



**Australian Government**  
**Department of Health and Ageing**



Australia and New Zealand Horizon Scanning Network

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TERRITORY GOVERNMENTS OF AUSTRALIA  
AND THE GOVERNMENT OF NEW ZEALAND

# **Horizon scanning technology Horizon scanning report**

## **Filter-type embolic protection devices for carotid artery stenting**

**February 2009**



**Australian  
Safety  
and Efficacy  
Register  
of New  
Interventional  
Procedures -  
Surgical**



**Royal Australasian  
College of Surgeons**

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ISBN: 1-74186-871-8

Online ISBN: 1-74186-872-6

Publications Approval Number: P3-5183

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The production of this horizon scanning report was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments, MSAC and the New Zealand District Health Boards. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This horizon scanning report was prepared by Mr. Irving Lee from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), Royal Australasian College of Surgeons, PO Box 553, Stepney, South Australia. 5069.

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## Executive Summary

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The rapid adoption of carotid artery stenting (CAS) for the treatment of carotid stenosis, particularly after the introduction and regulatory approval of embolic protection devices (EPD), has been a point of debate between some clinicians and researchers. Although the use of EPDs during CAS to prevent embolic events makes intuitive sense, some researchers have highlighted that the evidence supporting the effectiveness of EPDs is limited. A major point of contention is that due to the endorsement of EPDs by regulatory bodies, the support for the use of EPDs has risen exponentially despite the paucity of evidence. Some researchers have also highlighted that the pivotal SAPPHERE trial, which led to regulatory approval of EPDs, was severely flawed.

This horizon scanning report attempts to discuss the evidence available on the effectiveness of EPDs, particularly filter-type EPDs that are widely utilised, accounting for 90% of all protected CAS procedures. The evidence retrieved does not support the general perception that EPDs are absolutely necessary during CAS to reduce the incidence of neurological events or death due to emboli. The only randomised trial to date which compared protected and unprotected CAS did not demonstrate any advantages when EPDs are utilised. Five of the seven comparative studies retrieved to discuss the effectiveness of EPDs did not support the general consensus that EPDs significantly reduce stroke and death rates. Only one study demonstrated that the use of EPDs can reduce adverse event rates, while the other remaining study reported a substantial drop in adverse even rates but was not sufficient to achieve statistical significance. Diffusion weighted imaging indicated that the incidence of new ischaemic lesions after protected CAS ranged from comparable to significantly higher relative to CAS without EPD protection. Meanwhile, Doppler ultrasound analysis in another study suggests that the use of EPDs may result in greater microembolic load, although this did not translate to the incidence of more neurological events.

Comparisons between different classes of EPDs did not reveal any differences in terms of safety or effectiveness. However, one study highlighted that perhaps concentric filter EPDs may be more effective compared to eccentric filter EPDs, at least in symptomatic patients. The cost-effectiveness of EPDs remains unknown.

Overall, the supporting evidence for the use of EPDs (at least filter-type EPDs) appears to be relatively thin. Despite compelling evidence from manufacturer-sponsored trials, the majority of comparative studies did not demonstrate the purported significant reduction in stroke or death rates implied in non-comparative trials and registries. Further studies are warranted, despite the fact that randomised trials are unlikely to be conducted due to the established perception that EPDs are mandatory. In addition, more studies examining the use of patient-tailored EPDs based on pre-operative characteristics should be initiated.

There is limited and conflicting evidence regarding the risks and benefits of filter-type embolic protection devices during carotid artery stenting procedures. The stroke and death rates have not been significantly reduced in the majority of studies. Filters add significant cost to the procedures, making carotid artery stenting more expensive than endarterectomy. They also increase procedure time which may impact on morbidity.

While clinicians performing these procedures acknowledge the limitations of the available evidence and that the major trial supporting the use of Embolic Protection Devices in carotid stenting had significant methodological shortcomings, most still perceive their use to be mandatory.

Monitoring of outcomes with regards to these devices is recommended. This may be done through an examination of Australian databases to determine any suggestive evidence of the efficacy of EPD or otherwise, as a further large based multicentre trial is now unlikely.

The National Stroke Foundation Clinical Guidelines for acute stroke management (2008) state that carotid artery stenting should only be considered in patients too ill for endarterectomy.

## Introduction

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The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a horizon scanning report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play regarding the introduction and use of embolic protection devices for carotid artery stenting.

Embolic protection devices were introduced to reduce the incidence of embolism which leads to stroke during carotid angioplasty and stenting. These devices are widely utilised and are generally accepted as a necessary precaution. However, there is some controversy with regards to the evidence supporting this perception.

This horizon scanning report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of embolic protection devices, its present use, overall effectiveness, and the likely impact of the new and emerging evidence on Australian practice.

This horizon scanning report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with embolic protection devices, particularly filter-type devices.

### Condition

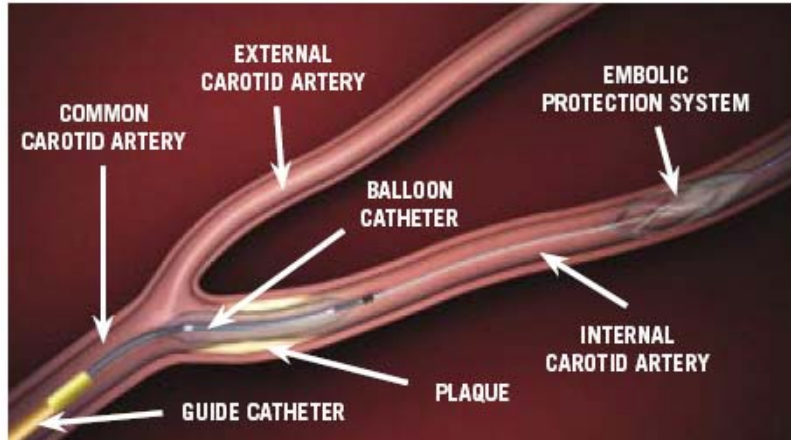
Stroke, otherwise known as cerebrovascular accident, is the rapid loss of brain function due to a disruption in the blood vessels that supply blood to the brain. Approximately 30% of strokes are caused by carotid artery occlusive disease (Schonholz et al 2006) in which the paired carotid arteries in the neck are narrowed (stenosis) or blocked by deposits of cholesterol within the lumen of the vessel, a phenomenon known as atherosclerosis. If these cholesterol deposits rupture, small blood clots and cholesterol fragments may travel to the vasculature of the brain, blocking blood vessels and causing a stroke (Sobieszczyk and Beckman 2006). Transient ischaemic attacks (TIA) are “mini-strokes” that are caused by a temporary disruption in blood supply that results in a brief neurological dysfunction that lasts for less than 24 hours.

### Treatment

Patients with mild or moderate asymptomatic carotid artery stenosis are usually prescribed an antiplatelet drug such as aspirin (Schonholz et al 2006). Symptomatic patients with moderate to severe carotid artery occlusive disease are often treated with carotid endarterectomy (CEA), an open surgical procedure that involves removing atherosclerotic plaque from the lumen of the carotid artery. Randomised controlled trials (RCTs) have shown that CEA significantly reduces the risk of stroke in patients with moderate to severe symptomatic ( $\geq 50\%$  stenosis) (Barnett et al 1998; MRC European Carotid Surgery Trial 1998) or asymptomatic ( $\geq 60\%$  stenosis) carotid stenosis (Asymptomatic Carotid Atherosclerosis Study Group 1989; Hobson et al 1993).

Carotid artery stenting (CAS) was first performed approximately 18 years ago as a less invasive alternative to CEA. In CAS, a catheter is introduced into an artery in the groin or arm. The catheter, which has an expandable balloon at the end, is guided to the blockage site where the balloon is then inflated to flatten out the plaque (balloon angioplasty). The catheter is withdrawn and then reinserted with a compressed slender mesh tube (stent) at the tip. The stent is deployed at the site of the plaque to act as a scaffold to keep the artery open. The procedure is usually performed under local anaesthetic. Early studies demonstrated that the morbidity and mortality rates associated with CAS were unacceptably high relative to CEA (Alberts 2001, Naylor et al 1998). However, the technique has evolved to the point where it is now accepted as a viable treatment option for patients in whom conventional CEA would be a high risk procedure because of existing comorbidities (Liu et al 2009). The greatest risk associated with CAS is peri-procedural stroke resulting from the release, migration and embolisation of debris during balloon angioplasty of the carotid artery stenosis (Faraglia et al 2007).

**Figure 1: Illustration of filter-type embolic protection system (ACCUNET™)**



## **Description of the technology**

In order to address the high rate of peri-operative neurological complications associated with CAS, embolic protection devices (EPDs) were developed to capture plaque material that may be dislodged during the procedure. There are three main types of EPDs: 1) filter; 2) balloon occlusion; and 3) flow reversal.

### *a) Filter EPDs*

Filters EPDs are the most widely available and used in approximately 90% of protected CAS procedures (MacDonald 2006). These filters are usually mounted on a 0.014-inch wire platform and consist of a nitinol skeleton or hoop with a laser-cut polyurethane filter membrane. The filters are collapsed within a delivery sheath that is removed when the filter is positioned distal to the target lesion. The filter is removed at the conclusion of CAS, along with the collected debris. Currently available filter type EPDs are listed in Table 1.

**Table 1: Filter type EPDs**

Device name	Manufacturer	Filter size (mm)	Pore size (µm)
EmboShield®	Abbott Vascular, Abbott Park, IL, USA	3 to 6	140
RX	Abbott Vascular, Abbott Park, IL, USA	4.5 to 7.5	120
ACCUNET™	Abbott Vascular, Abbott Park, IL, USA		
FilterWire EZ™, EX™	Boston Scientific, Natick, MA, USA	One size (suitable for 3.5 to 5.5mm vessels)	110
SpideRx™	ev3 Endovascular Inc, Plymouth, MN, USA	3 to 7	36
Rubicon Filter™	Boston Scientific, Natick, MA, USA	4 to 6	100
AngioGuard XP®, Rx®	Cordis Endovascular, Warren, NJ, USA	4 to 8	100
FiberNet®	Lumen Biomedical, Plymouth, MN, USA	1.75 to 7	40
Interceptor® PLUS	Medtronic, Minneapolis, MN, USA	4.25 to 6.25	100
Mednova, Neuroshield®	Abbott Vascular, Abbott Park, IL, USA	3 to 6	100

*b) Balloon occlusion EPDs*

The PercuSurge GuardWire® (Medtronic, Minneapolis, MN, USA) is the most commonly utilised distal balloon occlusion EPD. Other balloon occlusion systems include the TriActive Proguard (Kensey Nash, Exton, PA, USA) and the Mo.Ma® device (Invatec, Roncadelle, Italy). The PercuSurge is a 0.014 inch nitinol wire with a shapeable distal tip. A balloon on a wire catheter is advanced past the plaque site and inflated in the carotid artery. CAS is performed over the wire and embolic particles are captured in the standing column of blood, which is flushed and aspirated at the end of the procedure (Atkins and Bush 2007). The key disadvantages of balloon occlusion EPDs include the ischaemic time that occurs during balloon inflation and poor visualisation of the lesion during CAS (Ali et al 2006).

*c) Flow reversal EPDs*

The Gore Neuroprotection System (W.L. Gore & Associates, Flagstaff, AR, USA) is a flow reversal EPD that consists of three components, a 9.5 Fr balloon sheath and dilator, a balloon wire and an external filter. The main advantage of flow reversal is that the clinician does not have to cross the carotid artery lesion prior to establishing protection. The GORE Neuroprotection System reverses the flow of blood at the treatment site prior to crossing the lesion. Flow reversal is achieved by selectively occluding common carotid and external carotid artery blood flow. By establishing an arterio-venous shunt, blood from collateral vessels via the

Circle of Willis is redirected to the lower pressure venous return. Macro and micro emboli are continuously directed away from the brain during flow reversal. However, this advantage comes with the disadvantages associated with a bulky device and rigidity that makes insertion difficult (Atkins and Bush 2007).

## **Clinical need and burden of disease**

Stroke is a major cause of death and disability in Australia. It is the fifth leading cause of disease burden for males and the third leading cause for females. Approximately 40,000 Australians experience stroke each year (Australian Institute of Health and Welfare 2002), with approximately 80% occurring in adults over 60 years of age. In 2003, an estimated 146,400 Australians had a disability that was mainly attributed to stroke. In 2006, stroke resulted in the death of 8,484 Australians (Australian Institute of Health and Welfare 2008a).

From 2004 to 2005, total healthcare expenditure on stroke amounted to \$546 million, accounting for 9% of the total expenditure on cardiovascular diseases. The Australian Institute of Health and Welfare reported that 2,437 carotid endarterectomy procedures were performed in 2006 to 2007 (Australian Institute of Health and Welfare 2008b). The number of CAS procedures performed in Australia per annum is not known.

The Stroke Foundation of New Zealand highlights that stroke is the second single largest killer in New Zealand (>2,000 people per annum) and is a major cause of disability (Stroke Foundation of New Zealand 2009). The New Zealand Health Survey 2006/2007 noted that one in 56 adults (1.8%) have experienced stroke (excludes TIA), equating to approximately 57,700 adults. Approximately 8,000 New Zealanders a year will suffer from stroke, and a third of these will be fatal (Stroke Foundation of New Zealand 2009).

## **Stage of development**

The following table outlines the regulatory status of several filter-type EPDs:

**Table 2: Regulatory status of filter type EPDs.**

<b>Device name</b>	<b>Manufacturer</b>	<b>Regulatory status</b>
EmboShield	Abbott Vascular	CE mark and FDA approved.
Rx Accunet	Abbott Vascular	CE mark and FDA approved.
FilterWire EZ, EX	Boston Scientific	CE mark approved.
SpideRx	ev3	FDA approved.
Rubicon Filter	Boston Scientific	CE mark approved.
AngioGuard XP, Rx	Cordic	CE mark approved.
FiberNet	Endovascular Lumen Biomedical	Undergoing trials (EPIC).
Interceptor PLUS	Medtronic	CE mark approved. Undergoing US trials.
Mednova, Neuroshield	Abbott Vascular	CE mark approved.

Guidelines for CAS prepared by the American Society of Interventional and Therapeutic Radiology, the American Society of Neuroradiology and the Society of Interventional Radiology note that the benefit of EPDs has not been tested with randomised controlled trials (Barr et al 2003; Connors et al 2003). However, in a conference of opinion leaders, a consensus was reached on the uniform use of EPDs once they are available (Veith et al 2001).

The pivotal SAPPHERE<sup>1</sup> trial has been credited as one of the key reasons for the exponential increase in protected CAS procedures because it formed the basis for the US Food and Drug Administration approval (Angioguard). The randomised study noted that CAS with filter protection (AngioGuard) resulted in significantly better results with respect to the primary endpoint (composite of death, stroke and myocardial infarction) compared to patients who underwent CEA (12 % versus 20.1%; p<0.05). However, this difference was mostly the result of the higher myocardial infarction rate in the CEA group. Discounting myocardial infarction, the SAPPHERE study showed that stroke and death rates were similar between CAS and CEA patients. Other studies, such as the ARCHeR<sup>2</sup> and the CABERNET<sup>3</sup> registries demonstrated that CAS performed with filter EPDs substantially reduced the incidence of stroke compared with unprotected CAS.

Several researchers have highlighted that the SAPPHERE trial was severely flawed because it was underpowered to detect clinically meaningful differences in outcomes. In addition, the trial ended prematurely after a change in legislation allowed the recruitment of patients for protected CAS from data registers

<sup>1</sup> SAPPHERE: Stenting and Angioplasty with Protection in Patients at High Risk.

<sup>2</sup> ARCHeR: Acculink for Revascularization of Carotids in High Risk Patients.

<sup>3</sup> CABERNET: Carotid Artery Revascularization using Boston Scientific EPI FilterWire EX/EZ and the EndoTex NexStent.

(Bonneux et al 2005, LoGerfo 2007). In addition to this, LoGerfo (2007) noted that some patients were not actually randomly assigned to treatment in the SAPPHERE trial but were assigned using an opinion-based entry criterion, which could have introduced substantial bias. (Macdonald 2006, Atkins and Bush 2007).

Emboic protection devices approved by the Therapeutic Goods Administration (TGA) are: FilterWire EZ (Boston Scientific), Rubicon (Boston Scientific), Rx Accunet (Abbott Vascular), Spider FX (ev3), AngioGuard (Johnson & Johnson), Emboshield (Abbott Vascular), Defender (Medtronic), Interceptor Plus (Medtronic).

### Existing comparators

#### *Carotid endarterectomy*

The gold standard surgical treatment of carotid stenosis is CEA. The procedure involves exposing the artery via an incision at the side of the neck and clamping the internal, common and external carotid arteries. The target artery is then opened and the atheromatous plaque is removed by dissection. The artery is then closed and the wound sutured. Some surgeons use a temporary shunt to preserve blood flow to the brain during CEA.

The surgical outcomes for CEA have been studied extensively and the superiority of CEA over medical therapy in preventing stroke in patients with high-grade (>50% stenosis) symptomatic carotid artery disease is well documented (Moore et al 1995, Biller et al 1998). Other studies have indicated that CEA is also effective in asymptomatic patients when combined with medical/pharmacological management of risk factors. The benefits of this combined approach are apparent within two years of surgery and are superior to those obtained with medical management alone (North American symptomatic carotid endarterectomy trial 1991; McCrory et al 1993; Coyle et al 1995).

#### *Unprotected carotid artery stenting*

CAS, as described earlier in the report, without the use of a protection device is the other main comparator. The widespread opinion is that embolic protection is necessary during CAS, as it appears to be intuitively logical and evidence from non-randomised clinical trials and registries is considered sufficiently compelling. Indeed, in the United States, Medicare will not reimburse carotid stent placement if it is performed without distal protection (Cloft 2008). Despite the apparent benefits of using EPDs during CAS, concerns remain regarding the use of these devices.

This horizon scanning report will consider the current comparative evidence for protected and unprotected CAS. As the large majority of EPDs used in clinical practice are filter EPDs, this report will only primarily focus on evidence relating to this category of protective devices.

The primary focus of this report is to explore the evidence available on the use of *filter EPDs* during CAS. Although CEA is a comparator to protected CAS, this report will only focus on CAS with or without protection, as the main issue to be discussed is the effectiveness of EPDs. Therefore CAS versus CEA studies were not included. The comparative studies retrieved will therefore focus specifically on the use of embolic protection with CAS and its purported advantages over CAS without protection. Studies with  $\leq 10$  patients per treatment group will be excluded. When overlapping patient groups were reported in studies, only the paper quoting the most complete data set was used.

One RCT (Level II intervention evidence) and seven comparative studies (Level III intervention evidence) on the safety and effectiveness of EPDs were identified and selected for inclusion. Three additional comparative studies (Level III intervention evidence) were retrieved to discuss the potential differences in outcomes between specific EPDs. One systematic review (Kastrup et al 2003) on EPDs was identified but was not selected for inclusion because the results were derived from retrospective case series studies, many with severe methodological weaknesses. Thus, the review represented level IV intervention evidence. The profiles of the included studies are outlined in Appendix B.

No details were provided on the randomisation process utilised for the RCT. Baseline patients characteristics for the treatment groups were comparable in five of the non-randomised comparative studies (Boltuch et al 2005; Castriota et al 2002; Kastrup et al 2008; Kastrup et al 2006; Vos et al 2005) but were not described or analysed in detail in two studies (Iyer et al 2007; Ouriel et al 2005). The RCT (Barbato et al. 2008) had a greater proportion of octogenarians in the protected CAS group than in the unprotected group ( $P=0.04$ ). There were substantial differences among the studies with respect to patient age, disease severity, preoperative characteristics and EPD models, which limited inter-study comparisons. The majority of studies included focused mainly on filter-typed EPDs. However, due to the paucity of evidence, mixed-EPD studies were included as well, with the condition that  $>90\%$  of treated patients received filter EPDs.

Since the measure of effectiveness of EPDs is their effect on the occurrence of adverse events, safety and effectiveness issues were reported together.

### Safety and Effectiveness

#### *Adverse events*

The key measures of effectiveness for EPDs are peri-procedural or post-treatment stroke (major or minor) and death rates. The only RCT available that compared protected and unprotected CAS (Barbato et al 2008) demonstrated that neurologic

events (major and minor stroke) were similar between both groups and occurred exclusively in asymptomatic patients (Table 3). At one-year follow-up, one patient in each group died of unrelated causes that were not detailed. One additional patient experienced an ipsilateral internal carotid artery occlusion that developed shortly after CAS, but which remained asymptomatic (Barbato et al 2008). This RCT was terminated early because of unsuccessful recruitment after the market release of EPDs and the realisation that target enrolment would not be reached.

Five of the eight level III comparative studies corroborated the findings of Barbato et al (2008) and did not observe any significant differences in major or minor stroke rates and mortality between CAS with an EPD and unprotected EPDs up to 30-days after treatment (Boltuch et al 2005; Iyer et al 2007; Kastrup et al 2008; Kastrup et al 2006; Vos et al 2005) (Table 3). One study stated that there was no statistically significant clinical benefit for the use of EPDs despite a 60% lower procedural adverse event rate (Iyer et al 2007). The authors stated that this may be due to the small sample size of the unprotected group or low event rates.

**Table 3: Clinical outcomes from studies comparing protected CAS and unprotected CAS.**

Study details	Outcomes																																							
Barbato et al (2008)	<b><u>Serious adverse events post-CAS (≤24 hours post-CAS)</u></b>																																							
Level II evidence																																								
Patients (n=35)																																								
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<p><b>CAS with EPD:</b> 180 patients <b>CAS only:</b> 471 patients</p> <p><b>EPD:</b> Filterwire (n=153); Accunet (n=12); Mo.Ma (n=9); Spider (n=5); Interceptor (n=1).</p> <p>Follow-up: 30 days</p>	<table border="1"> <tr><td>Residual stenosis (10% to 30%)</td><td>8 (4.4%)</td><td>14 (3%)</td><td>0.35</td></tr> <tr><td><b>Any complication</b></td><td>18 (10.0%)</td><td>86 (18.3%)</td><td>0.010</td></tr> <tr><td>Haemodynamic instability</td><td>5 (2.8%)</td><td>39 (8.3%)</td><td>0.012</td></tr> <tr><td>Prolonged hypertension</td><td>3 (1.7%)</td><td>32 (6.8%)</td><td>0.009</td></tr> <tr><td>Severe bradycardia</td><td>1 (0.6%)</td><td>11 (2.3%)</td><td>0.13</td></tr> <tr><td>Asystole (&gt;4s)</td><td>1 (0.6%)</td><td>8 (1.7%)</td><td>0.26</td></tr> <tr><td>Angiographic intracranial embolisation</td><td>0</td><td>4 (0.8%)</td><td>0.22</td></tr> <tr><td><b>Any neurological complication</b></td><td>7 (3.9%)</td><td>33 (7.0%)</td><td>0.14</td></tr> <tr><td>TIA</td><td>5 (2.8%)</td><td>15 (3.2%)</td><td>0.076</td></tr> <tr><td>Minor stroke</td><td>1 (0.6%)</td><td>8 (1.7%)</td><td></td></tr> <tr><td>Major stroke</td><td>1 (0.6%)</td><td>10 (2.1%)</td><td></td></tr> <tr><td>30-day stroke rate</td><td>2 (1.2%)</td><td>18 (3.8%)</td><td>0.073</td></tr> <tr><td>30-day mortality</td><td>0</td><td>2 (0.4%)</td><td>0.38</td></tr> <tr><td>Access site complications</td><td>7 (3.9%)</td><td>19 (4.0%)</td><td>0.93</td></tr> </table>	Residual stenosis (10% to 30%)	8 (4.4%)	14 (3%)	0.35	<b>Any complication</b>	18 (10.0%)	86 (18.3%)	0.010	Haemodynamic instability	5 (2.8%)	39 (8.3%)	0.012	Prolonged hypertension	3 (1.7%)	32 (6.8%)	0.009	Severe bradycardia	1 (0.6%)	11 (2.3%)	0.13	Asystole (>4s)	1 (0.6%)	8 (1.7%)	0.26	Angiographic intracranial embolisation	0	4 (0.8%)	0.22	<b>Any neurological complication</b>	7 (3.9%)	33 (7.0%)	0.14	TIA	5 (2.8%)	15 (3.2%)	0.076	Minor stroke	1 (0.6%)	8 (1.7%)		Major stroke	1 (0.6%)	10 (2.1%)		30-day stroke rate	2 (1.2%)	18 (3.8%)	0.073	30-day mortality	0	2 (0.4%)	0.38	Access site complications	7 (3.9%)	19 (4.0%)	0.93
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<p>Castriota et al (2002)</p> <p>Level III-3 intervention evidence</p> <p><u>Patients</u> <b>CAS with EPD:</b> 150 patients <b>CAS only:</b> 125 patients</p> <p><b>EPD:</b> AngioGuard (63%); Guardwire (16.7%); TRAP filter (12.7%); EPI filter (4.7%); NeuroShield (2%); Parodi Anti-embolic system (1.3%); Medicorp occlusive balloon (0.7%).</p> <p>Follow-up: not stated</p>	<p><b>Adverse events post-CAS</b></p> <table border="1"> <thead> <tr> <th></th> <th>With EPD (n=148)</th> <th>Without EPD (n=120)</th> </tr> </thead> <tbody> <tr><td>Major stroke/death</td><td>0 (0%)</td><td>0 (0%)</td></tr> <tr><td>Minor stroke</td><td>1 (0.7%)</td><td>3 (2.4%)</td></tr> <tr><td>TIA</td><td>0 (0%)</td><td>1 (0.8%)</td></tr> <tr><td>Subarachnoid haemorrhage</td><td>1 (0.7%)</td><td>0 (0%)</td></tr> <tr><td>Overall complication rate</td><td>4%(3.2% embolic in origin)</td><td>1.3% (0.7% embolic in origin)</td></tr> </tbody> </table>		With EPD (n=148)	Without EPD (n=120)	Major stroke/death	0 (0%)	0 (0%)	Minor stroke	1 (0.7%)	3 (2.4%)	TIA	0 (0%)	1 (0.8%)	Subarachnoid haemorrhage	1 (0.7%)	0 (0%)	Overall complication rate	4%(3.2% embolic in origin)	1.3% (0.7% embolic in origin)																																						
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<p>Iyer et al (2007)</p> <p>Level III-3 intervention evidence</p> <p><u>Patients</u> <b>CAS with EPD:</b> 3030 procedures <b>CAS only:</b> 130 procedures</p> <p><b>EPD:</b> <i>Filters:</i> FilterWire, Spider, EmboShield, AngioGuard, Trap, Accunet (92.8%) <i>Distal occlusion:</i> NPS, Mo.Ma (6.3%), <i>Proximal occlusion:</i> Percusurge (0.9%).</p> <p>Follow-up: 30 days</p>	<p><b>Procedural and 30-day adverse events</b></p> <table border="1"> <thead> <tr> <th></th> <th>Frequency</th> <th>RR</th> <th>95% CI</th> <th>p-value</th> </tr> </thead> <tbody> <tr><td colspan="5"><b>30-days</b></td></tr> <tr><td colspan="5">Protected (n=3030)</td></tr> <tr><td>Unprotected (n=130)</td><td>87 (2.9%) [68 TIA; 13 stroke; 7 death]</td><td>1.25</td><td>0.40-3.88</td><td>1.00</td></tr> <tr><td colspan="5"><b>Procedural</b></td></tr> <tr><td colspan="5">Protected (n=3030)</td></tr> <tr><td>Unprotected (n=130)</td><td>26 (0.9%) [20 TIA; 6 stroke]</td><td>0.38</td><td>0.12-1.24</td><td>0.12</td></tr> </tbody> </table> <p>RR: relative risk compared with protected CAS; CI: confidence interval; TIA: transient ischaemic attack.</p>		Frequency	RR	95% CI	p-value	<b>30-days</b>					Protected (n=3030)					Unprotected (n=130)	87 (2.9%) [68 TIA; 13 stroke; 7 death]	1.25	0.40-3.88	1.00	<b>Procedural</b>					Protected (n=3030)					Unprotected (n=130)	26 (0.9%) [20 TIA; 6 stroke]	0.38	0.12-1.24	0.12																					
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Kastrup et al (2008)	<b><u>New DWI lesions after CAS (within 48 hours post-CAS)</u></b>			
Level III-3 intervention evidence	<b>Variable</b>	<b>With EPD</b>	<b>Without EPD</b>	<b>p-value</b>
<b>Patients</b> <b>CAS with EPD: 138 patients</b> <b>CAS only: 52 patients</b>	<b>Ages ≤75 years</b>			
<b>EPD: NeuroShield;</b> <b>AngioGuard;</b> <b>EmboShield; FilterWire.</b>	No. of lesions	138	52	
Follow-up: 30 days	Median (interquartile range)	0 (0-2)	1 (0-4)	<0.01
	No. of procedures with any new ipsilateral DWI lesion	64/138 (46%)	35/52 (67%)	<0.05
	<b>Age &gt;75 years</b>			
	No. of lesions	37	16	
	Median (interquartile range)	1 (0-4)	1.5 (0-5.75)	0.6
	No. of procedures with any new ipsilateral DWI lesion	27/37 (73%)	11/16 (69%)	0.7
	<b>Symptomatic patients</b>			
	No. of lesions	87	47	
	Median (interquartile range)	1 (0-3)	2 (0-6)	<0.05
	No. of procedures with any new ipsilateral DWI lesion	49/87 (56%)	35/47 (74%)	<0.05
	<b>Asymptomatic patients</b>			
	No. of lesions	88	21	
	Median (interquartile range)	0 (0-2)	1 (0-2.5)	0.6
	No. of procedures with any new ipsilateral DWI lesion	42/88 (48%)	11/21 (52%)	0.8
	<b>30-day peri-procedural complications after CAS</b>			
	<b>Variable</b>	<b>With EPD</b>	<b>Without EPD</b>	<b>p-value</b>
	<b>Ages ≤75 years</b>			
	No.	138	52	
	Minor stroke	5/138 (3.6%)	4/52 (7.7%)	0.3
	Major stroke	0/138 (0%)	0/52 (0%)	NA
	Death	0/138 (0%)	0/52 (0%)	NA
	Any stroke or death	5/138 (3.6%)	4/52 (7.7%)	0.3
	<b>Age &gt;75 years</b>			
	No.	37	16	
	Minor stroke	2/37 (5.4%)	2/16 (12.5%)	0.6
	Major stroke	1/37 (2.7%)	0/16 (0%)	1.0
	Death	1/37 (2.7%)	0/16 (0%)	1.0
	Any stroke or death	4/37 (10.8%)	2/16 (12.5%)	1.0
	<b>Symptomatic patients</b>			
	No.	87	47	
	Minor stroke	5/87 (5.7%)	5/47 (10.6%)	0.3
	Major stroke	0/87 (0)	0/47 (0)	NA
	Death	1/87 (1.1)	0/47 (0)	1.0
	Any stroke or death	6/87 (6.9%)	5/47 (10.6%)	0.5
	<b>Asymptomatic patients</b>			
	No.	88	21	
	Minor stroke	2/88 (2.2%)	1/21 (4.8%)	0.5
	Major stroke	1/88 (1.1%)	0/21 (0%)	1.0
	Death	0/88 (0%)	0/21 (0%)	NA
	Any stroke or death	3/88 (3.4%)	1/21 (4.8)	0.6

<p>Kastrup et al (2006)</p> <p>Level III-3 intervention study</p> <p>Patients <b>CAS with EPD:</b> 139 patients <b>CAS only:</b> 67 patients</p> <p><b>EPD:</b> Neuroshield (n=31); AngioGuard (n=11); EmboShield (n=61); Filterwire (n=36).</p> <p>Follow-up: 30 days</p>	<p><b><u>New ipsilateral DWI lesions after CAS (within 48 hours post-CAS)</u></b></p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Cerebral protection</th> <th rowspan="2">p-value</th> </tr> <tr> <th>Yes</th> <th>No</th> </tr> </thead> <tbody> <tr> <td colspan="4"><i>No. of lesions</i></td> </tr> <tr> <td>Total</td> <td>235</td> <td>404</td> <td></td> </tr> <tr> <td>Range</td> <td>0-29</td> <td>0-50</td> <td></td> </tr> <tr> <td>Median (IQR)</td> <td>1 (0-4)</td> <td>0 (0-3)</td> <td>&lt;0.05</td> </tr> <tr> <td>No. of procedures with any new DWI lesion</td> <td>45/67 (67%)</td> <td>68/139 (49%)</td> <td>&lt;0.05</td> </tr> <tr> <td colspan="4"><i>Size</i></td> </tr> <tr> <td>&lt;10mm</td> <td>223/235 (95%)</td> <td>392/404 (97%)</td> <td>0.2</td> </tr> <tr> <td>10 to 20mm</td> <td>9/235 (4)</td> <td>10/404 (2)</td> <td>0.3</td> </tr> <tr> <td>&gt;20mm</td> <td>2/235 (1%)</td> <td>2/404 (0%)</td> <td>0.4</td> </tr> </tbody> </table> <p><b><u>Peri-procedural complications (within 30 days post-CAS)</u></b></p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Cerebral protection</th> <th rowspan="2">p-value</th> </tr> <tr> <th>Yes</th> <th>No</th> </tr> </thead> <tbody> <tr> <td>Minor stroke</td> <td>4/67 (6%)</td> <td>4/139 (2.9%)</td> <td>0.3</td> </tr> <tr> <td>Major stroke</td> <td>1/67 (1.5%)</td> <td>1/139 (0.7%)</td> <td>0.5</td> </tr> <tr> <td>Death*</td> <td>0.67 (0%)</td> <td>1/139 (0.7%)</td> <td>1.0</td> </tr> <tr> <td>Any stroke or death</td> <td>5/67 (7.5%)</td> <td>6/139 (4.3%)</td> <td>0.3</td> </tr> </tbody> </table> <p>p-values from X2 analysis; all major and minor strokes occurred ipsilateral to the treated artery; *nonstroke related death secondary to pneumonia 3 weeks post-CAS.</p>		Cerebral protection		p-value	Yes	No	<i>No. of lesions</i>				Total	235	404		Range	0-29	0-50		Median (IQR)	1 (0-4)	0 (0-3)	<0.05	No. of procedures with any new DWI lesion	45/67 (67%)	68/139 (49%)	<0.05	<i>Size</i>				<10mm	223/235 (95%)	392/404 (97%)	0.2	10 to 20mm	9/235 (4)	10/404 (2)	0.3	>20mm	2/235 (1%)	2/404 (0%)	0.4		Cerebral protection		p-value	Yes	No	Minor stroke	4/67 (6%)	4/139 (2.9%)	0.3	Major stroke	1/67 (1.5%)	1/139 (0.7%)	0.5	Death*	0.67 (0%)	1/139 (0.7%)	1.0	Any stroke or death	5/67 (7.5%)	6/139 (4.3%)	0.3
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Note: There is substantial patient overlap between Kastrup et al (2006) and Kastrup et al (2008). However, both studies were selected for inclusion as they reported different outcomes. Kastrup et al (2006) provided DWI results, which were not presented in Kastrup et al (2008).

Two comparative studies reported safety results that favoured EPDs (Ouriel et al 2005; Castriota et al 2002). Ouriel et al (2005) noted that the rate of major adverse events, death and minor ipsilateral stroke was similar between protected and unprotected CAS patients (Table 3). However, the risk of major ipsilateral stroke was significantly lower in patients with protection (0% vs. 2.3%;  $p=0.05$ ). Castriota et al (2002) stated that the use of EPDs reduced acute neurological event rates related to embolic complications by 79% (3.2% to 0.7%). However, no statistical tests were presented to verify the significance of this result. Vos et al (2005) argued that the difference observed by Castriota et al (2002) was not statistically significant.

#### *Diffusion-weighted imaging and transcranial Doppler analysis*

Diffusion-weighted magnetic resonance imaging (DWI) is used to detect early cerebral ischaemia and to identify small or asymptomatic thromboembolic lesions (Gass et al 2004). DWI was conducted in two of the included comparative studies (Barbato et al 2008; Kastrup et al 2006), while one study utilised transcranial Doppler ultrasound (Vos et al 2005).

The randomised trial by Barbato et al (2008) reported that new defects were noted during DWI in 13 patients (72%) who received EPDs, which was comparable to those who did not receive EPDs (44%;  $p=0.09$ ). The incidence of ipsilateral defects and defect sizes were comparable as well (Table 3). Patients with major or minor strokes had evidence of new DWI defects ipsilateral to the stented side and appeared to have larger DWI lesions relative to those who did not suffer clinically obvious neurological events ( $39.9 \pm 42.5$  vs.  $7.2 \pm 9.6$  [mean  $\pm$  standard deviation]), but this was not statistically significant (Barbato et al 2008) (Table 3).

In contrast, Kastrup et al (2006) noted that the proportion of patients with new ipsilateral DWI lesion(s) after CAS with EPD was significantly lower relative to those treated without EPD (49% vs. 67%;  $p<0.05$ ). In both groups, the majority of new DWI lesions had a diameter of  $<10\text{mm}$  (Table 3) and were asymptomatic. Statistical analysis did not identify any correlations between the incidences or number of any new ipsilateral DWI lesion and the type of EPD utilised, the degree of stenosis, or the presence of a contralateral stenosis. The incidence of new DWI lesions outside the vascular territory of the target lesion was comparable between protected and unprotected CAS groups (17% vs. 21%;  $p=0.1$ ). The 30-day overall clinical complication rate (any stroke or death) was comparable between both groups. As expected, patients who suffered a major or minor stroke had significantly more new DWI lesions compared to those who did not suffer stroke (Median: 7.5 vs. 1;  $p<0.01$ ) (Kastrup et al 2006).

Vos et al (2005) utilised transcranial Doppler ultrasound to register the number of isolated microembolic signals, as well as microembolic showers<sup>4</sup>, in the middle cerebral artery during each phase of the CAS procedure (Table 3). The results

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<sup>4</sup> Microembolic showers: cardiac cycle with too many microembolic signals to be counted separately.

demonstrated significant differences between patients in groups 2<sup>5</sup> and 3<sup>6</sup> for all phases of the CAS procedure. This difference was observed in both the number of isolated microemboli (p<0.001 for all phases) and the number of microembolic showers (p=0.001 for post-dilation phase, p<0.001 for others). In every instance, the results indicated that microembolic load was significantly higher in patients who received EPDs and the total number of isolated microemboli and microembolic showers that occurred during the entire procedure was higher (p<0.001). Interestingly, the higher microembolic load observed for EPD patients did not translate to higher stroke or death rates (Table 3). The investigators stated that particulate embolus was not evident in group 2 patients, but was detected in two group 3 patients. However, distal thrombus formation was exclusively present in group 2 patients only (n=6; 4.8%). It is unclear if these results were statistically significant.

#### *Device-related complications*

The majority of the included studies did not provide sufficient detail with regards to the incidence of device-related complications. It is not clear whether this information was not reported or complications were not observed. One comparative study (Castriota et al 2002) reported device failure rates of 0.8% (3 patients) due to distal spiral dissection (2 patients; GuardWire occlusive balloon) and a trapped wire (1 patient; AngioGuard filter) in the proximal edge of a stent (Castriota et al 2002).

#### *Comparison of different EPD types*

Four studies compared different EPD types. Iyer et al (2007) reported procedural and 30-day event rates for some of the most commonly utilised EPDs (Table 4; Table 5). The data was expressed as absolute and relative risks relative to the most common EPD in this study, the FilterWire:

**Table 4: Procedural adverse events for various EPDs (Iyer et al 2007).**

<b>System</b>	<b>Frequency</b>	<b>RR</b>	<b>95% CI</b>	<b>p-value</b>
FilterWire (n=1640)	16 (1.0%) [11 TIA; 5 stroke]			
Spider (n=191)	0 (0)	0.00	0.00-∞	0.40
Emboshield (n=177)	0 (0)	0.00	0.00-∞	0.40
Accunet (n=204)	1 (0.49%) [1 TIA]	0.50	0.07-3.75	1.00
AngioGuard (n=518)	5 (0.97%) [5 TIA]	0.99	0.36-2.86	1.00
Trap (n=82)	1 (1.22%) [1 TIA]	1.24	0.17-9.20	0.57
Mo.Ma (n=150)	1 (0.67%) [1 TIA]	0.68	0.09-5.09	1.00
NPS (n=42)	1 (2.38%) [1stroke]	2.39	0.32-17.57	0.35
Percusurge (n=26)	1 (3.85%) [1 TIA]	3.80	0.52-27.59	0.24

RR: relative risk compared with protected CAS; CI: confidence interval; TIA: transient ischaemic attack.

<sup>5</sup> Group 2: Patients treated with CAS and filter type EPDs.

<sup>6</sup> Group 3: Patients treated with CAS only (no EPD) after the introduction of commercially available EPDs.

**Table 5: 30-day adverse events for various EPDs (Iyer et al 2007)**

System	Frequency	RR	95% CI	p-value
FilterWire (n=1640)	36 (2.2%) [23 TIA; 9 stroke; 4 death]			
Spider (n=191)	4 (2.1%) [4 TIA]	0.95	0.34-2.64	1.00
EmboShield (n=177)	6 (3.39%) [5 TIA; 1 death]	1.54	0.66-3.60	0.29
Accunet (n=204)	12 (5.88%) [11 TIA; 1 stroke]	2.67	1.41-5.04	0.005
AngioGuard (n=518)	17 (3.28%) [14 TIA; 2 stroke; 1 death]	1.49	0.85-2.64	0.19
Trap (n=82)	2 (2.44%) [2 TIA]	1.10	0.27-4.48	0.70
Mo.Ma (n=150)	6 (4.0%) [6 TIA]	1.81	0.78-4.23	0.16
NPS (n=42)	2 (4.76%) [1 stroke; 1 death]	2.12	0.53-8.52	0.24
Percusurge (n=26)	2 (7.69%) [2 TIA]	3.38	0.86-13.29	0.12

RR: relative risk compared with protected CAS; CI: confidence interval; TIA: transient ischaemic attack.

It is important to note that the comparisons in Tables 4 and 5 were not adjusted for risk factors due to the low sample size for some EPDs. A statistically significant increase in the 30-day event rate was noted for Accunet ( $p=0.005$ ). In addition, an increased 30-day procedural event rate was observed for the Percusurge distal occlusion balloon, but this was not statistically significant. Risk ratios of procedural and 30-day events comparing the various EPDs before the adjustment for risk factors demonstrated a significant difference in favour of eccentric filters compared to concentric filters at 30-days ( $p=0.04$ ). When adjusted for risk factors, the significance was no longer apparent ( $p=0.06$ ), but a trend remained. After adjustment for stent type (closed cell vs. open cell), this difference was no longer apparent ( $p=0.51$ ) (Iyer et al 2007).

Zahn et al (2005) compared the effectiveness of filter-type EPDs (FilterWire, Trap, Spider, EmboShield, Accunet) with distal occlusion EPDs (GuardWire) and demonstrated no difference in clinical event rates between both protective devices. Multivariate analysis on the occurrence of the composite end point of in-hospital death or stroke did not reveal any differences between filter and distal occlusion-type EPDs (1.8% vs. 2.3%, respectively;  $p=0.958$ ) (Zahn et al 2005). However, it is important to note that patients who received distal occlusion-type EPDs were more likely to be treated for symptomatic stenosis (64.5% vs. 53.4%,  $p=0.011$ ) and had more complicated lesions, characterised by more ulcers ( $p=0.035$ ), severe calcification ( $p=0.039$ ), longer lesion length ( $p=0.025$ ) and higher pre-CAS stenosis grade ( $p<0.001$ ) (Zahn et al 2005).

In contrast, Hart et al (2006) noted that subgroup analysis on symptomatic patients showed that 30-day combined stroke, death and TIA rate was 10.4% for concentric filters<sup>7</sup> and 3.4% with eccentric filters<sup>8</sup> (odds ratio: 3.3; 95% confidence interval: 1.016-10;  $p=0.0525$ ). The authors postulated that better wall apposition in the distal internal carotid artery due to axial flexibility may explain the better results demonstrated for eccentric filters. Meanwhile, the wire

<sup>7</sup> Concentric filters utilised: AngioGuard XP/RX, EmboShield and Trap (Hart et al 2006).

<sup>8</sup> Eccentric filters utilised: FilterWire EX/EZ and SpydeRx (Hart et al 2006).

scaffolding of concentric filters may pull the EPD away from the vessel wall when used in tortuous anatomy (Hart et al. 2006).

Utilising DWI, El-Koussy et al (2007) compared the efficacy of proximal balloon occlusion EPDs versus distal filter-type EPDs<sup>9</sup> during CAS and demonstrated that the incidence of new lesions was comparable between both EPD groups (proximal: 28.0% vs. distal: 32.6%). New lesions within the vascular territory of the stented carotid artery tended to be fewer in proximal EPD patients, but this was not statistically significant.

## Other Issues

As with all medical devices, EPDs have limitations and issues that warrant attention. The retrospective comparative review by Eskandari et al (2007) revealed that up to 10% of patients within this study had lesions that were too narrow or tortuous to allow the safe passage of the filter-type EPDs (AccUNET, AngioGuard, FilterWire or EmboShield). The authors recommended that distal balloon occlusion systems should be utilised in place of filter EPDs when necessary.

To date, there is no clear indication on the specific EPD (or stent) to use during CAS for patients with different baseline characteristics. In view of this, Pieniazek et al (2008) conducted a study to develop an algorithm for the selection of EPDs and stents depending on the presence of symptoms and the status of the access vessels, target vessel anatomy and lesion location by duplex ultrasound, computed tomographic angiography (CTA) and angiography. High risk lesions were treated predominantly with a proximal EPD and closed-cell stent and less frequently by direct stenting. No intra-procedural deaths or major strokes were observed. However, there were 5 (0.9%) minor strokes and 12 (2.2%) TIAs. The cumulative in-hospital stroke, death and myocardial infarction rate was 2.0% (95% confidence interval: 0.85%-3.23%). Meanwhile, the 30-day cumulative stroke, death and myocardial infarction rate was 2.2% (Pieniazek et al 2008). This was substantially lower compared to the 30-day cumulative stroke, death and myocardial infarction rate of other studies that utilised “one stent and EPD for all” treatment protocols, such as SAPHIRE (4.8%), ARCHeR (8.3%), CREATE (6.2%) and CAPTURE (5.0%).

Interim results of the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) trial demonstrated that an increasing proportion of patients suffered stroke and death with increasing age ( $p=0.0006$ ). Furthermore, these increasing complication rates were not mediated by adjustment for symptomatic status, use of EPDs, gender, severity of stenosis or the presence of distal arterial tortuosities. Therefore, additional care is warranted when treating older patient populations

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<sup>9</sup> Proximal EPDs: Mo.Ma; Distal: FilterWire, Neuronet and EmboShield (El-Koussy et al 2007).

with CAS (Hobson et al 2004). In contrast, Kastrup et al (2008) did not observe any significant differences in neurologic complication rates within 30 days among younger, older, symptomatic or asymptomatic patients treated with or without EPDs.

### Cost Analysis

There are several published studies evaluating the cost effectiveness of CAS (including protection) relative to CEA, which suggest that CAS with protection is substantially more expensive compared to CEA.

The analysis by Kilaru et al. (2003) noted that the immediate procedural costs of CEA and CAS (with protection) were US\$7,871 and US\$10,133, respectively. Meanwhile, Park et al (2006) noted that utilising the cost to charge ratio methodology, CAS was associated with higher total procedural costs compared to CEA (US\$17,402 vs. US\$12,112;  $p=0.029$ ) and direct costs<sup>10</sup> (US\$10,522 vs. US\$7,227;  $p=0.017$ ). Indirect costs<sup>11</sup> were comparable between both treatments (US\$6,879 vs. US\$4,885). In a more recent economic evaluation of CEA versus CAS (with protection) for carotid artery stenosis, Pawaskar et al (2007) conducted a retrospective database analysis on pair-matched patients who underwent CEA ( $n=31$ ) and CAS ( $n=31$ ) at the Richard M Ross Heart Hospital in Columbus, Ohio. Similar to Park et al (2006), total direct cost associated with CEA was significantly lower than CAS cost (US\$3,765.12  $\pm$  2170.82 vs. US\$8,219.71  $\pm$  2958.54;  $p<0.001$ ). Mean procedural cost for CAS was significantly lower as well (US\$2,720.00  $\pm$  926.38 vs. US\$7,543.61  $\pm$  2886.54;  $p<0.001$ ). Overall, CAS was significantly more expensive than CEA with a major portion of cost attributed toward total procedural cost (Pawaskar et al 2007).

The estimated average cost of an EPD is approximately US\$2,000. The use of EPDs also increase procedural time, with one study (Zahn et al 2004) demonstrating that CAS with protection takes significantly longer compared to CAS without protection (median and quartiles: 45 [35 to 62] vs. 35 [25 to 50];  $p<0.001$ ). These factors indicate the CAS with protection may increase CAS costs substantially, but the cost effectiveness of EPDs remains unclear. Factors such as duration of hospital stay and adverse event rates must be considered.

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<sup>10</sup> Cost directly associated with the procedure and admission (e.g. material and room charges).

<sup>11</sup> Cost not directly related to procedure (e.g. administrative cost, meals, parking).

### Informed Consent

Patients undergoing treatment for carotid artery stenosis should be aware of the risks associated with CAS and CEA as well as the advantages of these procedures. In cases where CEA is not advisable due to significant comorbidities, CAS with protection appears to be an acceptable alternative. Despite the contradictory evidence on the true effectiveness of EPDs, it is unlikely that the general perception on the necessity of EPDs during CAS will change in the near future. However, clinicians should be familiar with the latest developments on EPDs and its limitations.

### Access Issues

CAS requires a facility with optimal radiological, monitoring and patient support equipment. This includes high resolution fluoroscopy, continuous information on patient oxygenation, electrocardiogram, heart rate, heart rhythm and blood pressure; resuscitative equipment and temporary pacing. Furthermore, the necessary interventional equipment (sheaths, catheters etc.) and quality assessment monitoring (neurological assessment etc.) is required (Bates et al 2007).

The CAPTURE<sup>12</sup> registry suggests that the transfer of protected CAS to the community practice setting via carotid stent training programs is effective in preparing physicians with varying experience levels and specialty training backgrounds (Gray et al 2006). Therefore the skills required to conduct protected CAS can be diffused to a broader cross-section of physicians and hospitals and is not limited to highly selected physicians and hospitals typically utilised in trials and registries.

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<sup>12</sup> CAPTURE: Carotid Acculink/AccuNet Post-Approval Trial to Uncover Unanticipated or Rare Events.

### Training

The CAS procedure requires specific training as carotid artery revascularisation using stent placement with embolic protection requires capable operators, well prepared facilities and appropriate patient selection. Industry-sponsored device certification may also assist to ensure familiarisation with the specific equipment approved by the TGA. The clinical competence statement by Rosenfield et al (2005) notes that completion of an industry-sponsored certification courses should not in itself confer adequate qualifications for performance of CAS as a primary operator.

### Clinical Guidelines

The ACCF/SCAI/SVMB/SIR/ASITN<sup>13</sup> 2007 Clinical Expert Consensus Document on Carotid Stenting states that the use of EPDs appears to be important in reducing the risk of stroke during CAS. However, the document concluded that there was insufficient evidence to support CAS in high-risk patients with asymptomatic stenosis of  $\leq 80\%$  or in any patient without high-risk features (Bates et al 2007).

In Australia, the Clinical Guidelines for Stroke and TIA Management by the Stroke Foundation states that CAS should *not* be routinely considered for patients with symptomatic stenosis. However, the guidelines state that CAS can be considered as an alternative surgical treatment in patients who meet the criteria for CEA but are deemed unfit due to medical comorbidities (e.g. serious heart/lung disease, age >80 years) or conditions that make them unfit for open surgery (e.g. high or low carotid bifurcation, carotid restenosis). The Stroke Foundation rates the levels of evidence for this recommendation as Grade B: body of evidence can be trusted to guide practice in most situations. There was no specific mention of EPDs in this guideline (National Stroke Foundation 2008).

The Medical Services Advisory Committee (MSAC) reviewed the use of CAS in 2005 and concluded that the evidence available at that time supports the conclusion that when CAS is performed, it should be performed with EPDs, whenever this is feasible (MSAC 2005). However, it is important to note that at the time of this MSAC assessment, the majority of studies retrieved evaluated balloon EPDs which have been phased out in recent years in favour of filter-type EPDs.

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<sup>13</sup> American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions/Society for Vascular Medicine and Biology/Society of Interventional Radiology/American Society of Interventional & Therapeutic Neuroradiology

## Limitations of the Assessment

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Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of health technology assessment; however, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A horizon scanning report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost-effectiveness of a technology.

In the context of a rapidly evolving technology, a horizon scanning report is a ‘state of play’ assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of embolic protection device for carotid artery stenting, its present and potential use in the Australian public health system, and future implications for the use of this technology.

## Search Strategy used for the Report

The sources utilised in this assessment are listed in Table 7. The medical literature was searched with the search terms outlined in Table 8 to identify relevant studies up to January 2009 in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

**Table 6: Literature sources utilised in assessment**

Source	Location
<b>Electronic databases</b>	
AustHealth	University of Adelaide library
Australian Medical Index	University of Adelaide library

CINAHL	University of Adelaide library
Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University of Adelaide library
Current Contents	University of Adelaide library
Embase	Personal subscription
Pre-Medline and Medline	University of Adelaide library
PyscINFO	Personal subscription
RACS electronic library	Personal subscription
<b>Internet</b>	
Blue Cross and Blue Shield Association's Technology Evaluation Center	<a href="http://www.bcbs.com/tec/">http://www.bcbs.com/tec/</a>
Canadian Agency for Drugs and Technologies in Health	<a href="http://www.cadth.ca">http://www.cadth.ca</a>
Current Controlled Trials metaRegister	<a href="http://www.controlled-trials.com/">http://www.controlled-trials.com/</a>
EuroScan	<a href="http://www.euroscan.bham.ac.uk/">http://www.euroscan.bham.ac.uk/</a>
Health Technology Assessment International	<a href="http://www.htai.org/">http://www.htai.org/</a>
International Network for agencies for Health Technology Assessment	<a href="http://www.inahta.org">http://www.inahta.org</a>
Medicines and Healthcare products Regulatory Agency (UK)	<a href="http://www.mhra.gov.uk/">http://www.mhra.gov.uk/</a>
US Food and Drug Administration, Center for Devices and Radiological Health	<a href="http://www.fda.gov/cdrh/index.html">http://www.fda.gov/cdrh/index.html</a>
US Food and Drug Administration, Manufacturer and User Facility Device Experience Database	<a href="http://www.fda.gov/cdrh/mUDE.html">http://www.fda.gov/cdrh/mUDE.html</a>
UK National Research Register	<a href="http://www.nrr.nhs.uk/">http://www.nrr.nhs.uk/</a>
Websites of specialty organisations	<a href="http://www.strokefoundation.com.au">http://www.strokefoundation.com.au</a>

**Table 7: Search terms utilised**

<b>Search terms</b>
<b>MeSH</b>
Carotid stenosis/therapy*, Carotid stenosis/surgery*, Embolism/prevention & control*
<b>Text words</b>

Embolic protection device, Carotid artery stenting, neuroprotection, Carotid angioplasty and stenting

**Limits**

English, human

## **Availability and Level of Evidence**

The medical literature (Table 6) was searched utilising the search terms outlined in Table 7 to identify relevant studies and reviews until January 2009. In addition, major international health assessment databases were searched.

One randomised controlled trial (Level II evidence) and 10 comparative studies (Level III evidence) were retrieved for inclusion in this horizon scanning report. Three additional case series studies (Level IV evidence) were included to highlight other issues relating to the use of EPDs that were not covered in the RCT and comparative studies. The profiles of the included studies are summarised in Appendix B.

## Sources of Further Information

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List of ongoing clinical trials on EPDs for CAS:

Carotid Revascularization With ev3 Arterial Technology Evolution Post Approval Study (CREATE PAS). Estimated Study Completion Date: April 2011. Device: PROTÉGÉ® GPS™ and PROTÉGÉ® RX Carotid Stent Systems and SpiderFX™ Embolic Protection Device. ClinicalTrials.gov Identifier: NCT00530504.

PROTECTed Carotid Artery Stenting in Subjects at High Risk for Carotid Endarterectomy (CEA). Estimated Study Completion Date: July 2011. Device: Xact Stent with either Emboshield Pro or Emboshield (Gen 3). ClinicalTrials.gov Identifier: NCT00402740.

A Carotid Stenting Boston Scientific Surveillance Program (CABANA). Estimated Study Completion Date: July 2010. Device: FilterWire EZ™ System™. ClinicalTrials.gov Identifier: NCT00741091.

CAPTURE 2 Post-Marketing Registry. Estimated Study Completion Date: December 2010. Device: RX ACCULINK, RX ACCUNET Embolic Protection System. ClinicalTrials.gov Identifier: NCT00302237.

Proximal Protection With The MO.MA Device During Carotid Stenting (ARMOUR). Estimated Study Completion Date: March 2009. Device: Carotid Artery Stenting with cerebral protection with the MO.MA device. ClinicalTrials.gov Identifier: NCT00744523.

Diffusion Weighted-MRI Based Evaluation of the Effectiveness of Endovascular Clamping During Carotid Artery Stenting With the Mo.Ma Device (DESERVE). Estimated Study Completion Date: April 2009. Device: Carotid Artery Stenting with cerebral protection with the MO.MA device. ClinicalTrials.gov Identifier: NCT00798512.

Carotid Stenting vs. Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I). Estimated Study Completion Date: May 2018. Device: Carotid artery stenting with filter (interventional). ClinicalTrials.gov Identifier: NCT00106938.

## Conclusions

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High level evidence on the true effectiveness of EPDs remains scarce, with only one randomised trial comparing the clinical outcomes of CAS patients with or without embolic protection. The randomised trial suggests a lack of demonstrable benefit with the use of EPDs. Five of the seven comparative studies retrieved to determine the safety and effectiveness of EPDs supported this view, with several studies indicating that major and minor stroke rates remain comparable up to 30-days post-treatment. Only one comparative study indicated that significant reduction in peri-operative and post-operative stroke rates is possible. The one remaining comparative study observed a 79% reduction in stroke rates with EPDs, but this was not statistically significant.

Utilising DWI, one study observed that the proportion of patients with new lesions was significantly lower with the use of EPDs. In contrast, the randomised trial highlighted that the occurrence of new DWI-detected lesions were comparable between protected or unprotected patients. One comparative study demonstrated that the number of microembolic signals and showers during each phase of the CAS procedure was significantly higher in protected patients compared to those without EPD. This raises doubt to the widely held perception that EPDs reduce embolic load. However, it is interesting to note that this higher microembolic load did not translate to higher stroke or death rates in EPD patients. It is postulated that macroembolus may be propelled into the filter and consequently disintegrated into smaller particles that passes the micropores of the filter. Alternatively, it is possible the filter EPDs do not adequately cover the entire internal carotid artery.

Three studies demonstrated that there is virtually no difference in effectiveness between various filter EPDs and proximal or distal occlusion EPDs. However, subgroup analysis of symptomatic patients in another study suggested that eccentric filters perform better relative to concentric filters. One retrospective case series study has demonstrated that the use of patient specific EPDs, selected based on characteristics such as plaque characteristics and internal carotid artery tortuosity, results in very low in-hospital death or stroke rates which compare favourably to several trials that utilised one specific EPD for all CAS patients. This indicates that the “one size fits all” approach to EPDs in certain trials is not optimal and warrants further investigation.

Overall, the evidence supporting the efficacy of EPDs remains controversial. The only randomised trial to date does not support the general view that EPDs are beneficial during CAS. Meanwhile, most of the comparative studies retrieved indicate that patients with EPDs experience similar stroke and death rates to those who underwent unprotected CAS. The observation that microembolic load may be higher in EPD recipients is of concern despite the fact that it does not have immediate neurological relevance. It is highly unlikely that new randomised controlled trials investigating the benefits of EPDs during CAS compared with

unprotected CAS will be conducted in the near future. The only randomised trial to investigate the true effectiveness of filter EPDs did not achieve its target cohort as the FDA approval of EPDs and widespread consensus for mandatory protection during CAS severely impaired patient recruitment. Nevertheless, there is some evidence that EPDs (at least filter-type EPDs) may not be as beneficial as widely thought and might be a contributing factor to higher embolic load in patients while burdening the healthcare system with potentially unnecessary costs. Larger well-designed comparative studies are clearly warranted. It is likely that comparative studies with historical controls derived from registries will form the majority of future attempts to determine the effectiveness of EPDs. Additional research is also necessary to determine if all classes of EPDs are truly comparable.

## Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

Level	Intervention §	Diagnosis **	Prognosis	Aetiology †††	Screening
I †	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among consecutive patients with a defined clinical presentation ††	A prospective cohort study †††	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, §§ among non-consecutive patients with a defined clinical presentation ††	All or none ††††	All or none ††††	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial † Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study † Interrupted time series without a parallel control group	Diagnostic case-control study ††	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ††	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

## Tablenotes

\* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C, to determine A vs. C).

‡ Comparing single arm studies i.e. case series from two studies.

\*\* The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: [www.msac.gov.au](http://www.msac.gov.au).

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

†† Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

\*\*\* At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Blandier editorial 1999)

## Appendix B: Profiles of studies

Study	Location	Study design	Study population	Outcomes assessed
Barbato et al (2008)	Pennsylvania, Unite States	RCT  Level II intervention evidence	CAS with EPD: 18 procedures CAS only: 18 procedures <i>Inclusion criteria</i> Age $\geq 18$ years, $\geq 70\%$ stenosis of CCA or ICA, $\geq 1$ high risk criteria confirmed by 2 physicians. <i>Exclusion criteria</i> Intracranial haemorrhage/stroke with mass effect in last 30 days, residual deficits after ischaemic stroke, allergy to heparin, ticlopidine or clopidogrel, intraluminal thrombus or highly calcified lesions that are potentially resistant to angioplasty.	Neurological events, MRI findings.
Boltuch et al (2005)	Vienna, Austria	Comparative  Level III-3 intervention evidence	CAS with EPD: 180 patients Age: 73 (65 to 78) years Symptomatic stenosis: 48 (27%) Ipsilateral degree of stenosis: 85.2%  CAS only: 471 patients Age: 72 (64 to 77) years Symptomatic stenosis: 147 (31%) Ipsilateral degree of stenosis: 84.8%	Technical success, combined stroke/death rates, neurological events, procedural complications.
Castriota et al (2002)	Cotignola, Italy	Comparative  Level III-3 intervention evidence	CAS with EPD: 150 patients Age: 71 $\pm$ 6 years Diameter stenosis: 81 $\pm$ 6% Symptomatic and positive CT: 52% Asymptomatic and positive CT: 27.3% Asymptomatic and negative CT but with rapidly progressing lesion: 20.7%  CAS only: 125 patients Age: 70 $\pm$ 8 years Diameter stenosis: 79 $\pm$ 8% Symptomatic and positive CT: 29.6% Asymptomatic and positive CT: 51.2% Asymptomatic and negative CT but with rapidly progressing lesion: 19.2%	Stroke/death rates, neurological events, device complications.
El-Koussy et al (2007)	Bern, Switzerland	Comparative  Level III-3 intervention evidence	Proximal EPD: 25 patients Age (median): 67 years Symptomatic: 60% $\geq 70$ stenosis: 96%  Distal EPD: 19 patients Age (median): 71 years Symptomatic: 52.6% $\geq 70$ stenosis: 100%	Procedural success, new DWI lesions, complications.
Hart et al (2006)	Belgium	Comparative  Level III-3 intervention evidence	Total population: 701 patients Age $\geq 80$ years: 16% Symptomatic: 43% Concentric EPD: 17%  Symptomatic patients: 301 patients Age $\geq 80$ years: 16% Symptomatic: 100% Concentric EPD: 16%	30-day combined stroke, death or TIA rate.

Study	Location	Study design	Study population	Outcomes assessed
Iyer et al (2007)	Cotignola, Italy	Comparative  Level III-3 intervention evidence	CAS with EPD: 3030 procedures CAS only: 130 procedures	Procedural and 30-day adverse events.
Kastrup et al (2008)	Germany	Comparative  Level III-3 intervention evidence	CAS with EPD: 138 patients CAS only: 52 patients <i>Overall baseline characteristics</i> Age (median): 68±9 years Symptomatic stenosis: 55% Degree of stenosis: 88±8%	DWI lesions, periprocedural complications (stroke/death rate).
Kastrup et al (2006)	Germany	Comparative  Level III-3 intervention evidence	CAS with EPD: 139 patients Age: 68±9 years Degree of stenosis: 86±8%  CAS only: 67 patients Age: 69±9 years Degree of stenosis: 88±8%	DWI lesions, lesion load and stroke outcomes.
Ouriel et al (2005)	United States	Comparative  Level III-3 intervention evidence	CAS with EPD: 85 patients CAS only: 176 patients <i>Overall baseline characteristics</i> Age: 70.9±9.7 years Symptomatic: 54.3% Average stenosis: 74±9.6%	Technical success, adverse events (death, myocardial infarction, neurological).
Vos et al (2005)	Netherlands	Comparative  Level III-3 intervention evidence	Group 1 (CAS only, before EPDs available): 161 patients Age (median): 70 Ipsilateral symptoms: 34.2%  Group 2 (CAS with EPD): 151 patients Age (median): 72 Ipsilateral symptoms: 34.4%  Group 3 (CAS only, after EPDs available): 197 patients Age (median): 71 Ipsilateral symptoms: 29.4%	Embolitic load (transcranial Doppler), adverse events/complications (neurological).
Zahn et al (2005)	Germany	Comparative  Level III-3 intervention evidence	Filter EPD: 553 patients Age (median): 70 years Symptomatic carotid stenosis: 53.4% Stenosis (median): 90%  Distal occlusion EPD: 176 patients Age (median): 70 years Symptomatic carotid stenosis: 64.5% Stenosis (median): 90%	Embolitic events, strokes, deaths.

## Appendix C: HTA internet sites

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### AUSTRALIA

- Centre for Clinical Effectiveness, Monash University  
<http://www.med.monash.edu.au/healthservices/cce/evidence/>
- Health Economics Unit, Monash University  
<http://chpe.buseco.monash.edu.au>

### AUSTRIA

- Institute of Technology Assessment / HTA unit  
<http://www.oeaw.ac.at/ita/welcome.htm>

### CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) <http://www.aetmis.gouv.qc.ca/en/>
- Alberta Heritage Foundation for Medical Research (AHFMR)  
<http://www.ahfmr.ab.ca/publications.html>
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)  
<http://www.cadth.ca/index.php/en/>
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database <http://www.mycabot.ca>
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University <http://www.chepa.org>

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia <http://www.chspr.ubc.ca>
- Health Utilities Index (HUI) <http://www.fhs.mcmaster.ca/hug/index.htm>
- Institute for Clinical and Evaluative Studies (ICES) <http://www.ices.on.ca>

## **DENMARK**

- Danish Institute for Health Technology Assessment (DIHTA) [http://www.dihta.dk/publikationer/index\\_uk.asp](http://www.dihta.dk/publikationer/index_uk.asp)
- Danish Institute for Health Services Research (DSI) <http://www.dsi.dk/engelsk.html>

## **FINLAND**

- Finnish Office for Health Technology Assessment (FINOHTA) <http://finohta.stakes.fi/FI/index.htm>

## **FRANCE**

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) <http://www.anaes.fr/>

## **GERMANY**

- German Institute for Medical Documentation and Information (DIMDI) / HTA <http://www.dimdi.de/dynamic/en/>

## **THE NETHERLANDS**

- Health Council of the Netherlands Gezondheidsraad  
<http://www.gr.nl/adviezen.php>

## **NEW ZEALAND**

- New Zealand Health Technology Assessment (NZHTA)  
<http://nzhta.chmeds.ac.nz/>

## **NORWAY**

- Norwegian Centre for Health Technology Assessment (SMM)  
<http://www.kunnskapssenteret.no/>

## **SPAIN**

- Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud “Carlos III” / Health Technology Assessment Agency (AETS)  
[http://www.isciii.es/htdocs/investigacion/Agencia\\_quees.jsp](http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp)
- Catalan Agency for Health Technology Assessment (CAHTA)  
<http://www.aatrm.net/html/en/dir394/index.html>

## **SWEDEN**

- Swedish Council on Technology Assessment in Health Care (SBU)  
<http://www.sbu.se/www/index.asp>
- Center for Medical Health Technology Assessment  
<http://www.cmt.liu.se/>

## **SWITZERLAND**

- Swiss Network on Health Technology Assessment (SNHTA)

<http://www.snhta.ch/>

## **UNITED KINGDOM**

- NHS Quality Improvement Scotland  
<http://www.nhshealthquality.org>
- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)  
<http://www.hta.nhsweb.nhs.uk/>
- University of York NHS Centre for Reviews and Dissemination (NHS CRD)  
<http://www.your.ac.uk/inst/crd/>
- National Institute for Clinical Excellence (NICE)  
<http://www.nice.org.uk/>

## **UNITED STATES**

- Agency for Healthcare Research and Quality (AHRQ)  
<http://www.ahrq.gov/clinic/techix.htm>
- Harvard School of Public Health – Cost-Utility Analysis Registry  
<http://www.tufts-nemc.org/cearegistry/index.html>
- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)  
<http://www.bcbs.com/tec/index.html>

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