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The Angioguard™ embolic protection device

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Abstract

Endovascular management of cardiovascular disease is quickly becoming a more popular treatment. The effectiveness in using embolic protection devices (EPDs), such as the Angioguard™ XP filter, during carotid artery stenting (CAS) is a topic of ongoing controversy and scrutiny. Early clinical results indicate that EPDs can reduce complications associated with CAS. However, the incidence of stroke and postprocedural embolic events are statistically similar when comparing CAS with the gold standard in carotid stenosis repair, carotid endarterectomy (CEA). The focus of this manuscript is the critical evaluation of Angioguard XP with respect to numerous *in vitro* and *ex vivo* experiments, and clinical trials that have been conducted by the authors and other researchers to investigate the efficacy of EPDs with the objective of suggesting engineering design considerations for future generations of these devices. Angioguard XP has had mixed performance outcomes in *in vitro* testing reported in the literature. In our laboratory, this device had undesirable measures of performance in bench-top testing protocols using *in vitro* flow models. Technical considerations relevant to design of EPDs, such as ideal pore size, effective wall apposition in tortuous geometry and maximization of capture efficiency have not been addressed adequately in the literature. It is likely that in the future both CAS and CEA will coexist as potential forms of treatment in the clinical management of cerebrovascular disease.

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Keywords

cerebral protection; design of medical devices; embolic protection device; flow modeling; pressure gradient; stenosis; stenting

Carotid artery stenting

Stroke is the third leading cause of death in the USA, with approximately 1 million stroke-related events each year. An estimated US\$57.9 billion was spent in 2006 on stroke, including both direct and indirect costs [1]. Approximately 50% of strokes occur due to atherosclerotic plaque in the carotid bifurcation and carotid occlusive disease amenable to revascularization accounts for 5–12% of strokes [2]. Minimally invasive procedures are quickly becoming a widespread alternative treatment for cardiovascular disease. Carotid artery stenting (CAS) consists of the percutaneous access of the internal carotid artery (ICA) via the femoral artery. A tubular wire mesh is expanded over a plaque lesion. Potential embolization during lesion crossing has led to concern about serious periprocedural complications due to occlusion of cerebral blood vessels. Embolic protection devices (EPDs) have been developed to reduce the death and stroke rate and other neurological disorders following CAS and are currently considered the standard of care for CAS by some [3,4]. In order for CAS to have the same widespread use as its surgical counterpart, carotid endarterectomy (CEA), the equivalent efficacy of CAS used in conjunction with an EPD in comparison with CEA needs to be shown. According to the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the 30-day death and stroke rate was 5.8% for CEA [5]. The World Registry has reported that in 4221 cases of protected CAS, the stroke and procedure-related death was 2.23% compared with 5.29% for unprotected CAS [6]. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial is the first randomized trial comparing protected CAS and CEA. This trial concluded that the two procedures are not inferior to each other, with a 30-day postprocedure primary end-point rate (composite of stroke, death or myocardial infarction [MI]) of 4.4% for CAS and 9.9% for CEA [7].

Alternative devices

There are three types of EPD available for use. The first is the distal balloon occlusion device, which is a balloon inflated distal to the lesion in the ICA to block all flow during stenting. Distal occlusion devices usually consist of a 0.014-inch hollow nitinol wire with floppy tip distal to a compliant elastomeric polyurethane occlusion balloon that can be inflated to a diameter of 3–6 mm [8]. A coaxial exchange system allows for over-the-wire (OTW) delivery of the stent and angioplasty balloons. Plaque particles embolized during stenting are trapped in a column of blood proximal to the balloon. Following stenting, the column of trapped blood and any embolized plaque generated during the procedure is aspirated, the balloon deflated and the device retrieved. Advantages of distal balloon occlusion devices include a lower crossing profile and the ability to capture particles of all sizes. There are several disadvantages associated with distal balloon occlusion devices, including possible embolization into the external carotid artery (ECA) during lesion crossing, inability to perform angiograms during CAS, possible injury to the ICA and the potential for patient intolerance to complete occlusion (typically for 5–15 min) [8].

The second type of EPD is the distal filter device, which is deployed distal to the lesion to capture any embolic material generated during CAS in the basket of the filter. Distal filters frequently consist of a delivery catheter, retrieval catheter and a 0.014-inch guidewire with a floppy tip distal to the filter. The filter itself is frequently manufactured of nitinol wire struts

and a polyurethane membrane with laser cut pores. Other designs include filters made entirely of wire mesh or polymer fibers. Similar to distal occlusion devices, distal filters take advantage of the OTW system for filter deployment. Distal filters are also available as a second monorail system for delivery [8]. Once deployed, the compressed filter opens and can capture any emboli released during the procedure. After stenting, the filter is collapsed into a separate retrieval catheter, trapping any debris inside the sheath. Distal filters have the advantage over distal balloon occlusion devices in that they allow distal perfusion (and thus the ability to perform angiograms) during CAS. Disadvantages of distal filters include a larger crossing profile than distal balloon occlusion devices, embolization of particles smaller than the pore size of the device, possible embolization during lesion crossing or device retrieval, difficulty in navigating severely stenosed or tortuous vessels, potential for spasm or dissection of the ICA, filter basket detachment and possible incorrect wall apposition of the filter against the vessel wall [8,9].

The third and final category of cerebral protection devices used for carotid interventions are the proximal balloon occlusion devices. These are represented by the Neuroprotection System™ (formerly known as the Parodi Anti-Emboli System™ [PAES; WL Gore, AZ, USA]) and the Mo.Ma™ device (Invatec, Roncadelle, Italy), which achieve their goal of embolic protection by using different mechanisms. Both devices exclude antegrade flow into the ICA during the intervention by using a proximal occlusion balloon in the common carotid artery (CCA) and an occlusion balloon in the ECA. The primary difference between the two systems is that continuous passive flow reversal is maintained by creating a filtered external arteriovenous fistula between the femoral artery and vein with the Neuroprotection System device, while flow stagnation occurs with Mo.Ma. However, both can provide active flow reversal by aspirating from the CCA sheath. The obvious advantages of these devices are that they:

- Provide complete protection of any size of particulate debris
- Protect against emboli via the ICA or ECA
- Provide protection before crossing the target lesion
- Give diversity in ICA crossing wire choices

Current disadvantages are the larger delivery sheath sizes (9–10 Fr) and lack of antegrade flow during portions of the procedure.

Angioguard™ XP

The Angioguard™ XP device (Cordis Endovascular, FL, USA), consists of a 0.014-inch guidewire with a basket frame made of nitinol and a porous polyurethane membrane over the frame (Figure 1). The polyurethane membrane contains 1100 laser-drilled pores with a 100 µm diameter. The device is manufactured in several basket sizes and crossing profiles: 4 mm (3.2 Fr), 5 mm (3.3 Fr), 6 mm (3.5 Fr), 7 mm (3.7 Fr) and 8 mm (4.0 Fr), intending to fit vessels sized from 3.0 to 7.5 mm in diameter [8,9]. Currently the delivery system of Angioguard XP is available in both OTW and monorail configurations [8]. This profile evaluates the Angioguard device based on both experimental and clinical outcomes, and from these results, we provide design considerations for future generations of EPDs.

Performance assessment: *in vitro* testing

Several *in vitro* experiments have been conducted on Angioguard and Angioguard XP. Müller-Hülsbeck circulated a 0.9% saline solution through a bench-top flow model [10–13]. A constant flow rate of 700 ml/min and a mean CCA pressure of 78–80 mmHg were used. The carotid artery bifurcation was modeled by straight 5-mm inner diameter silicone tubes

arranged with a 35° angle between the ECA and ICA. Embolization was simulated by injection of both polyvinyl alcohol (PVA) and human plaque particles of varying sizes. The PVA particles used (average mass; 5 mg) ranged in size between small (150–250 µm), medium (250–355 µm) and large (710–1000 µm) [10,12]. The human plaque consisted of 8–12 particles ranging from 500–1500 µm in size and weighing 6 mg [11,13]. The particles were injected into the system and the capture efficiency of each device calculated based on the particles missed by the device.

The first investigation tested the efficiency of GuardWire® (Medtronic, MN, USA), a distal occlusion device, and Angioguard, with and without aspiration techniques [10]. Overall Angioguard missed 0.80 mg (5.0%) of PVA particles of all sizes in the ICA injected without aspiration, compared with Guard-Wire, which missed 1.1 mg (7.0%). Angioguard missed the smallest mass of medium particles (0.24 mg vs GuardWire's 0.28 mg), followed by small (0.25 vs 0.37 mg) and large (0.31 vs 0.45 mg) particles in the ICA. There was a significant effect among the devices tested ($p < 0.001$) but no statistically significant effects between the mass of the captured particles and the device for the three particles sizes ($p = 0.259$). A subsequent study using PVA particles evaluated GuardWire Plus®, Angioguard, and three additional EPDs: FilterWire EX™ (predecessor to FilterWire EZ™, nitinol frame and polyurethane membrane; Boston Scientific, MA, USA), Neuroshield® (first-generation Emboshield®, nitinol frame and polyurethane membrane; Abbott Vascular, IL, USA), and Trap® (nitinol mesh; formerly Microvena, MN, USA) [12]. For all three sizes of PVA particles, Angioguard was second to Trap for the most missed PVA particles in the ICA (Angioguard: 8.03%, 1.21 mg; Trap: 8.2%, 1.24 mg). Angioguard missed the smallest mass of large particles (0.26 mg, 5.1%), followed by medium (0.41 mg, 8.1%) and small (0.56 mg, 11.3%) particles in the ICA [11,12]. Human plaque particles were also used to test Angioguard, FilterWire EX, Neuroshield and Trap [11,13]. Angioguard had the most missed human plaque particles in the ICA of the models tested (0.27 mg, 4.4%), which was significantly more than the other devices ($p < 0.001$). The reasons for the seeming discrepancy between the two studies are the slightly different subset of devices tested and that the common devices between the two studies all performed better in the human plaque particle study than in the PVA particle study. Note, however, when comparing Angioguard's performance using large PVA (710–1000 µm) and human plaque (500–1500 µm) particles, that although Angioguard's relative performance was different in the two studies (performing the best with large PVA particles and performing the worst with large human plaque particles), the absolute performance was very similar (missing 0.26 and 0.27 mg, respectively).

Order *et al.* investigated *in vitro* the effect tortuosity has upon the efficacy of EPDs [14]. The capture efficiency of Angioguard, FilterWire EX, Neuroshield and Trap was measured in normal, mildly tortuous and severely tortuous geometries with PVA particles. To simulate a mildly tortuous and severely tortuous geometry, a 6- and 7-cm curved silicone tube replaced the straight silicone for the ICA, respectively. Angioguard missed the most PVA particles in the ICA for all sizes in both the mildly tortuous (small: 1.19 mg, 23.71%; medium: 0.78 mg, 15.51%; large: 0.57 mg, 11.30%) and severely tortuous geometry (small: 1.47 mg, 29.71%; medium: 0.99 mg, 19.92%; large: 0.68 mg, 13.57%). Angioguard had a significantly greater percentage of particles missed for all particle sizes and all geometries ($p < 0.001$; except large particles comparing mild to severe: $p = 0.0059$). Hendriks investigated the effect the presence of a EPD has on the pressure gradient of a blood-mimicking solution flowing through a straight tube [15]. Angioguard RX had the largest pressure gradient (8.80 mmHg) compared with the other devices tested (FilterWire EZ, RX Accunet® (Abbott Vascular), Spider™ (ev3, MN, USA)). A significant correlation between the flow rate and pressure gradient was found ($r = -0.77$; $p < 0.01$).

Results from our laboratory

Performance assessment: *in vitro* testing

Finol and colleagues tested, *in vitro*, the capture efficiency of Angioguard XP, FilterWire EZ and RX Accunet in straight silicone tubes of varying inner diameter (5.0, 5.5 and 6.0 mm) [16,17]. The bench-top flow system circulated distilled water at 180 ml/min at 80 mmHg. Embolization was simulated by injection of blue-dyed polymer microspheres. Angioguard XP missed the most particles of all three devices for all three inner diameters (5.0 mm: 8.08%; 5.5 mm: 11.83%, 6.0 mm: 16.73%). The difference was significant ($p < 0.05$; except Angioguard XP and FilterWire EZ, 5.0 mm: $p = 0.051$). Siewiorek and others have tested *in vitro* the capture efficiency of Angioguard XP, FilterWire EZ, Emboshield, RX Accunet and Spider RX and its effect on the pressure gradient, flow rate and vascular resistance in the ICA [18]. A blood-mimicking solution of 36/64% glycerol/deionized water was circulated at a constant flow rate of 737 ml/min, representing the time-averaged mean peak velocity of the CCA. The mean CCA pressure was 95 mmHg. The carotid artery bifurcation was modeled by a silicone phantom having average human dimensions and a 70% symmetric ICA stenosis. Embolization was simulated by injection of 5 mg of dyed polymer microspheres having a nominal diameter of 200 μm , larger than the devices' pore size (Spider RX was tested with microspheres having a nominal diameter of 300 μm , due to a variable pore size of 70–200 μm). The pressure and flow rate at the common, internal and external carotid arteries were measured at initial, empty filter (device deployed) and full filter (device filled with microspheres) conditions. Of the five EPDs tested (Angioguard XP, FilterWire EZ, Emboshield, RX Accunet, Spider RX), Angioguard XP captured the fewest particles (missing 36.3%, significantly more than all other devices at $p < 0.05$ except Emboshield), yet had the greatest pressure gradient (an increase of 36.6%) in the ICA. Angioguard XP performed average for the flow rate in the ICA (decreasing 9.4%). It was only second to RX Accunet for the greatest vascular resistance increase in the ICA (+45.4 and +82.2%, respectively). It is worth noting that *in vitro* testing conducted by Siewiorek and Finol were on Angioguard XP, a more recent generation of the device, while testing conducted by Müller-Hülsbeck and Order were on the original Angioguard filter. All percentages are the values when the device is filled with emboli compared with preoperative flow conditions. Table 1 summarizes the results.

Design characteristics: pore size, porosity, pore density, length of basket & wall apposition

Several design characteristics affecting distal filter performance were evaluated by Siewiorek *et al.* [Siewiorek *et al.*, Unpublished Data]. Although the most important design characteristics of distal filters are not known, previous investigators have found that filters with larger pore sizes and composed of wire mesh (as with Spider RX) obstruct flow the least [18–20] and performed the best *in vitro* [18]. High resolution images of the Angioguard XP polyurethane membrane were obtained with the filter membrane removed from the nitinol struts and mounted on a microscope slide with deionized water. The pore size of Angioguard XP was verified by a projection taken with a Zeiss LSM 510 Meta laser confocal microscope through a 5 $\times$ Fluar[®] objective with a numerical aperture of 0.25 (Figure 2). An argon laser emitting light at 488 nm was used to create serial images through the thickness of the filter. These images were then collapsed into a single image through a maximum-intensity projection. Filter pore size measurements were made with software built in to the microscope interface. The quantification of pore size is only an approximation since the positioning of an individual pore was not precisely perpendicular to the objective.

An image of the entire surface of Angioguard XP was taken with a Microfire[®] Microscope Digital CCD camera mounted on an Olympus BX51 upright microscope through a 4× UplanFl objective with a numerical aperture of 0.13 (Figure 3). Mosaic images were acquired using an automated stage controlled with the software package Neurolucida[®] v5 (MicroBrightfield, Inc., VT, USA). The resulting pixel resolution was 1.83 μm/pixel. The polyurethane membrane autofluoresces under an excitation light of 488 nm. Finol and Siewiorek conjectured that the microspheres had to have passed between the filter basket and vessel wall, assuming that filters capture all debris that is larger than their pore size [17,18]. A photograph (Canon EOS Digital Rebel XT, Canon USA Inc., NY, USA) was taken of a device of size 6.0 deployed in a 5.5-mm ID vessel, an appropriate size for this vessel (6.0-sized devices are appropriate for vessels with 4.5–5.5 mm inner diameter). Any portion of the filter that is not flush against the wall was colored in red to illustrate incorrect wall apposition qualitatively (Figure 4). The wall apposition of each device was quantified by taking the ratio of the surface area of the device-wall gap and the total surface area of the vessel cross-section with ImageJ 1.38×. Angioguard XP had the greatest wall apposition gap of the devices studied (4.2%).

Porosity is defined as the ratio of the surface area of all pores to the total surface area of the filter basket. The latter was estimated by tracing the perimeter of the filter basket in the high-resolution image with ImageJ 1.38×. The surface area of the pores was calculated by counting the number of pores and knowing the diameter of the circular pores, as reported by the manufacturer (and verified by the confocal image; Figure 2). We have defined pore density as the ratio of the number of pores to the total surface area of the basket. Basket length was measured excluding portions of the nitinol struts not covered by the filter membrane. The work of Hendriks and Siewiorek has shown that Angioguard XP has a greater effect on the pressure and vascular resistance than other distal filters [15,18]. Of the devices evaluated (Angioguard XP, FilterWire EZ, Emboshield, RX AccUNET and Spider RX), Angioguard XP had a median number of pores. It had the smallest basket surface area and basket length. Angioguard XP may benefit from having more pores, a deeper basket and improving wall apposition. Table 2 summarizes the design characteristics for the five devices evaluated.

Performance assessment: *ex vivo* testing

Müller-Hülsbeck investigated the vessel wall damage incurred by the use of distal protection devices on *ex vivo* porcine carotid arteries [21]. The carotid arteries were inserted into a bench-top flow system and 0.9% saline solution was circulated at a constant flow rate of 470 ml/min, which is the estimated flow rate necessary to maintain sufficient blood supply during contralateral carotid artery occlusion, at a mean pressure of 91 mmHg. Angioguard, FilterWire EX, Neuroshield, Trap and Percusurge (distal occlusion device; currently Guardwire, Medtronic, Minneapolis, MN, USA) were deployed in the blood vessel and an adverse movement (1 cm up in cranial direction, 2 cm down, 1 cm up) was initiated. Vessel wall damage was evaluated histologically by light and scanning electron microscopes and the amount of debris generated was quantified. In all trials, Angioguard caused less than 50% partial endothelial damage, performing as well as FilterWire EX and better than the other devices tested. Angioguard generated significantly less debris during placement compared with the other devices except FilterWire EX ($p < 0.014$). Overall, it generated significantly less ($p < 0.001$) debris than the other devices (4.75 mg). However, Angioguard generated significantly more debris during device retrieval (2.06 mg) than during device placement and adverse movement (1.32 and 1.37 mg, respectively; $p < 0.05$). Note that the reported masses are not the mass of particles missed by the device tested; it is the mass of particles generated by contact of the device against the vessel wall, which is captured distal to the device, not in the device.

Performance assessment: clinical testing

The SAPPHERE trial is a multicenter randomized study comparing the efficacy of protected CAS (using Angioguard or Angioguard XP) and CEA [7]. In total, 334 subjects having coexisting conditions potentially increasing their risk for surgery and who were either symptomatic with at least 50% stenosis or asymptomatic with at least 80% stenosis were randomly assigned to the two procedures. The subjects were evaluated for death, stroke or MI within 30 days of the procedure and death and ipsilateral stroke between 31 days and 1 year after the procedure. The primary end point was a cumulative incidence of adverse events at 1 year postprocedure. The subjects who underwent protected CAS had a 12.2% incidence rate while CEA subjects had 20.1%. Within 30 days of the procedure, the rate was 4.4% among CAS patients and 9.9% among CEA patients in the pool of patients actually treated with respective procedures. The *in vitro* capture efficiency may have the most clinical correlation with stroke rate; the stroke rate in the actual treatment pool of patients SAPPHERE trial was a total of 5.8% (major ipsilateral: 0%; nonmajor ipsilateral: 0.6%; minor ipsilateral: 3.8%; minor nonipsilateral: 2.0%). The study indicated that protected CAS with a distal filter is not inferior to CEA ($p = 0.004$ for noninferiority; $p = 0.053$ for superiority).

The ACCULINK for Revascularization of Carotid in High-Risk Patients (ARCHeR) trial was a prospective, nonrandomized, multicenter trial that had three parts: unprotected (ARCHeR 1) and using RX Accunet both over the wire (ARCHeR 2) and rapid exchange (ARCHeR 3) [22]. The composite end point consisted of all deaths, strokes and MIs within 30 days, plus ipsilateral strokes up to 1 year. The composite end point was 8.3% for ARCHeR 1 versus 10.2% for ARCHeR 2. Although the study cannot make any conclusive statements about the advantage of using a distal filter, the 30-day composite end point was not significantly different for the three phases (7.6, 8.6 and 8.3%).

The Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH) trial was a prospective, multicenter study for patients undergoing protected CAS with FilterWire EX®/EZ™ [23]. The 30-day composite end point (all death, stroke and MI within 30 days of the procedure) for all patients was 5.8%. The Carotid Artery Revascularization Using the Boston Scientific FilterWire and the EndoTex NexStent (CABERNET) trial was a prospective, nonrandomized, multicenter study that used FilterWire EX®/EZ™ [24]. The composite 30-day end point of death, stroke and MI was 3.8%. It is worth noting that this trial had slightly different enrollment criteria than other registries; namely, plaque lesions longer than 30 mm were excluded and asymptomatic patients with 60% stenosis were included. The patients enrolled in this registry had less extensive disease and the surgeons had considerable experience with CAS [25].

The Carotid Revascularization with ev3 Arterial Technology Evolution (CREATE) pivotal trial was a prospective, multicenter study for high-risk patients treated by CAS protected with Spider RX [26]. The composite 30-day end point, which consisted of death, ipsilateral stroke, procedure-related contralateral stroke and MI, was 6.2%. The composite 30-day end point (death, stroke, MI) was 7.2% in the prospective, multicenter SECURITY trial, which studied the treatment of high-risk patients with Emboshield-protected CAS [27].

Roffi *et al.* retrospectively reviewed 115 protected CAS procedures and differentiated periprocedural flow conditions by filter (Angioguard, FilterWire EZ or Spider) [20]. Flow obstruction in ICA occurred more frequently with Angioguard (32.2%) than with FilterWire EZ (6.2%) or Spider (6.7%). No flow occurred in 13 procedures, all of them treated with Angioguard. Patients treated with the other two devices did not experience this event.

Much of the recent successful outcomes of CAS can be attributed to tremendous improvements in training and device development. Although solid level 1 evidence is lacking to support usage of an EPD for all CAS procedures, the overwhelming belief is that it is beneficial [28,29]. As bench testing has demonstrated, there exists a disparity between the theoretic and actual protection provided by currently available devices. This has been more thoroughly examined among the various distal filter devices, primarily because of their widespread use. Additionally, design modifications between particular devices naturally invite an attempt at a comparative analysis to determine the most effective system. Which category of EPD is more clinically efficacious is beyond the scope of this review, but suffice to say, the ideal EPD remains to be developed. Characteristics of an ideal device would be easy to use, complete capture of all released particulate debris, preservation of antegrade flow during the intervention, equally effective in straight and tortuous anatomy, and ability to achieve protection before crossing the target lesion.

Limitations of filter EPDs

While distal filter EPDs have been avidly accepted as a useful tool for CAS, three important unanswered questions remain:

- What is the ideal pore size?
- How effective is circumferential basket-vessel wall apposition in tortuous anatomy?
- How can capture efficiency be improved?

Currently, most filter devices have pore sizes of less than 200 μm . A clinical basis for this cutoff is data reported by Masuda *et al.*, in which the investigators showed that stroke victims had pathologic evidence of occluded arterioles ranging from 50 to 300 μm resulting in border-zone infarcts [30]. Additionally, two animal studies by Rapp *et al.* showed that small fragments (<100 μm) may cause late neuronal ischemia and that calcified fragments cause greater levels of infarction than fibrous plaques [31,32]. This also becomes relevant with regard to particulate debris that may escape around a poorly seated filter basket. As we have shown, basket-vessel wall apposition is not always complete particularly in tortuous arterial anatomy. Unfortunately, this is not necessarily evident at the time of the intervention and can lead the treating physician into a false sense of security, when in fact the EPD is not functioning as expected. The last item – capture efficiency – relates to the ability of a particular filter device to capture debris and the capacity of the basket while maintaining antegrade flow. Clinical evidence of exceeding capture capacity is an occluded or thrombosed filter basket. This can be altered by several mechanisms:

- Pore density
- Filter configuration (shape and length)
- Filter membrane composition

One of the other shortcomings of current filter elements is that embolic capture occurs in only one dimension, reducing capture efficiency. A newer design being evaluated in clinical trials, called Fibernet (Lumen Biomedical, MN, USA), uses a woven polytetrafluoroethylene filter membrane that captures particles in two dimensions and may enhance capture efficiency.

The aforementioned circumstances – pore size and wall apposition – lead to release of particulate debris in the cerebral circulation. Surprisingly, the clinical manifestations of distal embolization may be relatively minor or absent despite pathologic or radiographic evidence of ischemia (diffusion weighted [DW]-MRI) [33–35]. What remains to be seen is

the long-term sequelae of silent cerebral infarcts detected by DW-MRI. Some investigators have suggested silent infarcts may lead to diminished neurocognitive function, vascular dementia and Alzheimer's disease, while others have shown improvements in cognitive function after CAS [36–38]. In addition, it is necessary to establish a better correlation between *in vitro* testing and clinical outcomes. Although there is no known difference in complication rates between patients that do and do not exhibit periprocedural hemodynamic depression, defined as systolic blood pressure of lower than 90 mmHg and/or heart rate of over 50 beats/min, interventionists should be cautioned to decrease hemodynamic depression for patients with severely calcified plaque lesions [39].

Cost-effectiveness

Studies have found that protected CAS is associated with significantly higher total and direct costs than CEA due to the use of stents, embolic protection devices, catheters and other devices used during stenting [40–43]. Park *et al.* found that the clinical outcomes of protected CAS were equivalent to those found in the SAPHIRE trial, but was associated with significantly higher total procedural costs (\$17,402 vs \$12,112; $p = 0.029$) [42]. A portion of the higher cost of protected CAS is due to the difference in surgical supplies versus angiography suite supplies such as stents, embolic protection devices and other catheters (\$1953 vs \$15,407; $p = 0.001$). Another study found the central supply costs of CAS, consisting of stents, catheters, guiding sheaths, balloons, inflating devices, an arterial closure device and an embolic protection device, to be significantly more than CEA (\$4548 vs \$338; $p < 0.001$) [43]. Arrebola-Lopez *et al.* found that the average cost of CAS was greater than CEA (3963 vs 5158, respectively) and that CEA had a greater cost:benefit ratio [40]. In addition, the survival of patients post-procedure, calculated as quality-adjusted life years, was fewer for CAS than CEA (8.20 vs 8.36 years, respectively) and the lifetime cost for CAS was greater than CEA (\$35,789 vs \$28,772, respectively) [41]. The decreased procedural times and hospital time associated with CAS is not enough to offset the cost of stents and embolic protection devices. In order for the two procedures to be equally cost effective, the major stroke and mortality rate of CAS must approach that of CEA.

Application of technology

Although there are no randomized clinical studies comparing protected and unprotected CAS, the use of embolic protection devices for CAS is considered by some to be the standard of care [3,4]. Furthermore, it is unlikely that these clinical trials will be pursued [2]. Angioguard XP Embolic Protection System, for use with Cordis Endovascular's Precise RX Nitinol Self-Expanding Stent, was approved by the FDA for CAS interventions in September of 2006.

Conclusion

Complications resulting from or during CAS have been reduced by the use of embolic protection devices such as Angioguard XP. Based on our own bench-top testing, we find Angioguard XP to have undesirable performance measures when compared with other EPDs under *in vitro* conditions mimicking *in vivo* carotid flow. In the literature, Angioguard has had mixed results in *in vitro* tests. Future generations of filter EPDs should be designed to minimize the vascular resistance in the ICA once they are deployed. Pore size, porous surface area, basket length and wall apposition have been observed experimentally as the most important design characteristics influencing EPD performance *in vitro*. Further testing and design modifications are necessary to improve the performance of current EPDs and to correlate design parameters with peri- and post-procedural outcomes in CAS.

Expert commentary

Carotid artery stenting is an exciting, evolving field for the treatment of extracranial carotid artery disease and stroke prevention. Improvements in training and devices appear to have led to better clinical outcomes. While the exact role of CAS is assessed through prospective, randomized clinical trials, further advances to diminish distal cerebral embolization are needed. The Angioguard device, along with other distal filter elements, may be beneficial, yet they lack the sophistication required for more complex anatomy and plaque morphology. More stringent bench testing to address the shortcomings of current devices is necessary to enhance current technology particularly with regards to pore size, wall apposition and capture efficiency.

Five-year view

Medical therapy will remain the mainstay for stroke prevention; however, CAS and CEA will continue to be necessary in certain patient cohorts. The role of these complimentary procedures will become more clearly defined with CAS likely to be reserved for high-risk surgical candidates (i.e., recurrent carotid stenosis, prior neck irradiation, contralateral recurrent laryngeal nerve palsy or severe cardiopulmonary disease) and CEA advocated for standard-risk patients. Newer EPDs will become available that allow for capture of all particulate debris to reduce the short- and long-term sequelae of distal cerebral embolization.

Key issues

- Endovascular management of cardiovascular disease is becoming a more popular treatment option.
- The use of embolic protection devices (EPDs) such as Angioguard™ XP during carotid artery stenting (CAS) may reduce the risk of periprocedural complications.
- There are three main types of EPDs: distal filter devices, distal balloon occlusion devices and proximal balloon occlusion devices.
- Angioguard XP, like other distal filter devices, has the advantage of preserving antegrade flow during CAS.
- The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial indicates that protected CAS is not inferior to carotid endarterectomy (CEA).
- *In vitro* testing with the Angioguard device reveals mixed results at best. Finol *et al.* indicate that Angioguard XP does not capture 100% of embolized plaque (up to 36.3% missed) and has significant effects on the pressure drop (36.6% increase), flow rate (9.4% decrease) and vascular resistance (45.4% increase) in the internal carotid artery when compared with the predeployment flow conditions. These are below-average performance measures when compared with the other EPDs currently available in the market.
- The ideal EPD is easy to use, captures all embolized plaque, preserves antegrade flow during the intervention, is equally effective in straight and tortuous anatomy, and achieves protection before crossing the target lesion.
- The ideal pore size, improved wall apposition in tortuous vessels and improved capture efficiency are three main areas of improvement for EPDs.

- Capture efficiency can be improved by the alteration of pore density, filter shape and length and filter membrane composition.
- In the future CAS and CEA will likely coexist as potential patient treatments for cerebrovascular disease.

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• of interest

•• of considerable interest

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Figure 1.
The Angioguard™ XP embolic protection device.

Figure 2. Confocal image projection of the Angioguard™ XP filtering membrane verifying the pore size reported by the manufacturer (100 μm)
Figure originally published by Finol *et al.* [17].

Figure 3. High-resolution image of the Angioguard™ XP basket removed from its nitinol frame and mounted on a microscope slide
Reproduced from data by Finol *et al.* [17].

Figure 4. Angioguard™ XP size 6.0, an appropriate size for the vessel, shown in the coronal plane of a 5.5 mm inner diameter silicone tube

Gaps between the device basket and the vessel wall are shown in red.

Figure originally published by Finol *et al.* [17].

Table 1

Features of the internal carotid artery for five devices filled with emboli.

	Angioguard XP	FilterWire EZ	Emboshield	RX Accunet	Spider RX
Capture efficiency (%)	63.7%	96.1%	64.6%	95.1%	99.9%
Pressure gradient (mmHg)	106.8 (+36.6%)	86.8 (+11.0%)	92.5 (+18.3%)	97.2 (+24.3%)	81.5 (+4.2%)
Flow rate proportion (%)	37.4 (−9.4%)	38.6 (−3.5%)	36.7 (−13.0%)	35.3 (−11.5%)	40.1 (−2.0%)
Vascular resistance * (mmHg/l·min ^{−1})	375 (+45.4%)	301 (+16.7%)	347 (+35.4%)	470 (+82.2%)	272 (+5.4%)

* Vascular resistance is defined by $R = (P_{CCA} - P_{ICA})/Q_{ICA}$ and it is calculated at 258 mmHg/l·min^{−1} for preoperative *in vitro* flow conditions. Parentheses show the percentage change in the internal carotid artery with respect to these conditions.

Reproduced from data reported by Siewiorek *et al.* [18].

Table 2

Design characteristics of embolic protection devices.

Design characteristic	Angioguard XP	FilterWire EZ	Emboshield	RX AccUNET	Spider RX
Pore size (µm)	100	110	140	115	70–200
Number of pores	1100	2576	400	912	1563
Porous surface area (mm ²)	8.64	24.5	6.16	9.47	78.8
Basket surface area (mm ²)	76.5	190	282	208	157
Porosity (%)	11.3	12.9	2.2	4.5	50.4
Pore density (pores/mm ²)	14.4	13.6	1.4	4.4	10.0
Basket length [*] (mm)	5.90	13.4	17.2	15.1	17.3
Wall apposition [‡] (%)	4.2	0.65	0	0.075	0.49

^{*} Basket length excludes any metal struts not covered by the polyurethane membrane.

[‡] Wall apposition represented by a gap between the device and the arterial wall, expressed as a percentage of vessel cross-sectional area at the site of device deployment.

Reproduced from data reported by Finol and Siewiorek [17; Siewiorek *et al.*, Unpublished data].