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## Transcervical access, reversal of flow and mesh-covered stents: New options in the armamentarium of carotid artery stenting

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### Abstract

In the last 25 years, the very existence of carotid artery stenting (CAS) has been threatened on a number of occasions. The initial disappointing results that even lead to the discontinuation of an early randomized controlled trial have improved considerably with time. Novel devices, advanced stent and equipment technology, alternative types of access and several types of filters/emboli protecting devices have been reported to reduce stroke/death rates during/after CAS and improve CAS outcomes. The present review will provide a description of the various technology advances in the field that aim to reduce stroke and death rates associated with CAS. Transcervical access, reversal of flow and mesh-covered stents are currently the most promising tools in the armamentarium of CAS.

**Key words:** Carotid artery stenting; Stroke; Carotid artery stenosis; Filters

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**Core tip:** Carotid artery stenting (CAS) has improved considerably in the last few years. This comprehensive review provides the various technology advances in the field that aim to reduce stroke and death rates after CAS. These include transcervical access, reversal of flow and mesh-covered stents.

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## INTRODUCTION

During its evolution, carotid artery stenting (CAS) has often gone through some difficult times. One of the first randomized controlled trials comparing CAS with carotid endarterectomy (CEA), the Leicester trial, had to be stopped prematurely after randomizing less than 20 patients<sup>[1]</sup>. All 10 patients that were randomized to CEA proceeded without complications. On the other hand, 5 of the 7 patients who were randomized to CAS suffered a stroke ( $P = 0.0034$ ), three of which were disabling at 30 d<sup>[1]</sup>.

Fortunately, CAS outcomes have improved considerably since then and continue to improve constantly. Technological advances such as proximal/distal embolic protection devices (EPDs), flow reversal, transcervical/transradial access and double layer mesh stent technology are adjuncts that have been developed to improve CAS outcomes. The current article presents an overview of these technological advances.

## EPDS

Proximal and distal EPDs are commonly utilized with CAS with the aim of preventing atherosclerotic debris from embolizing to the brain. Catheter manipulation within the aorta and supra-aortic arteries causes plaque embolization. Up to 90% of CAS procedures can be complicated by embolic events and EPDs may capture these embolized particles<sup>[2]</sup>. Although some studies report good outcomes for various distal EPDs (also known as filtering devices)<sup>[3-5]</sup>, others studies argue that distal filters may not be able to prevent all perioperative emboli<sup>[6-9]</sup>. The pore size of most available filter devices is  $> 80 \mu\text{m}$ <sup>[3]</sup>, but many emboli are  $< 80 \mu\text{m}$  in size<sup>[10,11]</sup>. Furthermore, due to the rigidity of many filter devices and a required minimal distal landing zone depending on the length of the basket of the filter device, the vessel wall apposition may not be optimal (especially in tortuous vessel segments) and could therefore allow cerebral embolization<sup>[12]</sup>. These studies have supported that, compared with distal EPDs, proximal EPDs reduce the perioperative microembolic signals detected by transcranial Doppler and the number of new ischemic lesions<sup>[6-9]</sup>.

A study from Milan, Italy compared the rate of cerebral microembolization during CAS with a proximal EPD [Mo.Ma system (Invatec, Roncadelle, Brescia, Italy);  $n = 26$ ] vs distal protection with a filter [FilterWire EZ (Boston Scientific Corporation, Santa Clara, California);  $n = 27$ ] in patients with high-risk, lipid-rich plaques<sup>[7]</sup>. Compared with use of the FilterWire EZ, the Mo.Ma system significantly reduced mean microembolic signal counts during lesion crossing (mean: 18 vs 2, respectively;  $P < 0.0001$ ), stent crossing (mean: 23 vs 0, respectively;  $P < 0.0001$ ), stent deployment (mean: 30 vs 0, respectively;  $P < 0.0001$ ), stent dilation (mean: 16 vs 0, respectively;  $P < 0.0001$ ) and total microembolic signals (mean: 93 vs 16, respectively;  $P$

$< 0.0001$ )<sup>[7]</sup>.

The Mo.Ma proximal EPD is a safe and effective neuro-protection system during CAS that achieves very low periprocedural stroke rates. A registry of 1300 patients undergoing CAS using the Mo.Ma device reported very low major adverse cardiac or cerebrovascular events including 5 deaths (0.38%), 6 major strokes (0.46%), 5 minor strokes (0.38%) and 0 myocardial infarctions (MIs)<sup>[13]</sup>. The incidence of postprocedural events did not increase even in the presence of theoretical anatomical contraindications to proximal endovascular occlusion (e.g., contralateral carotid occlusion). The excellent results reported for the Mo.Ma device suggest that it is a promising technique for the achievement of low stroke rates after CAS.

A prospective randomized study, the Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting study, compared the embolic load of filter-protected ( $n = 31$ ) vs proximal balloon-protected CAS ( $n = 31$ )<sup>[9]</sup>. Proximal balloon occlusion lead to a considerable reduction in the percentage of new cerebral ischemic lesions (45.2% vs 87.1%, for proximal balloon occlusion vs filter protection, respectively;  $P = 0.001$ ). Proximal balloon occlusion reduced both the number [median (range): 2 (0-13) vs 0 (0-4);  $P = 0.0001$ ] and the volume [ $0.47$  (0-2.4)  $\text{cm}^3$  vs 0 (0-0.84)  $\text{cm}^3$ ;  $P = 0.0001$ ] of new cerebral ischemic lesions. Furthermore, contralateral hemisphere lesions were detected in 29.0% vs 6.5% of patients receiving a filter vs balloon occlusion, respectively ( $P = 0.047$ ). Finally, the 30-d major adverse cardiovascular and cerebral events rate was 3.2% for filter protection vs 0% for balloon occlusion, respectively ( $P = \text{not significant}$ )<sup>[9]</sup>.

A meta-analysis ( $n = 8$  studies; 357 patients) evaluated and compared the results of filter cerebral protection vs proximal balloon occlusion in preventing embolization during CAS as evaluated by diffusion-weighted magnetic resonance imaging (DW-MRI)<sup>[14]</sup>. The incidence of new ischemic lesions after CAS/patient detected by DW-MRI (effect size: -0.43; 95%CI: -0.84 to -0.02;  $I^2 = 70.08$ ;  $Q = 23.40$ ) and the incidence of contralateral site lesions (effect size: -0.50; 95%CI: -0.72 to -0.27;  $I^2 = 0.00$ ;  $Q = 3.80$ ) were both significantly lower in the proximal balloon occlusion group<sup>[14]</sup>. The results of this meta-analysis support the superiority of proximal balloon occlusion as compared with filter cerebral protection with respect to the degree of CAS-related brain embolization<sup>[14]</sup>.

Others, however, have supported that proximal EPDs have similar results with distal filter EPD<sup>[15]</sup>. The lack of difference in proximal occlusion vs distal filter EPD results was also verified in a meta-analysis<sup>[16]</sup>. This meta-analysis included 7 studies ( $n = 392$  patients; 193 with proximal occlusion; 199 with distal filters). The use of proximal occlusion vs distal filter did not reduce the risk of new cerebral lesions (OR = 0.65; 95%CI: 0.28-1.52;  $P = 0.32$ ) or the risk of death/cerebrovascular event (OR = 0.59; 95%CI: 0.22-1.60;  $P = 0.30$ )<sup>[16]</sup>. A more

recent meta-analysis verified the equipoise in clinical outcomes between proximal balloon occlusion and distal filter protection<sup>[17]</sup>. This meta-analysis ( $n = 18$  studies; 12281 patients) did not demonstrate any significant difference between the two modalities in terms of the risk of stroke or mortality, nor was there any difference in the incidence of new cerebral lesions on DW-MRI or contralateral DW-MRI lesions. The conclusion reached was that both proximal and distal EPDs provide similar levels of protection from periprocedural stroke and 30-d mortality<sup>[17]</sup>. Finally, a national cardiovascular data registry analysis from the United States compared stroke/death rates between proximal EPDs and distal filter EPDs in 10,246 consecutive elective CAS procedures. Both EPDs were associated with similar 30-d adverse event rates (2.7% vs 4.0%, after proximal vs distal filter EPDs, respectively;  $P = 0.22$ )<sup>[18]</sup>.

## TRANSCERVICAL ACCESS WITH FLOW-REVERSAL

The first description of flow reversal as a cerebral protection device was in 2000<sup>[19]</sup>. Although initially CAS with flow reversal was performed *via* the transfemoral approach<sup>[19]</sup>, a subsequent modification was the use of transcervical approach for CAS with flow reversal<sup>[20]</sup>. This technique is described in detail elsewhere<sup>[20]</sup>. Several independent studies have published very low 30-d stroke/death/MI rates and low incidence of complications for transcervical CAS with flow reversal<sup>[21-25]</sup>. It was recently demonstrated that transcervical CAS with flow reversal demonstrates embolization rates comparable with CEA<sup>[26]</sup>. Transcervical CAS with flow reversal thus seems a promising method for the reduction of strokes associated with CAS<sup>[27]</sup>.

Elderly patients ( $> 70$  years) have inferior outcomes with transfemoral CAS compared with CEA<sup>[28]</sup>. The poor outcome of transfemoral CAS in this age group may be explained by the anatomic characteristics of the aortic trunk and supra-aortic vessels as well as by a high prevalence of aortic arch atheromatosis<sup>[21]</sup>. Transcervical CAS with flow reversal for cerebral protection avoids these unfavorable characteristics. An early study reported a 2.2% 30-d combined stroke/death/MI rates in 219 patients  $> 70$  years of age (55.7% asymptomatic; 44.3% symptomatic)<sup>[21]</sup>. Symptomatic patients had a 5.1% combined stroke/death/MI rates whereas asymptomatic patients had a 0% rate<sup>[21]</sup>. Thus, transcervical CAS with flow reversal may be the preferred option for this age group.

Not long ago, the Reverse Flow Used During CAS Procedure (ROADSTER) multicenter trial reported its results from the evaluation of the safety and efficacy of the ENROUTE Transcarotid NPS (Silk Road Medical Inc, Sunnyvale, Calif), a novel transcarotid neuroprotection system that provides direct surgical common carotid access and cerebral embolic protection *via* high-rate flow reversal during CAS<sup>[29]</sup>. This study reported an

overall stroke rate of 1.4%, which is the lowest reported for any prospective multicenter clinical trial of CAS. The stroke/death rates (2.8%) and the stroke/death/MI rates (3.5%) reported were also similarly low<sup>[29]</sup>.

Direct percutaneous carotid access is an alternative access that has been described for CAS. This access can be used in individuals with difficult anatomies, high-risk patients and certain emergent situations that warrant easy and rapid access to the CCA<sup>[30]</sup>. A systematic review ( $n = 12$  studies; 739 CAS procedures) showed that direct CAS with transcervical access (filter protected or unprotected;  $n = 250$  patients) and CAS with transcervical access under reversed flow (with arteriovenous shunt in most cases;  $n = 489$  patients) are both associated with a low incidence of stroke and complications<sup>[31]</sup>. The incidence of stroke, MI and death was 1.1%, 0.14% and 0.41%, respectively. The incidence of stroke was 1.2% (3 of 250) in direct CAS with transcervical access and 1.02% (5 of 489) in CAS under reversed flow ( $P =$  not significant). Transient ischemic attack occurred in 20 patients (2.7%)<sup>[31]</sup>.

## HEAD-TO-HEAD COMPARISON/ COMBINATION OF STRATEGIES

Several studies have compared/combined the various proposed adjuncts to improve CAS outcomes in an attempt to identify those measures that would help improve CAS results to a greater extent. A study from Argentina compared transradial vs transfemoral CAS<sup>[32]</sup>. A total of 775 consecutive patients undergoing CAS during 16 years were included (101 transradial vs 674 transfemoral). The primary combined end-point was in-hospital major adverse cardiac and cerebral events, whereas secondary end-points included angiographic outcome after the procedure and cross-over rate to another puncture site. Angiographic success was achieved in all 775 patients. There was a significant difference in cross-over rate (4.9% vs 0%, for the transradial vs the transfemoral approach, respectively;  $P < 0.05$ ), but not in the incidence of in-hospital major adverse cardiac and cerebral events (2% vs 3.6%, for the transradial vs transfemoral approach, respectively;  $P =$  not significant)<sup>[32]</sup>. It was concluded that both approaches are safe and efficacious. These results verified the results of an earlier study<sup>[33]</sup>.

An earlier study from Atlanta, Georgia, United States compared revascularization outcomes after CEA ( $n = 226$ ) vs CAS with a distal filter EPD ( $n = 216$ ) vs CAS with a proximal flow reversal system ( $n = 53$ )<sup>[34]</sup>. The 3 groups did not differ in the overall composite end-point of death, cerebrovascular accident and MI (4% vs 5.1% vs 0%, respectively;  $P = 0.1$ ) or any individual major adverse event<sup>[34]</sup>. Overall, patients undergoing CAS with EPD had a greater incidence of minor cerebrovascular accidents than CEA patients (6 vs 1, or 3.4% vs 0.5%, respectively;  $P = 0.031$ ). This was driven by the increased risk for a cerebrovascular accident for

asymptomatic patients. Of note, patients undergoing CAS with flow reversal ( $n = 53$ ) had zero adverse events (minor/major stroke, MI or death)<sup>[34]</sup>.

A study from Japan evaluated the effectiveness of the combined use of distal filter protection device [FilterWire EZ (Boston Scientific, Natick, MA)] and the Mo.Ma Ultra (Medtronic, Minneapolis, MN)<sup>[35]</sup>. The Mo.Ma Ultra is an EPD for interrupting the antegrade blood flow to the internal carotid artery. This study demonstrated that the combined use of a distal filter protection device and Mo.Ma Ultra could provide a more reliable embolic protection in CAS<sup>[35]</sup>.

A study from Italy reported the outcomes of 214 patients undergoing CAS *via* a transradial ( $n = 154$ ) or a transbrachial ( $n = 60$ ) approach with either the Mo.Ma proximal protection ( $n = 61$ ) or the distal filter protection ( $n = 163$ )<sup>[36]</sup>. As a result of technical difficulties in catheterizing the target vessel, crossover to a femoral approach was required in 11 of 153 (7.1%) filter patients, but only in 1 of the 61 (1.6%) Mo.Ma patients. On the other hand, 5 Mo.Ma patients developed acute intolerance to proximal occlusion (4 were subsequently shifted to filter protection). One patient undergoing CAS *via* the transradial approach was shifted to filter because the Mo.Ma system was too short. Overall, CAS was technically successful in 55 of the 60 (90%) Mo.Ma patients and in 142 of the 154 (93%) filter patients. The 30-d major adverse cardiovascular/cerebrovascular events rate did not differ significantly between the 2 groups (0% for Mo.Ma patients vs 2.8% for filter patient;  $P = 0.18$ ). There was similarly no difference in radiation exposure between the 2 groups. Major vascular complications occurred in 1 of the 61 (1.6%) Mo.Ma patients and in 3 of the 153 (1.96%) filter patients, respectively ( $P = 0.18$ ). All these complications occurred during the early learning phase of the transbrachial approach. After a mean follow-up of  $8.1 \pm 7.5$  mo, chronic radial artery occlusion was detected by Doppler ultrasound in 2 of the 30 (6.6%) Mo.Ma patients and by clinical assessment in 4 of 124 (3.2%) filter patients ( $P = 0.25$ ). The conclusion reached was that CAS with proximal protection *via* a transradial or a transbrachial approach is a safe, feasible and effective technique with low rate of vascular complications<sup>[36]</sup>.

A study from Japan compared the effectiveness of the embolization prevention mechanism of 2 types of EPDs - a distal protection balloon ( $n = 82$  patients) and a distal protection filter ( $n = 82$  patients)<sup>[37]</sup>. Positive findings on postoperative diffusion-weighted imaging were found in more patients with distal protection balloon compared with the distal protection filter (34 vs 22 patients, or 41.4% vs 26.8%, respectively). Furthermore, in the distal protection balloon group there were more strokes than in the distal protection filter group (2 minor and 2 major strokes vs 0 strokes, respectively)<sup>[37]</sup>. A combination of flow reversal and distal filter may be more effective than either modality alone<sup>[38]</sup>.

Controversial results were reported in a small study from Brazil<sup>[39]</sup>. This study compared flow reversal vs filter protection in 40 patients undergoing CAS using a femoral approach. Compared with flow reversal ( $n = 21$ ), filter protection ( $n = 19$ ) resulted in a reduction in the incidence (15.8% vs 47.6%, respectively;  $P = 0.03$ ), number (0.73 vs 2.6, respectively;  $P = 0.05$ ) and size (0.81 mm vs 2.23 mm, respectively;  $P = 0.05$ ) of new ischemic brain lesions<sup>[39]</sup>. Flow reversal was associated with a tendency toward increased incidence of ipsilateral ischemic lesions more than those who had filter protection (70% vs 0.0%, respectively;  $P = 0.07$ ). In addition, flow reversal showed a greater tendency toward increased incidence of ipsilateral lesions than bilateral (70% vs 30%, respectively;  $P = 0.07$ )<sup>[39]</sup>. As the authors mentioned, this trial was the first to show better results using filter protection than a proximal protective technique during CAS. The authors attributed these good results to their considerable operator experience with CAS, the general anesthesia (which minimized the risk of movement accidents) and to the filter protection device profile<sup>[39]</sup>.

## ADVANCES WITH STENT DESIGN

Several important advances in stent design have also lead to improved CAS outcomes. For instance, the Inspire MD technology (Tel Aviv, Israel) includes a bare-metal stent (Inspire MD C-Guard stent) covered by a micron level mesh (MicroNet). Preliminary results appear encouraging<sup>[40]</sup>. A prospective multicenter study, the C-Guard CARotid Embolic protection using microNET trial evaluated the feasibility of the C-Guard carotid embolic protective stent system<sup>[41]</sup>. This is a novel thin-strut nitinol stent combined with a polyethylene terephthalate mesh covering. This study reported a 0% 30-d major adverse cardiac or cerebrovascular events rate in 30 patients<sup>[41]</sup>. Another stent that has demonstrated promising results is the double-layer CASPER-RX stent<sup>[42]</sup>. Finally, the Roadsaver Micromesh stent is a novel nitinol double-layer micromesh stent. Preliminary results from high-volume centres showing a low incidence of embolic events and new ipsilateral ischemic brain lesions are encouraging<sup>[43,44]</sup>.

During CAS, debris is often trapped in stent interstices. When flow is restored following CAS, the trapped debris may prolapse through the stent struts and result in delayed cerebral embolization<sup>[45]</sup>. Three companies (Roadsaver™ Micromesh Carotid Stent, Terumo, Japan; C-Guard™ MicroNet-Covered Embolic Prevention Stent System, InspireMD, Boston, MA, United States; and Scaffold Stent, W.L. Gore and Associates, Flagstaff, AZ, United States) are evaluating membrane or mesh covered carotid stents with smaller interstices to prevent such delayed strokes<sup>[45]</sup>.

The advances in carotid stent material and the new types of stents introduced in the market are beyond the scope of this review and are more extensively described elsewhere<sup>[46]</sup>.



## CONCLUSION

The battle for CAS is not lost<sup>[47]</sup>. The long-term results of the Carotid Revascularization Endarterectomy vs Stenting Trial did not show a significant difference in periprocedural stroke, MI or death and subsequent ipsilateral stroke between symptomatic and asymptomatic patients undergoing CAS or CEA<sup>[48]</sup>. Similarly, the Asymptomatic Carotid Trial demonstrated non-inferiority for CAS compared with CEA for asymptomatic patients with respect to the primary composite end-point of 30-d death, stroke or MI and ipsilateral stroke within 1 year<sup>[49]</sup>. New devices, membrane- and mesh-covered stents, alternative approaches and a combination of EPDs are tools in the armamentarium of CAS to improve its results. There is more to see in the future and we will all be awaiting the results of new trials incorporating the advances in CAS technology.

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