Proximal Protection Devices and Flow Reversal for Embolic Protection

By John M. Weber, MD, and Daniel G. Clair, MD
From the Cleveland Clinic Foundation, Cleveland, Ohio.

ABSTRACT: Carotid artery disease leading to stroke is one the primary causes of serious long-term disability in the United States today. Carotid artery stenting (CAS) has proven to be a reasonable alternative to carotid endarterectomy in patients who are felt to be at high risk for endarterectomy. Appropriate indications for CAS include patients with both high physiologic and anatomic risk for the standard therapy of carotid endarterectomy. It is this patient population that has caused the dramatic upsurge in new technologies and techniques to reduce perioperative stroke rates. A good deal of that effort has been focused on embolic protection devices (EPD). The body of literature supporting the use of proximal embolic protection continues to grow. Also, as is the case with other means of embolic protection, the rate of periprocedural cerebrovascular events continues to decline over time as surgeons and interventionalists become more experienced performing CAS with proximal protection and flow reversal. Current data are supportive of the use of proximal protection devices. However, all of the data are from single-arm registry studies. Head-to-head studies comparing proximal protection devices vs distal embolic protection devices are still warranted.

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C aristinal artery disease leading to stroke is one of the primary causes of serious long-term disability in the United States today. Currently, carotid endarterectomy (CEA) is the gold standard to reduce the risk of stroke in both symptomatic and asymptomatic patients. This has been borne out in large, multicenter, prospective, randomized controlled trials. For symptomatic patients, the North American Symptomatic Endarterectomy Trial (NASCET) and the European Carotid Study Trial (ECST) demonstrated a significant risk reduction in the incidence of stroke in patients undergoing CEA compared to maximal medical therapy alone.1,2 In the case of asymptomatic patients, the investigators for the Asymptomatic Carotid Atherosclerosis Study (ACAS) were able to show that in patients where there was a 60% or greater stenosis, CEA provided significant risk reduction from ipsilateral stroke compared to those patients who were receiving best medical management of their carotid artery disease.3

More recently with the increase in expertise and technologic advancement in endovascular therapies, there has been a push to demonstrate CAS as a reasonable alternative to CEA in patients deemed to be higher risk for open surgery. In 2004, the results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Study (SAPPHIRE) were published, which demonstrated very favorable results for CAS vs CEA. Their data for composite endpoints of death, stroke, or myocardial infarction at 30 days and ipsilateral stroke at 1 year were dramatically lower for CAS vs CEA (12.2% vs 20.1%, P=.05).4 However, more recent studies comparing CAS to CEA have failed to demonstrate the same benefit and actually illustrate a higher risk for neurologic events in patients undergoing CAS.

Arguably the most important study to date comparing CEA with CAS is the Carotid Revascularization versus Stent Trial (CREST). CREST was a very large multicenter study, which randomized 2,502 patients to either CEA or CAS. The primary composite endpoints of stroke, myocardial infarction, or death showed no significant difference between CEA and CAS (6.8% vs 7.2%, P=.051, respectively). Further analysis
of the individual endpoints however revealed that while CAS patients were less likely to experience MI (1.1% vs 2.3%, \(P=0.02\)), this benefit was offset by a peri-procedural stroke rate of 4.1% vs 2.3%, \(P=0.01\), when compared with CEA.5

More recently, two large European trials have also failed to demonstrate CAS noninferiority when compared to CEA. The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was ended early for patient safety secondary to higher 30-day stroke or death compared to CEA (9.6% vs 3.9%), leading to a relative risk of any stroke or death after stenting as compared with endarterectomy of 2.5.6 The Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial also failed to demonstrate noninferiority of CAS when compared to CEA. Its composite rate of primary endpoints of ipsilateral stroke or death within 30-days were 6.84% vs 6.34%, respectively.7 For now, the evidence is clear that CEA is superior to CAS at reducing the risk for stroke in patients that are asymptomatic, and evidence suggests that asymptomatic patients may benefit from CEA as well.8

There are appropriate indications for CAS, such as in patients with previous radical neck dissection, radiation therapy, or high carotid bifurcations, so called “anatomic” high-risk patients.9,10 It is this patient population that has caused the dramatic upsurge in new technologies and techniques to improve perioperative stroke rates. A good deal of that effort has been focused on embolic protection devices (EPD).

Currently there are three categories of EPD. These are distal occlusion devices, distal embolic protection devices with flow preservation (filters), and proximal protection devices, which includes flow reversal systems. These different methods of providing embolic protection, while ultimately sharing the same desired effect, have their own intrinsic risks and benefits.

At this time there is only one FDA-approved distal occlusion device available in the United States. The GuardWire Temporary Occlusion and Aspiration System (Medtronic) uses a compliant balloon affixed to a hollow-bore wire. Once the guide wire crosses the lesion, the balloon is taken up past the lesion over the wire and inflated to induce circulatory arrest through the ipsilateral internal carotid artery (ICA). Subsequently the angioplasty balloon and stent are taken up over the hollow-bore wire of the distal occlusion balloon. After the stent is deployed, an aspiration catheter is then taken up over the hollow-bore wire and any debris from the procedure is suctioned out of the internal carotid artery.

The shortcomings of this system are the lesion must be crossed with the wire and device prior to any protection being achieved, care must be taken not to injure the distal vessel by over inflating the occlusion balloon, and a significant portion of patients will not be able to tolerate the ipsilateral circulatory arrest. In addition, embolic debris could still reach the brain if it is not adequately aspirated from the flow channel at the completion of the procedure and prior to the removal of the balloon.11 Finally, imaging of the lesion to be treated is difficult because contrast cannot flow into the internal carotid artery. For these reasons distal occlusion devices are not as commonly used as the other embolic protection devices.

Filters, distal embolic protection devices with flow preservation, represent the largest group of embolic protection devices. While deployed, they allow for continuous uninterrupted antegrade flow. This is beneficial for the patient with incomplete Circle of Willis, contralateral occlusions, or poor perfusion pressures from posterior circulation collaterals. It also has the benefit of allowing for intraprocedural cerebral angiograms. However, no cerebral protection is offered until after the lesion is crossed with both the wire and the filter device. In the situation where a critical stenosis is present, predilation may be required prior to crossing the lesion and deploying the device. In addition, in some instances the filter can become so clogged with debris during the procedure that antegrade flow can be impaired or completely obstructed, and risk spillage of collected emboli during retrieval of the device.12,13 Finally, all of these devices mandate that at least some embolic debris will pass through the filter. Varied devices have differing sizes of embolic particles they allow and reported pore sizes have been noted to vary anywhere from 40 microns to 200 microns. Notwithstanding the above limitations, this group continues to be very popular with interventionalists due to ease of use and device familiarity.

The final group of EPD are the proximal occlusive protection systems. Currently there are only two devices approved for use in the United States. The Mo.Ma system (Medtronic) and the GORE Flow Reversal System are commercially available and each provide embolic protection by stopping...
or reversing blood flow by functionally “clamping” the common and external carotid arteries. The Mo.Ma system is employed by placing a stiff wire into the external carotid artery, then an 8 Fr introducer sheath is advanced into the common carotid artery (CCA). The sheath has an external carotid artery balloon, which allows occlusion of vessels 3 mm to 6 mm in diameter, and a common carotid artery balloon, which can occlude vessels 5 mm to 13 mm in diameter. Once both of the balloons are deployed, antegrade ICA blood flow is arrested. Through the working channel of the device, almost any desired guidewire and stent may be deployed. Periodic manual aspiration, via the working port, also allows for flow reversal and the removal of embolic debris. These devices allow initiation of cerebral protection prior to crossing the lesion provided the lesion is beyond the origin of the external carotid artery.13-15

The Gore Flow Reversal System shares the same fundamental design concept as the Mo.Ma system, insomuch as there are occlusive balloons used to achieve control of the common and external carotid artery. However, the Gore device allows for both passive and active reversal of blood flow through a filtration system connected to a sheath draining into the venous system. Because the pressure of the venous sheath is low enough to allow reverse flow through the arterial sheath, flow reversal occurs within the system without the need of intermittent aspiration by the operator via the working port. The GORE system is made up of three integral components. The first is a balloon sheath. The 9.5 Fr sheath is positioned in the ipsilateral common carotid artery where its integrated compliant balloon is deployed. Balloon sizes can accommodate arterial diameters of 6 mm to 12 mm. The second component is a balloon wire. This external carotid balloon wire is advanced up the separate port of the balloon sheath and placed into the proximal external carotid artery. The balloon can accommodate arterial diameters up to 6 mm. The final component is the filter system, which is outside of the patient. After balloon occlusion of the common and external carotid arteries, retrograde flow reversal occurs and is channeled back through the balloon sheath. It then passes through the filter, outside of the patient, and back into the patient via a 6 Fr venous sheath in the femoral vein.16-18 There have been two studies evaluating the safety and efficacy of the Mo.Ma device. Stabile et al conducted a prospective single-center registry of 1,300 consecutive patients who underwent CAS with the Mo.Ma device. Their data demonstrated a 30-day stroke and death rate of 1.4%. Symptomatic patients were at higher risk than asymptomatic patients, 3% vs 0.8% respectively. Also, high surgical risk patients were at higher risk than average surgical risk patients, 1.9% vs 1.1% respectively. Of note, in contrast to other categories of EPID, there was no difference in risk for patients greater than 80 years of age when compared to younger patients. Independent predictors of adverse outcome were lack of operator experience in CAS, symptomatic lesions, and the lack of clinically significant hypertension.19 The ARMOUR trial was an FDA approved prospective, multicenter registry evaluating the Mo.Ma device in high-risk, surgical patients. Two hundred twenty two patients, 15% of whom were symptomatic were enrolled in this nonrandomized trial. Of these patients, 29% were greater than 80 years of age. There were several exclusion criteria, but of particular significance, patients with a greater than 70% contralateral occlusion were excluded. In this study 13.8% of patients demonstrated some intolerance, however device deployment was successful 98.2% of the time. Importantly, as has been seen with other proximal protection studies, there was no difference in 30-day stroke, death, and MI rates between symptomatic and asymptomatic patients; the composite rate being 2.7%. Also, the 30-day stroke rate was an impressive 0.9%. The authors concluded that the Mo.Ma device is both safe and effective for use in high-risk surgical patients who need to undergo CAS.20

The EMPiRE trial evaluated the Gore Flow Reversal System. This prospective, multicenter registry enrolled 245 high-risk surgical patients. Of these, 32% were symptomatic and 16% were greater than 80 years of age. When compared to the ARMOUR study, it is important to note that critical stenosis and even occlusion of the contralateral ICA were not used as exclusion criteria, and 10.5% of patients had a total contralateral ICA occlusion. The rate of stroke, death, myocardial infarction, or transient ischemic attack within 30 days was 4.5%. The stroke and death rate was 2.9%, and no patient had a major ischemic stroke. Intolerance to flow reversal was noted in 2.4% of patients, however the device was successfully deployed in 99.2% of the patients. The stroke and death rates in the symptomatic, asymptomatic, and octogenarian subgroups were 2.6%, 3%, and 2.6% respectively.21
As with the Mo.Ma device, the authors concluded the Gore Flow Reversal System is a safe and effective means of providing embolic protection for patients undergoing CAS, and due to the study design the authors felt they were able to show the device can also be safely used in patients with contralateral ICA occlusions. The findings of this trial have been confirmed in a similarly designed registry more recently reported. These authors performed carotid stenting on 122 patients at varied levels of risk, nearly 30% of whom were symptomatic. The technical success rate of protection device deployment and use was 97.5%, with 2 patients requiring addition of a distal filter protection device because of intolerance to flow reversal. The 30-day MAE rate, including death, stroke, and MI was 1.6% for the group and importantly, there were no events in the symptomatic cohort.22

The Michi Neuroprotection System (Silk Road Medical) is another flow reversal system utilizing proximal vessel occlusion associated with a filtration system connected to the femoral venous system allowing flow reversal. While it is conceptually very similar to the Mo.Ma and GORE devices, it is fundamentally different in that it gains access to the CCA directly via a small supraclavicular incision. Antegrade stasis is achieved via surgical control of the CCA just proximal to the insertion of the 10 Fr working sheath. Flow reversal is then achieved, both through the ipsilateral ICA and ECA by establishing a circuit between the arterial working sheath and femoral venous access. This system does not require balloon occlusion of the ipsilateral ECA, because the short length and increased diameter of the sheath allow very rapid retrograde flow, which overcomes the pressure that can be generated in the external carotid artery. Also, flow can be manipulated by use of the handheld controller with options for high flow, low flow, or no flow through the arterial-venous circuit. The theoretical benefit of this design is that it obviates the need for any manipulation within the aortic arch, however it is currently a hybrid procedure requiring open surgical technique for proximal carotid artery exposure.

The PROOF study was a first-in-man, multicenter, single-armed German registry to establish safety and feasibility of the Michi device. There were a total of 44 subjects enrolled into the study with the primary composite endpoints being major stroke, myocardial infarction, or death within 30 days. Only one patient was lost to follow-up. All of the enrolled patients were successfully treated, and there were no major adverse events during the 30-day follow-up period. In this group of 44 patients, a subgroup of 31 consecutive subjects had DW-MRI examinations performed prior to the procedure and within 1 to 2 days after their procedure.

Independent neuroradiologists performed blinded evaluations of each of the DW-MRI studies and confirmed the presence or absence of any stroke-related lesions. Five of these patients (16%) had evidence of new ischemic brain lesions but no clinically significant neurologic events. As with the Mo.Ma and GORE devices, transient intolerance to reverse flow was observed. This occurred in 9% of cases, but in all cases the intolerance was managed by flow limitation in the system, and a stent was successfully placed using this protection system. Intolerance to the procedure was managed by lessening the duration of flow reversal during the procedure.23 Currently the ROADSTER study is enrolling patients in the United States to establish safety and efficacy of the Silk Road Michi device. Their goal is to enroll approximately 200 patients across 14 centers and conclude by the end of 2014.24

Conceptually one can reason that proximal embolic protection devices are more effective than distal protection devices for several reasons. As stated earlier, when using a distal protection device both the wire and the device, i.e. filter, must traverse the lesion prior to any protection being deployed, while proximal protection systems allow the protection to be initiated prior to lesion manipulation. Also, particularly with regard to distal protection systems, some lesions may be so tight as to require predilatation with a balloon prior to deployment of the filter. When using a proximal occlusion device, any manipulation of the culprit lesion only occurs after neuroprotection is established. In addition, proximal EPD have been shown to capture embolic debris very efficiently in ex vivo assessments,25 and were better when directly compared with filter devices.26

Currently, two widely used noninvasive techniques that offer the ability to measure for surrogate markers of atheroembolism are diffusion-weighted imaging (DWI) on MRI scan and transcranial Doppler (TCD). Bijuklic et al were able to demonstrate that when compared with filter protection, proximal balloon occlusion resulted in a significant reduction in the incidence of new cerebral ischemic lesions...
as recorded by DWI (45.2% vs 87.1%, P=.001).27 TCD measures cerebral microembolic signals (MES), and Montorsi et al showed that when compared with use of the FilterWire EZ (Boston Scientific), Mo.Ma significantly reduced mean MES counts during lesion crossing, stent crossing, stent deployment, stent dilation, and total MES (93 vs 16). These authors also included DWI MR postprocedurally to give a combination evaluation from both TCD and DWI. While more patients were noted to have new lesions on DWI with filter protection, the difference did not reach statistical significance, with new lesions in a minority of the Mo.Ma group (2 of 14, 14%) as compared with the FilterWire EZ group (9 of 21, 42.8%).28 Although both of these studies were small, taken together they are strong evidence that there is a greater embolic load to the brain when using distal embolic protection as compared to proximal occlusion devices.

A recently published meta-analysis by Bersin et al further demonstrates the safety and effectiveness of proximal embolic protection devices. They sought, and were granted, access to draw data from all available prospective multicenter studies assessing 30-day outcomes of patients in whom a proximal occlusive device was used during CAS. Thus, their analysis included 2,397 patients from 6 independent databases. The primary endpoint was the composite of total stroke, myocardial infarction, and death at 30 days. The incidence of stroke was 1.71%, while it was a much lower 0.02% for MI, and 0.40% for death. The composite primary endpoint at 30 days was 2.25%, with age and diabetic status as the only significant independent risk predictors. Also, total stroke rates were very impressive, below 2.6%, in all subgroups, including symptomatic octogenarians. There was no evidence to suggest patient demographic variables such as patient gender, symptomatic status, and contralateral carotid occlusions as independent risk predictors.29

The body of literature supporting the use of proximal embolic protection continues to grow. Also, as is the case with other means of embolic protection, the rate of periprocedural cerebrovascular events continues to decline over time as surgeons and interventionists become more experienced performing CAS with proximal protection and flow-reversal.

Although the above data support the use of proximal protection devices, more studies are needed. All of the data are from single-arm registry studies, and the head-to-head studies comparing proximal protection device vs distal embolic protection devices were small and used surrogate end points. A large multicenter randomized controlled trial comparing proximal protection devices to distal embolic protections devices with end points of stroke, MI, and death would be very helpful in determining the optimal EPD for our patients.

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Address for correspondence: John M. Weber, MD, Cleveland Clinic Foundation, Vascular Surgery, 9500 Euclid Avenue, Suite H32, Cleveland, Ohio 44195, United States. Email: weberj3@ccf.org

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