination aspirin and dipyridamole have been shown to be more effective than aspirin in reducing serious vascular events, with no differences in terms of safety (Hankey 2000). All ischaemic stroke patients undergo a lifelong antiplatelet regimen, normally either aspirin (325mg/day), clopidogrel (75mg/day) or combination aspirin and dipyridamole.

### Intravenous administration of thrombolytic agents

At the moment, the only treatment which has been registered for use for acute ischaemic stroke by the TGA in Australia is intravenous tissue plasminogen activator (tPA, at 0.9mg/kg up to a maximum of 90mg), which was approved in August 2003. According to their guidelines it must be administered within 3 hours of symptom onset (OTTT, time-to-treatment window). The use of IV tPA for patients presenting within 3 hours of acute stroke has also been approved in the USA (since 1996), Canada, South America and the European Union (Harrigan and Guterman 2005, Benchenane et al 2004). The large study on which these approvals were based compared intravenous tPA (0.9mg/kg) with placebo within 3 hours of symptom onset, and showed a significant improvement in patient outcome with thrombolytic treatment (NINDS 1995). Despite the rate of haemorrhage in the treatment group being much more than in the placebo at 36h post-treatment (6.4% vs 0.6%), the 90-day mortality rate was significantly improved (Fisher and Schaebitz 2000). The net benefit of intravenous tPA was reduced for older patients (greater than 70 years of age).

Other studies (ECASS and ATLANTIS) have investigated treatment with tPA between 3-6 hours after symptom onset, and reported less significant difference between the improvement of treatment and placebo groups, but a greater incidence of haemorrhage

in the treatment group compared to placebo (Hacke et al 1998, Clark et al 1999). Re-analysis of the NINDS study showed that intravenous tPA was of most benefit to patients treated within 90 minutes of stroke (Marler et al 2000). As few as 1-6% of patients with acute stroke meet the rigid 3-hour time constraints and other criteria for intravenous thrombolysis (Harrigan and Guterman 2005, Benchenane et al 2004), so the absolute benefits of this therapy are very limited. Thrombolytic agents are associated with a significant risk of bleeding (Harrigan et al 2004). The risk of haemorrhage seems to increase with increasing time after stroke onset and with increased size of the occlusion (Ringer and Tomsick 2002). Recent research in the CLOTBUST trial has shown that intravenous tPA therapy can actually be enhanced by the frequent use of diagnostic transcranial Doppler (TCD) ultrasound which acts to promote the thrombolytic effect (Alexandrov et al 2004).

Tissue plasminogen activator (tPA) acts as a thrombolytic agent by cleaving plasminogen into the active enzyme, plasmin. In plasma, the plasmin digests fibrin, which is the major component of blood clots. *In vivo*, tPA (a serine protease) is normally released from endothelial cells (Benchenane et al 2004). There are many other thrombolytic agents which have been used and developed to lyse clots (Harrigan and Guterman 2005). Urokinase (serine protease) and streptokinase (bacterial protein) are first-generation agents and activate plasminogen. Pro-urokinase (also known as saruplase, used in the PROACT trials (del Zoppo et al 1998, Furlan et al 1999) but not in clinical use) and alteplase (serine protease) are second-generation (fibrin-specific), and tenecteplase (tPA variant) and reteplase (deletion variant of tPA) and tPA are third generation. The agent tPA is the only one approved by the TGA for intravenous thrombolysis for ischaemic stroke, but all the above act on plasminogen. Other agents include ancrod, a protease derived from Malaysian pit viper venom which accelerates the cleavage of fibrinogen (Harrigan and Guterman 2005) and the anticoagulant bivalirudin, which is a direct thrombin inhibitor. Also, desmoteplase is a highly fibrin-specific recombinant plasminogen activator derived from the saliva of vampire bats, which has been shown to be effective up to 9 hours from stroke onset when used intravenously (Hacke et al 2005).

## Comparator

As there is no surgical intervention for treating stroke, the primary comparator to endovascular treatments are intravenous thrombolytics or best medical treatment.

## Choosing between endovascular and medical treatments

The decision about whether to treat a patient with an endovascular or a medical approach is complex and takes into consideration the following:

- Time-to-therapy is of vital importance in the treatment of stroke. Currently, tPA is approved for use in highly selected patients who are able to receive the treatment within 3 hours of stroke onset. Endovascular approaches may increase the time window for treatment in certain subsets of patients with acute ischaemic stroke (Leary et al 2003).

- An endovascular approach may be more effective when the patient has a severe disability or symptoms due to a severe occlusion.

- The endovascular experience of the team treating the occlusion.

## Clinical need / burden of disease

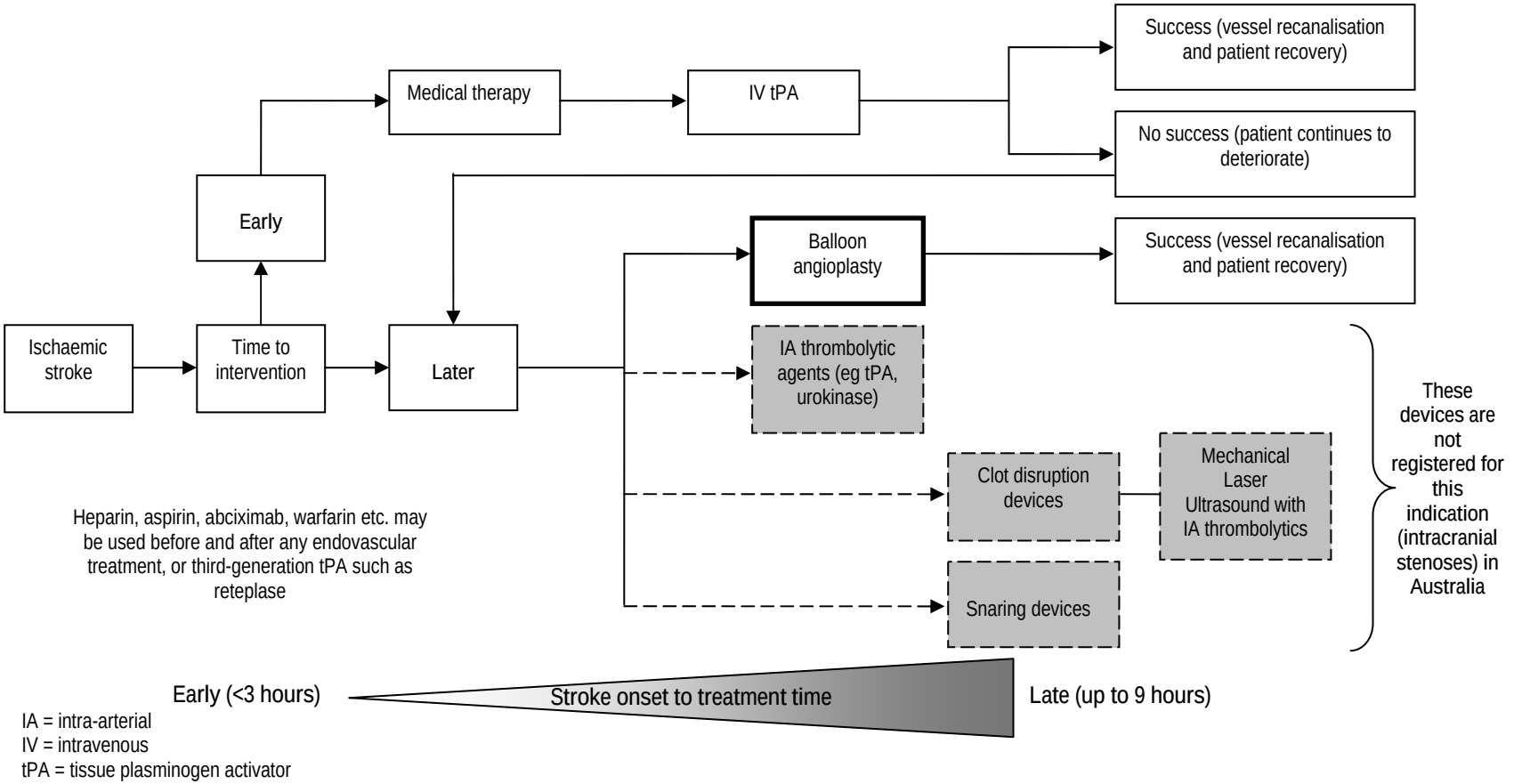
In USA, approximately 750,000 strokes occur per year, of which 85% are ischaemic (Smith et al 2005), costing the country $51.2 billion annually (Harrigan and Guterman 2005). These strokes result in over 150,000 deaths (Higashida 2003).

In Australia, stroke is the third most common cause of death and is a major cause of disability (Hankey 2000). According to the Australian Institute of Health and Welfare, nearly 50,000 Australians have a stroke annually (almost three-quarters of which are first ever strokes), with 33,416 hospitalisations for stroke in 2003-4. In 2003, a total of 9,006 Australians died of a stroke, accounting for 7% of all deaths during that year (see www.aihw.gov.au/cvd/strokeweek/index.cfm). These figures carry a large financial burden, as among those hospitalised for at least one night in 2003-4 the average length of stay was 12 days, and in 2003 there were 146,000 people with a disability resulting from stroke. The long-term Perth community stroke study showed that from a total population of 138,708 studied over a period of 18 months in 1989 to 1990, 492 people suffered acute stroke, 370 (75%) being first-ever strokes (Hankey et al 2002). There were 277 survivors at 30 days and 125 at 5 years (98% follow-up). The risk of death or new institutionalisation at 5 years was 54%. In the NEMESIS study, 133,816 residents of north and east Melbourne were studied during a 12 month period in 1996 and 1997 (Thrift et al 2001). 353 people suffered acute stroke during this period, 276 being first-ever strokes (72%). Of these, 72.5% were ischaemic strokes (an incidence of 149 per 100,000) of which there was a 12% mortality rate. In the 3 months follow-up (59% assessed) of patients who had suffered ischaemic stroke, 20% had died, whilst at 12 months 31% had died (64% assessed) (Sturm et al 2002). At 12 months, 66% of surviving patients stated that they had not made a complete recovery, although this figure was reduced to 51% using the Barthel Index to gauge disability.

Women are at higher risk of stroke than men, although this is because the risk of stroke increases with age and women have a longer life expectancy. The age-standardised incidence of stroke is 30% higher for men.

## Clinical decision pathway

Figure 5 Clinical decision pathway, treatment of intracranial arteries in acute stroke




IA = intra-arterial
IV = intravenous
tPA = tissue plasminogen activator

# Results: Endovascular treatment of intracranial arteries in acute stroke

## Non-randomised comparative studies

### Critical appraisal

Two non-randomised comparative studies (Ueda et al 1998, Ringer et al 2001) were identified for this topic. In both studies, all patients initially received thrombolysis using intra-arterial (IA) urokinase as the thrombolytic agent as treatment for acute stroke (which is not indicated for intracranial endovascular use in Australia). The patients who did not respond to this therapy were then treated with percutaneous transluminal angioplasty (PTA).

Ueda et al 1998 reported that the patient population were consecutively allocated. The two groups were similar in patient number (n=12 and 13) and were taken from a total of 95 patients treated within a given period. Nine patients treated with PTA had occlusions of the M1 segment of the middle cerebral artery (MCA), two had occlusions in the internal carotid artery and two in the basilar artery. Control patients all had an occlusion of the MCA. Ringer et al 2001 treated nine consecutively allocated patients with PTA, presenting with occlusions in the distal ICA (n=2), M1 segment of the MCA (n=3) and the intracranial vertebral artery (n=1). Control patients in the Ringer study were retrospectively allocated and were matched for age, medical comorbidities and NIHSS score on presentation.

An inclusion criterion in both studies was treatment within six hours of symptom onset, although in Ringer et al 2001 patients were designated to receive IA tissue plasminogen activator (tPA) therapy if they were available for treatment within 3 hours of symptom onset. Ueda et al 1998 did not report exclusion criteria, however Ringer et al 2001 excluded patients with cerebral haemorrhage visualised by CT, or hypodensity on CT consistent with an evolving infarction. Additionally, patients with a significant mass effect related to an infarction involving more than one third of the MCA territory were excluded. The surgical teams involved made treatment decisions in both studies. No blinding was undertaken for outcome analysis in either study.

Both studies reported 24-hour and 30-day follow-up, however perioperative mortality or losses to follow-up were not specifically reported in either study.

### Inclusion and exclusion criteria

The included studies (Ueda 1998, Ringer 2001) compared PTA after failed IA thrombolysis versus IA thrombolysis alone (Table 47).

Allocation of control group patients in both studies was retrospective although the treatment groups were consecutive. Both authors reported inclusion criteria for thrombolytic therapy and additional inclusion criteria for angioplasty treatment. Ringer et al 2001 reported the control group patients were matched for comorbidities and the age

range was within 5 years of the treatment group although the age of the control group was not specified (Table 49). Patients were included if they were available for treatment within 3-6 hours from symptom onset and with a National Institute of Health Stroke Scale (NIHSS) score of greater than 20 (Appendix C, Table 61). Patients were excluded if they had cerebral haemorrhage or an area of infarction, both detected through CT imaging. Ueda et al 1998 does not report any criteria for matching the control group to the treatment group in the study, although most of the group receiving angioplasty had already received intra-arterial thrombolytic therapy which was not successful. Ueda reported on 12 patients who underwent thrombolysis alone and 13 patients who underwent PTA (3 immediate, 3 delayed and 7 rescue angioplasty). Initial inclusion was limited to patients who could be treated within 6 hours of symptom onset (mean time-to-treatment of 5.3hrs for the PTA group, and 4.5 hrs for the IA thrombolysis alone group), in addition to those patients who showed no apparent hypodensity areas on CT scan. Prior to treatment, symptoms were confirmed via angiography. Patients were treated with angioplasty if stenosis remained, re-occurred within a few days after treatment, or if there were contraindications to treatment with thrombolysis.

Table 47 Stroke study information

| Study ID & location | L of E | Study period | Allocation | Treatment decision | Intervention | n |
|---|---|---|---|---|---|---|
| Ringer 2001 USA | III-2 | June 1995 – July 1999 | Retrospective | Surgical team | PTA (after failed intra-arterial thrombolysis) | 9 |
| | | | | | Intra-arterial thrombolysis | 9 |
| Ueda 1998 JAPAN | III-2 | April 1985 – August 1996 | Retrospective | Surgical team | PTA (after failed intra-arterial thrombolysis) | 13 |
| | | | | | Intra-arterial thrombolysis | 12 |

NOTE: L of E = level of evidence; PTA = percutaneous balloon angioplasty

## Description of technique

Ueda et al 1998 reported that IA thrombolysis was achieved using a femoral approach: the tip of a FasTracker-18 (Target Therapeutics, Fremont, Calif) was advanced into the thrombus or upstream from the occlusion site over a 0.014-in Taper Dasher guidewire (Target Therapeutics). Urokinase (240,000 U) dissolved in 20 mL of physiological saline with a max dose of 960,000 U (720,000 U for patients > 65 years) was injected manually for about ten minutes. In rescue angioplasty patients, the thrombus was mechanically disrupted by advancing the FasTracker-18 catheter with guidewire repeatedly through the occluded segment. Angioplasty was performed using a Stealth balloon catheter (Target Therapeutics) when residual stenosis reached <70%. All patients were given IV heparin (5000 U) before thrombolysis and 10% glycerol (200mL) or 20% mannitol (300mL) during treatment. Infusion with heparin continued post-operatively (10,000 U/24hrs) for 24 hours if there was no intracranial haemorrhage or systemic bleeding, and on the day after treatment, ticlopidine (200mg/d).

Ringer et al 2001 reported transfemorally advancing an infusion microcatheter (Rapidtransit: Cordis Endovascular Systems, Miami Lakes, Fl) with a guide catheter over a microguidewire (Transcend: Meditech, Watertown, MA). In most cases, after distal advancement through the occlusion, the catheter was gradually dragged back proximally

permitting infusion of the thrombolytic agent throughout the occlusion. Infusion of urokinase (10,000 U/mL) at the rate of 15,000 U per minute was discontinued when adequate recanalisation was achieved, extravasation of contrast material was noted on angiography, or the maximum dose of urokinase was reached without clinical or angiographic improvement. Angioplasty was performed where thrombolysis resulted in inadequate or failed recanalisation. The balloon was advanced to the point of stenosis where it was inflated to manufacturer's specifications with results evaluated immediately via angiography.

Table 48 Summary table of patient information

| Study ID | Treatments | Number in Study Group | Age (years) | Gender (M/F) | Follow-up (months) | Losses to follow-up |
|---|---|---|---|---|---|---|
| Ringer et al 2001 | Control | 9 | Matched to within 5 yrs 68 [9.3] (53 – 80) | 7/2 | 30 days | Nil |
| | PTA | 9 | | 7/2 | | |
| Ueda et al 1998 | Control | 12 | 69 [6.8] | NR | 30 days | Nil |
| | PTA | 9 | 66 [8.2] (48 – 74) | NR | | |

NOTE: PTA = percutaneous balloon angioplasty; NR = not reported

## Lead-time to treatment

Both Ueda et al 1998 and Ringer et al 2001 report treatment was performed within 6 hours of symptom onset; however, lead-time to angioplasty was not reported in either study. Although patients in both studies were treated within 6h of symptom onset, Ueda et al 1998 had three groups treated using PTA. Those treated with immediate angioplasty had residual stenosis of more than 70% immediately after thrombolysis (n=3/13), and those having rescue angioplasty when thrombolysis did not achieve any recanalisation (n=7/13). Patients also had delayed angioplasty if there was symptomatic restenosis within a few days after thrombolysis (n=3/13).

## Location of the occlusion

The location of the occlusion was very similar between the two treatment groups (Table 49). Ringer et al 2001 reported most occlusions were in the anterior circulation, and one or two patients requiring treatment in the posterior circulation of the brain. There was a slight difference in distribution of the occlusions in Ueda et al 1998. All of the occlusions in the group receiving only thrombolysis were present in the MCA, and whilst most of the occlusions in the PTA after thrombolysis group were in the MCA or in the anterior part of the brain, there were some occlusions in the posterior part of the brain.

Table 49 Location of occlusion in acute stroke

| | Ringer et al 2001 | | Ueda et al 1998 | |
|---|---|---|---|---|
| Location of occlusion | PTA after thrombolysis | Thrombolysis alone | PTA after thrombolysis | Thrombolysis alone |
| MCA | 6/9 (66%) | 5/9 (56%) | 9/13 (69%) | 12/12 (100%) |
| ICA | 2/9 (22%) | 2/9 (22%) | 2/13 (15%) | |
| VA | 1/9 (11%) | 2/9 (22%) | | |
| BA | | | 2/13 (15%) | |

NOTE: BA = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; VA = vertebral artery; PTA = percutaneous balloon angioplasty

# Is it safe?

Perioperative safety was not reported in either of the included studies.

## Mortality

Mortality rates were reported in both studies (Ringer 2001 & Ueda 1998) (Table 50). Ringer et al 2001 reported 4/9 (44%) deaths in the thrombolysis only group where one patient was declared brain dead and three patients had medical assistance withdrawn at the request of the family. The PTA groups also reported four deaths, with one patient suffering a cardiac arrest, and the remaining three patients having medical treatment withdrawn due to their deteriorated medical condition. All deaths were in patients who had not improved after thrombolysis or who had failed thrombolysis. Each of the mortalities occurred more than 24 hours post surgery but within 30 days of surgery. There were no deaths in the Ueda et al 1998 study.

Table 50 Safety outcomes in patients undergoing thrombolysis and PTA for ischaemic stroke

| Outcome | PTA (after failed thrombolysis) | | Adverse Event | Thrombolysis | | Adverse Event |
|---|---|---|---|---|---|---|
| Mortality | n/N | % | n/N | n/N | % | n/N |
| Ringer et al 2001 | 4/9 | 44 | 1/9 declared brain dead<br>3/9 medical assistance withdrawn | 4/9 | 44 | 1/9 cardiac arrest<br>3/9 medical assistance withdrawn |
| Ueda et al 1998 | 0/9 | 0 | Nil | 0/9 | 0 | Nil |

NOTE: PTA = percutaneous balloon angioplasty

# Is it effective?

## Functional outcomes

Functional outcomes using the National Institute of Health Stroke Scale (NIHSS) were reported by both Ueda et al 1998 and Ringer et al 2001 (Table 51). The NIHSS score strongly predicts the likelihood of the patient's recovery after stroke. A score of >16 forecasts a high probability of death or severe disability, whereas a score of <6 forecasts a good recovery. Ueda also reported effect size, and noted a significant improvement in the

outcomes for the PTA group over the thrombolysis alone group from baseline to one-day and one-month postoperative (p=<0.01 for both). The one-month postoperative results were not significantly different in either study at both time points.

Table 51 Summary table of outcomes – PTA versus thrombolysis

| NIHSS | Study | PTA (Mean NIHSS) | n | Thrombolysis (Mean NIHSS) | n | P value |
|---|---|---|---|---|---|---|
| Baseline | Ringer et al 2001 | 21.8 | 9 | 20.3 | 9 | NR |
| | Ueda et al 1998 | 17.6 | 9 | 15.4 | 12 | NR |
| 1 day postoperative | Ringer et al 2001 | 22.3 | 9 | 20.8 | 9 | NR |
| | Ueda et al 1998 | 8.8 | 9 | 11.8 | 12 | NR |
| 1 month postoperative | Ringer et al 2001 | 12.6 | 5 | 19.4 | 5 | NR |
| | Ueda et al 1998 | 3.5 | 9 | 5.6 | 12 | NR |
| Change in NIHSS | Study | PTA | n | Thrombolysis | n | P value |
| Next day - baseline | Ueda et al 1998 | - 8.8 | 9 | - 3.6 | 12 | <0.01 |
| 1 month – baseline | Ueda et al 1998 | - 14.0 | 9 | - 9.8 | 12 | < 0.01 |
| 1 month – next day | Ueda et al 1998 | - 5.2 | 9 | - 6.3 | 12 | NS |

NOTE: NIHSS = National Institute of Health Stroke Scale; PTA = percutaneous balloon angioplasty; NR = not reported; NS = not statistically significant

Ueda et al 1998 reported on the technical success, as judged from post-procedural angioplasty, including restenosis of the PTA group after thrombolysis (Table 52). Technical success was not expressly defined. The immediate and delayed groups reported a 100% success rate and the rescue group a 71% technical success. Ringer et al 2001 used the Thrombosis in Myocardial Infarction grading system (TIMI grade) to report on recanalisation of vessels in the rescue angioplasty group. The grade ranks perfusion from grade zero (no perfusion) to grade 3 (complete perfusion) (see Appendix C, Table 63). Ringer reported partial restoration of flow in 3/9 patients treated with rescue angioplasty (TIMI grade 2) and a complete restoration of flow in 2/9 patients (TIMI grade 3). In the thrombolysis alone group, TIMI grade 2 or 3 was achieved in five patients and residual occlusion in four patients.

Table 52 Angioplasty and angiography outcomes in the PTA group (Ueda 1998)

| Angioplasty | n/N | Time-to-treatment (mean hours from thrombolysis) | Technical success |
|---|---|---|---|
| Immediate | 3/13 | - | 100 % |
| Delayed | 3/13 | 18 (12 – 48) | 100 % |
| Rescue | 7/13 | - | 71 % |
| Follow-up angiography | Restenosis/occlusion | | |
| 9/13 | nil | - | |
| 4/13 | NR | - | |

More specifically, Ueda et al 1998 reported 8/13 patients (61%) in the PTA group had no stenosis after the procedure (Table 53) and no reocclusion in the follow-up period.

Table 53 Post procedural outcomes in the PTA group (Ueda 1998)

| | PTA | Thrombolysis |
|---|---|---|
| Site of Occlusion | | |
| M1 | 9/13* | 9 |
| M2 | 0 | 3 |
| Recanalisation | | |
| Complete | 9/9 | 6/12 |
| Partial | 0 | 4/12 |
| None | 0 | 2/12 |
| Reocclusion | | |
| Yes | 0 | 2/12 |
| No | 0/9 | 10/12 |
| Outcome | | |
| Excellent [a] | 3/9 | 3/12 |
| Good [b] | 3/9 | 3/12 |
| Fair [c] | 2/9 | 5/12 |
| Poor [d] | 1/9 | 1/12 |
| Dead | 0 | 0 |
| % Stenosis | | |
| 0 | 8/13 | NR |
| 20 | 1/13 | NR |
| 30 | 1/13 | NR |
| 65 | 1/13 | NR |
| 100 | 2/13 | NR |

NOTES: *Left M1 (7),* R M1 (2), Left ICA (2), basilar artery (2); a – no neurological defects were observed, and the patient had returned fully to previous daily activities; b – mild neurological defects remained, but the patient had returned partly to previous activities; c – rehabilitation was difficult, but no assistance needed in activities of daily life; d – assistance needed in activities of daily life. PTA = percutaneous transluminal angioplasty; NR = not reported.

## Discussion

Clinical outcomes appeared to be improved when using PTA, in addition to intra-arterial thrombolysis (which is not approved for intracranial use in Australia) in the treatment of acute stroke. Ueda et al 1998 reported a significant difference between the PTA and thrombolysis alone groups from the baseline to next day and the baseline to one-month outcomes using the NIHSS grade, in favour of PTA. Additionally, recanalisation was complete in all the PTA patients with no reocclusion whereas the thrombolysis alone group reported 50% complete recanalisation with 16% of the group having reocclusion. There was a slight improvement in clinical outcome following PTA treatment. Thirty percent of the PTA group reported an excellent outcome in terms of the NIHSS, with the thrombolysis alone group reporting an excellent outcome in 25% of patients.

A significant difference in the outcomes of each study was that there were no mortalities in Ueda et al 1998 but there were 8/18 deaths in Ringer et al 2001. This may be explained by

the baseline clinical condition of the patients in the studies. Within each study, the NIH stroke scale score between treatment groups at baseline was only slightly different. Between studies, the NIH stroke scale scores revealed that compared with the Ueda cohort, the patients in the Ringer study were in a worse clinical condition at baseline. The poorer patient outcomes in the Ringer study, specifically mortality, may be attributable to the poorer patient condition at baseline. Within each study group, there was no difference in the baseline and one day postoperative outcomes; however, the one month postoperative NIHSS outcomes were lower in the PTA group than the thrombolysis alone group.

## Summary

In summary, this evidence suggests there may be a better outcome with PTA and thrombolysis than with intra-arterial urokinase thrombolysis alone. A definitive conclusion regarding the safety and effectiveness of this procedure cannot be given as there were only two non-randomised studies with low patient numbers which reported outcomes for this treatment of acute stroke.

## What are the economic considerations?

No studies discussing costs for the use of endovascular procedures in the treatment of acute stroke were located. Therefore it was not possible to estimate the relative costs of endovascular and other procedures for treating acute stroke, and since effectiveness of endovascular treatments for stroke could not be established, a cost-effectivness analysis was not possible.

# Conclusions

This MSAC Assessment Report investigated endovascular neurointerventional procedures. It was limited by the lack of randomised comparative evidence available internationally for the techniques which had been included. There was only one RCT which met the inclusion criteria for this report, although this had only internal comparators. It was not possible to provide detailed economic evaluation for each topic due to a lack of published costing data, in addition to the inability to assess safety and effectiveness in each of the five topics. The lack of studies represented both the relatively innovative nature of many of these devices and techniques, together with the low volume of patient numbers which require, and are indicated for, these specific treatments. In addition to these drawbacks, although there were various international studies which looked at many different endovascular devices used intracranially, it was not possible to include these in this Assessment Report as most of these devices were not TGA-listed in Australia for use with the review indications. This was frequently due to the fact that many of these devices were novel, or had been adopted from use in cardiac vessels, so that their safety in intracranial vessels was not tested. It may be expected that endovascular routes are less invasive than microsurgery in the delicate cerebral tissue, and therefore would have improved patient outcomes, but due to the lack of evidence it was not possible to confirm this idea. Also, expert opinion suggested that for each of the topics discussed in this report, there are few people who can be treated with endovascular procedures for most of the conditions mentioned. The diseases and episodes are reasonably rare, and the timescale to presentation and size or location of the abnormality often precludes the use of endovascular approaches.

Therefore the safety, effectiveness and economics of these endovascular methods compared to currently used methods and procedures could not be assessed. It was also not possible to answer any of the subsidiary questions of the review.

# Recommendation

MSAC made the following recommendation for the first two indications:

MSAC has considered the respective evidence for safety, effectiveness and cost effectiveness for brain arteriovenous amalgamations and endovascular remobilisation of dural arteriovenous fistulae and carotid cavernous fistulae.

MSAC finds that there is evidence of safety compared with alternative therapies.

There is insufficient evidence to assess effectiveness and cost effectiveness. Given that there are limited treatment options MSAC recommends that current public funding arrangements should continue.

MSAC made the following recommendation for the final three indications:

MSAC has considered the strength of evidence for the safety and effectiveness for endovascular treatments for vasospasm as a complication of subarachnoid haemorrhage, endovascular treatments for arterial atherosclerosis and endovascular treatment of intracranial arteries in acute stroke and finds that there is insufficjent evidence of safety and effectiveness.

MSAC recommends that public funding for these interventions should not be supported.

- The Minister for Health and Ageing endorsed this recommendation on 30th August 2006 -

# Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

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

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

| **Member** | **Expertise or Affiliation** |
|---|---|
| Dr Stephen Blamey (Chair) | general surgery |
| Associate Professor John Atherton | cardiology |
| Professor Syd Bell | pathology |
| Dr Michael Cleary | emergency medicine |
| Dr Paul Craft | clinical epidemiology and oncology |
| Dr Kwun Fong | thoracic medicine |
| Dr David Gillespie | gastroenterology |
| Dr Debra Graves | medical administrator |
| Professor Jane Hall | health economics |
| Professor John Horvath | Chief Medical Officer, Department of Health and Ageing |
| Dr Terri Jackson | health economics |
| Professor Brendon Kearney | health administration and planning |
| Dr Ray Kirk | health research |
| Associate Professor Frederick Khafagi | nuclear medicine |
| Professor Alan Lopez | medical statistics and population health |
| Associate Professor Donald Perry-Keene | endocrinology |
| Dr Ewa Piejko | general practice |

| | |
|---|---|
| Ms Sheila Rimmer | consumer health issues |
| Ms Samantha Robertson | Department of Health and Ageing representative |
| Professor Jeffrey Robinson | obstetrics and gynaecology |
| Professor Ken Thomson | radiology |
| Dr Douglas Travis | urology |
| Dr Mary Turner | Australian Health Ministers' Advisory Council representative |
| Dr David Wood | orthopaedics |

# Appendix B Advisory Panel, Evaluators and Project Manager

## Advisory Panel for MSAC Application 1093: Endovascular neurointerventional procedures

| | |
|---|---|
| Dr Ewa Piejko (Chair),<br>General Practitioner<br>Melbourne | Member of MSAC |
| Professor Craig Anderson,<br>The George Institute for International Health<br>Royal Price Alfred Hospital<br>Sydney | Australian Association of Neurologists nominee |
| Professor Chris Bladin,<br>Department of Neurosciences<br>Box Hill Hospital<br>Melbourne | Australian Association of Neurologists nominee |
| Dr Terri Jackson,<br>Senior Research Fellow<br>School of Public Health<br>LaTrobe University<br>Melbourne | Member of MSAC |
| Professor Mark Khangure,<br>Radiology Department<br>Royal Perth Hospital<br>Perth | Royal Australian and New Zealand College of Radiologists nominee |
| Associate Professor Michael Murphy,<br>Department of Neurosurgery<br>St Vincent's Hospital<br>Melbourne | Royal Australasian College of Surgeons nominee |
| Ms Barbara Smith,<br>Consumer Representative<br>Consumers' Health Forum of Australia<br>Sydney | Consumers' Health Forum of Australia nominee |
| Dr Alun Cameron,<br>Research Officer<br>ASERNIP-S, SA | Evaluator |

| | |
|---|---|
| Ms Christine Barber,<br>Research Officer<br>ASERNIP-S, SA | Evaluator |
| Mr Nicholas Marlow,<br>Research Officer<br>ASERNIP-S, SA | Evaluator |
| Ms Amber Watt,<br>Research Officer<br>ASERNIP-S, SA | Evaluator |
| Ms Philippa Middleton,<br>Research Manager<br>ASERNIP-S, SA | Consultant to<br>ASERNIP-S |
| Ms Brenda Campe,<br>Acting MSAC secretary<br>Health Technology Section<br>Department of Health and Ageing<br>Canberra | Project Manager |

# Appendix C Clinical grading scales

Table 54 Aminoff-Logue scale

| | Grade | Definition |
|---|---|---|
| Gait | | |
| | 0 | Normal |
| | 1 | Leg weakness, abnormal gait or stance but no restriction or activity |
| | 2 | Restricted activity but not requiring support |
| | 3 | Requiring one stick for walking |
| | 4 | Requiring two sticks, crutches, or walker |
| | 5 | Confined to wheelchair |
| Micturition | | |
| | 0 | Normal |
| | 1 | Hesitancy, urgency, frequency, altered sensation, but continent |
| | 2 | Occasional urinary incontinence or retention |
| | 3 | Total incontinence or persistent retention |

Table 55 Barrow scale

| Grade | Functional Outcome |
|---|---|
| Type A | Fistulae are high-flow lesions that usually develop after trauma and often require urgent treatment because of progressive visual or neurological deterioration |
| Type B | Fistulae contain shunts between the dural branches of the Internal Carotid Artery (ICA) and the cavernous sinus, |
| Type C | Have shunts between the dural branches of the External Carotid Artery (ECA) and the cavernous sinus |
| Type D | Fistulae which are comprised of shunts from both the ICA and ECA to the cavernous sinus |

Table 56 Cognard scale of venous drainage

| Grade | Venous drainage |
|---|---|
| Type I | Drainage into a sinus with a normal antegrade flow |
| Type IIa | Drainage into a sinus with retrograde venous drainage into sinus(es) only |
| Type IIb | Drainage into a sinus with retrograde venous drainage into cortical vein(s) with retrograde drainage into sinus(es) |
| Type IIa+b | Drainage into dural venous sinus with retrograde flow and cortical veins |
| Type III | Drainage directly into a cortical vein without venous ectasia; |
| Type IV | Drainage into a cortical vein with venous ectasia larger than 5mm in diameter and three times larger than the diameter of the draining vein |
| Type V | Drainage into spinal perimedullary veins. |

From Chung et al 2002

Table 57 Drake scale

| Drake Scale | Characteristics |
|---|---|
| Excellent | Able to work with no neurological handicaps |
| Good | Having a neurological deficit but being able to live and work independently |
| Poor | Having a severe neurological deficit and dependant on family or nursing for help |
| Dead | |

Table 58 Fisher grading of subarachnoid haemorrhage

| Fisher Grade | Description |
|---|---|
| 1 | No blood detected |
| 2 | A diffuse deposition or thin layer with all vertical layers of blood less than 1mm thick |
| 3 | Localised clots and/or vertical layers of blood 1mm or greater in thickness |
| 4 | Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots |

Table 59 Glasgow outcome score scale

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

From www.trauma.org

Table 60 Hunt & Hess classification of subarachnoid haemorrhage

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

Table 61 NIH stroke scale

| Item number | Item Name | Score | |
|---|---|---|---|
| 1a | Level of consciousness questions | 0= | Alert; keenly responsive |
| | | 1= | Not alert; arousable by minor stimulation |
| | | 2= | Not alert; requires repeated stimulation |
| | | 3= | Response with reflex motor/unresponsive |
| 1b | Level of consciousness questions | 0= | Answers both correctly |
| | | 1= | Answers one correctly |
| | | 2= | Answers neither correctly |
| 1c | Level of consciousness commands | 0= | Performs both tasks correctly |
| | | 1= | Performs one task correctly |
| | | 2= | Performs neither task correctly |
| 2 | Gaze | 0= | Normal |
| | | 1= | Partial gaze palsy |
| | | 2= | Total gaze palsy |
| 3 | Visual fields | 0= | No visual loss |
| | | 1= | Partial hemianopsia |
| | | 2= | Complete hemianopsia |
| 4 | Facial palsy | 0= | Normal |
| | | 1= | Minor paralysis |
| | | 2= | Partial paralysis |
| | | 3= | Complete paralysis |
| 5a | Left arm | 0= | No drift |
| | | 1= | Drift before 10 seconds |
| | | 2= | Falls before 10 seconds |
| 5b | Right arm | 0= | No drift |
| | | 1= | Drift before 10 seconds |
| | | 2= | Falls before 10 seconds |
| 6a | Left leg | 0= | No drift |
| | | 1= | Drift before 5 seconds |
| | | 2= | Falls before 5 seconds |
| | | 3= | No effort against gravity |
| | | 4= | No movement |
| 6b | Right leg | 0= | No drift |
| | | 1= | Drift before 5 seconds |
| | | 2= | Falls before 5 seconds |
| | | 3= | No effort against gravity |
| | | 4= | No movement |
| 7 | Limb ataxia | 0= | Absent |
| | | 1= | Present in one limb |
| | | 2= | Present in two limbs |
| | | UN | Amputation or joint fusion |
| 8 | Sensory | 0= | Normal |
| | | 1= | Abnormal |
| 9 | Language | 0= | Normal |
| | | 1= | Mild aphasia |
| | | 2= | Severe aphasia |
| | | 3= | Mute or global aphasia |
| 10 | Dysarthria | 0= | Normal |
| | | 1= | Mild to moderate dysarthria |
| | | 2= | Severe dysarthria |
| | | UN | Intubated or other physical barrier |
| 11 | Extinction and inattention | 0= | No abnormality |
| | | 1= | Visual, tactile, auditory, spacial or personal inattention |
| | | 2= | Profound hemi-inattention or extinction of more than one modality |

NOTE: The NIHSS score strongly predicts the likelihood of the patient's recovery after stroke. A score of >16 forecasts a high probability of death or severe disability, whereas a score of <6 forecasts a good recovery (from www.ninds.nih.gov).

Table 62 Spetzler and Martin AVM grading scale for risk of neurological deficit after AVM surgery

| | Graded Feature | Points |
|---|---|---|
| AVM size | | |
| | Small (< 3cm) | 1 |
| | Medium (>3cm and < 6cm) | 2 |
| | Large (>6cm) | 3 |
| Pattern of venus drainage | | |
| | Cortical/superficial only | 0 |
| | Any draining veins into deep system | 1 |
| Eloquence of adjacent brain | | |
| | Non-eloquent | 0 |
| | Eloquent | 1 |

NOTE: Eloquent area = sensorimotor, visual and language cortex, thalamus and hypothalamus, internal capsule, brainstem, cerebellar peduncles/deep nuclei; Non-eloquent area = anterior frontal and temporal lobes, cerebellar hemisphere. Graded on a 1-5 scale; total points = (size) + (venous drainage) + (eloquence)

(From Spetzler and Martin 1986, Brown et al 2005).

Table 63 TIMI Scale – Definitions of perfusion

| Grade | Characteristics |
|---|---|
| 0 | (No perfusion). No antegrade flow beyond the point of occlusion. |
| 1 | (Penetration without perfusion). The contrast material passes beyond the area of obstruction but 'hangs up' and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence. |
| 2 | (Partial perfusion). The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. The rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from comparable areas not perfused by the previously occluded vessel – eg the opposite coronary artery or the coronary bed proximal to the obstruction. |
| 3 | (Complete perfusion). Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from involved bed as rapid as clearance from the uninvolved bed in the same vessel or the opposite artery. |

NOTE: From TIMI Study Group: The Thrombolysis in Myocardial Infarction (TIMI) trial: Phase 1 findings. N Eng J Med 312:932-936, 1985.

# Appendix D Abbreviations

| | |
|---|---|
| ACA | anterior cerebral artery |
| AChA | anterior choroidal artery |
| AcoA | anterior communicating artery |
| ACROSS | Australian Cooperative Research on Subarachnoid Haemorrhage Study |
| AICA | anterior inferior cerebellar artery |
| AIHW | Australian Institute of Health and Welfare |
| AN-DRG | Australian national diagnosis related group |
| ARTG | Australian Register of Therapeutic Goods |
| ASITN | American Society of Interventional and Therapeutic Neuroradiology |
| AVF | arteriovenous fistulae |
| AVM | arteriovenous malformations |
| BA | basilar artery |
| BasTip | basilar tip |
| BasTrunk | basilar trunk |
| CA | carotid artery |
| CCF | carotid-cavernous fistulae |
| CI | confidence interval |
| CS | cavernous sinus |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| cTi | cardiac troponin |
| DAVF | dural arteriovenous fistulae |
| DIND | delayed ischaemic neurological deficit |
| DMSO | dimethyl sulphoxide |
| ECA | external carotid artery |
| EDS | Ehlers-Danlos syndrome |
| EVAL | ethylene vinyl alcohol co-polymer |
| GCS | Glasgow Coma Score |
| GDC | Guglielmi Detachable Coil |
| GKS | Gamma knife surgery |
| GOS | Glasgow Outcome Scale |
| h | hour |
| HADS | Hospital Anxiety and Depression Scale |
| HIC | Health Insurance Commission |
| HIV | human immunodeficiency virus |
| HH | Hunt and Hess Scale |
| HHH | hypervolaemic, hypertensive, hyperdynamic therapy |
| IA | intra-arterial |
| IBCA | isobutyl 2-cyanoacrylate |
| ICA | internal carotid artery |
| ISAT | International Subarachnoid Aneurysm Trial |
| ISUIA | International Study of Unruptured Intracranial Aneurysms |
| IV | intravenous |
| L of E | level of evidence |
| LINAC | linear accelerator |
| LMWH | low molecular weight heparin |
| LT | left |
| LVEF | left ventricular ejection fraction |

| | |
|---|---|
| MBS | Medical Benefits Schedule |
| MCA | middle cerebral artery |
| MONICA | Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases |
| MRI | magnetic resonance image |
| MRS | Modified Rankin Scale |
| MSAC | Medical Services Advisory Committee |
| n | patient number (subgroup) |
| N | patient number (total) |
| NA | not applicable |
| NBCA | *n*-butylcyanoacrylate |
| NEMESIS | North East Melbourne Stroke Incidence Study |
| NHMRC | National Health and Medical Research Council |
| NR | not reported |
| OpthA | ophthalmic artery |
| OTTT | onset to treatment time |
| ParaOpthA | paraophthalmic artery |
| PCA | posterior cerebral artery |
| PcoA | posterior communicating artery |
| PeriA | pericallosal artery |
| PET | positron emission tomography |
| PICA | posterior inferior cerebellar artery |
| pns | p value not significant |
| PTA | percutaneous transluminal angioplasty |
| PTFE | polytetrafluoroethylene |
| PVA | polyvinyl alcohol |
| RCT | randomised controlled trial |
| RR | relative risk |
| RT | right |
| RWMA | regional wall motion abnormalities |
| SAH | subarachnoid haemorrhage |
| SCA | superior cerebellar artery |
| SF-36 | Medical Outcome Study Short Form 36 |
| SOV | superior ophthalmic vein |
| SPECT | single-photon emission computed tomography |
| SupCer | superior cerebellar artery |
| TCD | transcranial Doppler ultrasonography |
| TIA | transient ischemic attack |
| TIMI grade | Thrombosis in Myocardial Infarction grading system |
| TGA | Therapeutic Goods Administration |
| tPA | tissue plasminogen activator (human recombinant) |
| Triple-H | hypervolaemic, hypertensive, hyperdynamic therapy |
| VA | vertebral artery |
| VADA | vertebral artery dissecting aneurysms |
| VBJ | vertebrobasilar junction |
| WFNS | World Federation of Neurological Societies |
| WHO | World Health Organisation |

## Units of measurement

| | |
|---|---|
| [ ] | standard deviation |
| ( ) | range |
| { } | unit of variance not stated |
| U | units |
| µm | micrometers |
| mm | millimetres |
| cm | centimetres |
| µg | micrograms |

# Appendix E Studies included in the review


Bavinzski, G., Richling, B., Killer, M., Gruber, A., Levy, D., 1996. "Evolution of different therapeutic strategies in the treatment of cranial dural arteriovenous fistulas-report of 30 cases". *Acta Neurochirurgica,* 138 (2), 132-138.

Chung, S.J., Kim, J.S., Kim, J.C., Lee, S.K., Kwon, S.U., Lee, M.C., Suh, D.C., 2002. "Intracranial dural arteriovenous fistulas: Analysis of 60 patients". *Cerebrovascular Diseases,* 13 (2), 79-88.

Connors, J.J., III and Wojak, J.C., 1999. "Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results". *Journal of Neurosurgery,* 91 (3), 415-423.

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DeMeritt, J.S., Pile-Spellman, J., Mast, H., Moohan, N., Lu, D.C., Young, W.L., Hacein-Bey, L., Mohr, J.P., Stein, B.M., 1995. "Outcome analysis of preoperative embolization with N-butyl cyanoacrylate in cerebral arteriovenous malformations". *American Journal of Neuroradiology,* 16 (9), 1801-1807.

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Sasaki, T., Kurita, H., Saito, I., Kawamoto, S., Nemoto, S., Terahara, A., Kirino, T., Takakura, K., 1998. "Arteriovenous malformations in the basal ganglia and thalamus: management and results in 101 cases". *Journal of Neurosurgery,* 88 (2), 285-292.

Song, J.K., Vinuela, F., Gobin, Y.P., Duckwiler, G.R., Murayama, Y., Kureshi, I., Frazee, J.G., Martin, N.A., 2001. "Surgical and endovascular treatment of spinal dural arteriovenous fistulas: long-term disability assessment and prognostic factors". *Journal of Neurosurgery,* 94 (2 Suppl), 199-204.

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Ueda, T., Saburo, S., Nochide, I., Kumon, Y., Kanehisa, K., Ohta, S., 1998. "Angioplasty after intra-arterial Thrombolysis for acute occlusion of intracranial arteries" *Stroke,* 29 (12), 2568-2574.

# Appendix F Excluded studies

## 1. Endovascular treatments of arteriovenous malformations; excluded studies

### Comparative studies

None

### Case series


Berthelsen, B., Lofgren, J., Svendsen, P., 1990. Embolization of cerebral arteriovenous malformations with bucrylate. "Experience in a first series of 29 patients". *Acta Radiologica,* 31 (1), 13-21.

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mixture for cerebral arteriovenous malformations. Clinical Experience". *Interventional Neuroradiology,* 10 (SUPPL. 1), 135-142.

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Jahan, R., Murayama, Y., Gobin, Y.P., Duckwiler, G.R., Vinters, H.V., Vinuela, F., 2001. "Embolization of arteriovenous malformations with Onyx: clinicopathological experience in 23 patients". *Neurosurgery,* 48 (5), 984-995.

Kinouchi, H., Mizoi, K., Takahashi, A., Ezura, M., Yoshimoto, T., 2002. "Combined embolization and microsurgery for cerebral arteriovenous malformation". *Neurologia Medico-Chirurgica,* 42 (9), 372-378.

Lasjaunias, P., Hui, F., Zerah, M., Garcia-Monaco, R., Malherbe, V., Rodesch, G., Tanaka, A., Alvarez, H., 1995. "Cerebral arteriovenous malformations in children. Management of 179 consecutive cases and review of the literature". *Childs Nervous System,* 11 (2), 66-79.

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Yakes, W.F., Krauth, L., Ecklund, J., Swengle, R., Dreisbach, J.N., Seibert, C.E., Baker, R., Miller, M., VanderArk, G., Fullagar, T., Prenger, E., Barnwell, S.L., Rothbart, D.R., Spetzler, R.F., Teitelbaum, G.P., Debrun, G., 1997. "Ethanol endovascular management of brain arteriovenous malformations: Initial results". *Neurosurgery,* 40 (6), 1145-1154.

# 2. Endovascular treatments of dural arteriovenous fistulae and carotid-cavernous fistulae; excluded studies

## Comparative studies

None for dural arteriovenous fistulae and carotid-cavernous fistulae

## Case series – carotid-cavernous fistulae


Annesley-Williams, D.J., Goddard, A.J., Brennan, R.P., Gholkar, A., 2001. "Endovascular approach to treatment of indirect carotico-cavernous fistulae". *British Journal of Neurosurgery,* 15 (3), 228-233.

Bavinzski, G., Killer, M., Gruber, A., Richling, B., 1997. "Treatment of post-traumatic caroticocavernous fistulae using electrolytically detachable coils: Technical aspects and preliminary experience". *Neuroradiology,* 39 (2), 81-85.

Biondi, A., Milea, D., Cognard, C., Ricciardi, G.K., Bonneville, F., Van Effenterre, R., 2003. "Cavernous sinus dural fistulae treated by transvenous approach through the facial vein: Report of seven cases and review of the literature". *American Journal of Neuroradiology,* 24 (6), 1240-1246.

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Klisch, J., Huppertz, H.J., Spetzger, U., Hetzel, A., Seeger, W., Schumacher, M., 2004. "Transvenous treatment of carotid cavernous and dural arteriovenous fistulae: results for 31 patients and review of the literature". *Neurosurgery,* 53 (4), 836-856.

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Koebbe, C.J., Horowitz, M., Jungreis, C., Levy, E., Pless, M., 2003. "Alcohol embolization of carotid-cavernous indirect fistulae". *Neurosurgery,* 52 (5), 1111-1115.

Lewis, A.I., Tomsick, T.A., Tew, Jr J.M., Standard, S.C., Chavis, T.D., Hopkins, L.N., Moret, J., 1995. "Management of 100 consecutive direct carotid-cavernous fistulas: Results of treatment with detachable balloons". *Neurosurgery,* 36 (2), 239-245.

Lewis, A.I., Tomsick, T.A., Tew, Jr J.M., Lawless, M.A., 1996. "Long-term results in direct carotid-cavernous fistulas after treatment with detachable balloons". *Journal of Neurosurgery,* 84 (3), 400-404.

Luo, C.B., Teng, M.M., Yen, D.H., Chang, F.C., Lirng, J.F., Chang, C.Y., 2004. "Endovascular embolization of recurrent traumatic carotid-cavernous fistulas managed previously with detachable balloons". *Journal of Trauma-Injury Infection & Critical Care,* 56 (6), 1214-1220.

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Meyers, P.M., Halbach, V.V., Dowd, C.F., Lempert, T.E., Malek, A.M., Phatouros, C.C., Lefler, J.E., Higashida, R.T., 2002. "Dural carotid cavernous fistula: definitive endovascular management and long-term follow-up". *American Journal of Ophthalmology,* 134 (1), 85-92.

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Teng, M.M., Chang, C.Y., Chiang, J.H., Lirng, J.F., Luo, C.B., Chen, S.S., Chang, F.C., Guo, W.Y., 2000. "Double-balloon technique for embolization of carotid cavernous fistulas". *Ajnr: American Journal of Neuroradiology,* 21 (9), 1753-1756.

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### Case series – dural arteriovenous fistulae

Behrens, S. and Thron, A., 1999. "Long-term follow-up and outcome in patients treated for spinal dural arteriovenous fistula". *Journal of Neurology,* 246 (3), 181-185.

Irie, K., Kawanishi, M., Kunishio, K., Nagao, S., 2001. "The efficacy and safety of transvenous embolisation in the treatment of intracranial dural arteriovenuous fistulas". *Journal of Clinical Neuroscience,* 8 (SUPPL. 1), 92-96.

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Jellema, K., Tijssen, C., van Rooij, W., Sluzewski, M., Koudstaal, P., Algra, A., van Gijn, J., 2004. "Spinal dural arteriovenous fistulas. Long term follow-up of 44 treated patients". *Neurology,* 62, 1839-1841.

Kim, B.S., Lee, S.K., TerBrugge, K.G., 2003. "Endovascular treatment of congenital arteriovenous fistulae of the internal maxillary artery". *Neuroradiology* 45 (7), 445-450.

Kincaid, P.K., Duckwiler, G.R., Gobin, Y.P., Uela, F., 2001. "Dural arteriovenous fistula in children: Endovascular treatment and outcomes in seven cases". *American Journal of Neuroradiology,* 22 (6), 1217-1225.

Marey, J., Pego, R., Alonso, G., Lopez-Facal, M.S., Marin, M., Martinez, A., Diaz-Valino, J.L., 1998. "[Endovascular treatment of dural arteriovenous fistulas with medullary venous drainage. Experience with 18 patients]". [Spanish]. *Revista de Neurologia,* 26 (153), 793-799.

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Schick, U. and Hassler, W., 2003. "Treatment and outcome of spinal dural arteriovenous fistulas". *European Spine Journal,* 12 (4), 350-355.

Song, J.K., Eskridge, J.M., Chung, E.C., Blake, L.C., Elliott, J.P., Finch, L., Niakan, C., Maravilla, K.R., Winn, H.R., 2000. "Preoperative embolization of cerebral arteriovenous malformations with silk sutures: analysis and clinical correlation of complications revealed on computerized tomography scanning". *Journal of Neurosurgery,* 92 (6), 955-960.

Song, J.K., Gobin, Y.P., Duckwiler, G.R., Murayama, Y., Frazee, J.G., Martin, N.A., Vinuela, F., 2001. "N-butyl 2-cyanoacrylate embolization of spinal dural arteriovenous fistulae". *Ajnr: American Journal of Neuroradiology,* 22 (1), 40-47.

Westphal, M. and Koch, C., 1999. "Management of spinal dural arteriovenous fistulae using an interdisciplinary neuroradiological/neurosurgical approach: experience with 47 cases". *Neurosurgery,* 45 (3), 451.

# 3. Endovascular treatments of vasospasm as a result of subarachnoid haemorrhage; excluded studies

## Comparative studies


Elliott, J.P., Newell, D.W., Lam, D.J., Eskridge, J.M., Douville, C.M., Le Roux, P.D., Lewis, D.H., Myberg, M.R., Grady, M.S., Winn, H.R., 1998. "Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage". *Journal of Neurosurgery,* 88 (2), 277-284.

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## Case series involving angioplasty


Bejjani, G.K., Bank, W.O., Olan, W.J., Sekhar, L.N., Mericle, R.A., Hopkins, L.N., Debrun, G., Barnwell, S.L., Rosenwasser, R.H., 1998. "The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage". *Neurosurgery,* 42 (5), 979-987.

Coyne, T.J., Montanera, W.J., Macdonald, R.L., Wallace, M.C., 1994. "Percutaneous transluminal angioplasty for cerebral vasospasm after subarachnoid hemorrhage". *Canadian Journal of Surgery,* 37(5), 391-396.

Eskridge, J.M., McAuliffe, W., Song, J.K., Deliganis, A.V., Newell, D.W., Mayberg, M.R., Winn, H.R., Rosenwasser, R.H., Solomon, R.A., Stoodley, M., Weir, B.K.A., Hopkins, L.N., 1998. "Balloon angioplasty for the treatment of vasospasm: Results of first 50 cases". *Neurosurgery,* 42 (3), 510-517.

Fujii, Y., Takahashi, A., Yoshimoto, T., 1995. "Effect of balloon angioplasty on high grade symptomatic vasospasm after subarachnoid hemorrhage". *Neurosurgical Review,* 18 (1), 7-13.

Higashida, R.T., Halbach, V.V., Cahan, L.D., Brant-Zawadzki, M., Barnwell, S., Dowd, C., Hieshima, G.B., 1989. "Transluminal angioplasty for treatment of intracranial arterial vasospasm". *Journal of Neurosurgery,* 71 (5 I), 648-653.

Higashida, R.T., Halbach, V.V., Dowd, C.F., Dormandy, B., Bell, J., Hieshima, G.B., 1992. "Intravascular balloon dilatation therapy for intracranial arterial vasospasm: Patient selection, technique, and clinical results". *Neurosurgical Review,* 15 (2), 89-95.

Le Roux, P.D., Newell, D.W., Eskridge, J., Mayberg, M.R., Winn, H.R., 1994. "Severe symptomatic vasospasm: The role of immediate postoperative angioplasty". *Journal of Neurosurgery,* 80 (2), 224-229.

Newell, D.W., Eskridge, J.M., Mayberg, M.R., Grady, M.S., Winn, H.R., 1989. "Angioplasty for the treatment of symptomatic vasospasm following subarachnoid hemorrhage". *Journal of Neurosurgery,* 71 (5 I), 654-660.

Zubkov, Y.N., Alexander, L.F., Smith, R.R., Benashvili, G.M., Semenyutin, V., Bernanke, D., 1994. "Angioplasty of vasospasm: is it reasonable?" *Neurological Research,* 16 (1), 9-11.

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None

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