CAS Technology Advancement

The opportunity to improve outcomes with new device approaches.

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In order to address improvement in outcomes for carotid artery stenting (CAS), the relative weaknesses of carotid intervention by endovascular means as compared with surgical revascularization (carotid endarterectomy [CEA]) must be frankly acknowledged.

CAS WEAKNESSES: INCONVENIENT TRUTHS

Excess Minor Stroke Rate

The excess minor stroke rate for CAS (as compared to CEA) may be limited to older patients, as noted in the carotid stenting trialists' collaboration report of a prespecified subset meta-analysis of outcomes by age for CAS in the ICSS, EVA-3S, and SPACE randomized trials. CREST, in fact, did not show this pattern, counter to the original claims.[1] However, there remains some uncertainty with regard to the relation between age and outcome for CAS, especially with "standard" techniques (ie, distal filter protection with an approach via the transfemoral route). Certainly, elongation of the arch with aging and increasing risks of arch atheroma increase catheterization hazard. There is also less reserve capacity in older brains, making them more vulnerable to the effect of embolization. Indeed, in an evaluation of the ICSS data set, patients with more marked small-vessel disease (which was linearly related to age) were more prone to procedural stroke after CAS.

Although by 6 months any excess disability from the minor stroke rate for CAS at the time of event within CREST had significantly resolved such that there were no differences in disability between CAS and CEA on NIH Stroke Scale assessment or the Modified Rankin Scale, this is a vital issue and must be addressed in order for CAS to evolve. Although minor stroke affects quality of life evaluations much less than major stroke, this outcome is a major concern for any carotid interventionist and for every patient.[2,3]

Excess Microembolic Burden

CAS has been shown to carry excess microembolic burden compared to CEA.[4,5] Embolic protection devices, designed to improve the safety profile of CAS, have variable impact on the microembolic burden of CAS, which may manifest as new hyperintensities on diffusion-weighted magnetic resonance imaging (DWMRI) of the brain. CEA remains the gold standard by effecting embolic control through clamping of the ipsilateral external and common carotid arteries and by back-bleeding. There is a growing and compelling evidence base to suggest that distal filter protection is suboptimal: These systems might actually increase the microembolization rate compared to unprotected CAS[4,6,7] and are inferior to proximal embolic protection systems within two small randomized trials.[8,9] A small but elegant nonrandomized study revealed that CEA was superior to filter-protected CAS and flow-reversal–protected CAS, but that flow reversal was superior to filter protection.[5] Moreover, the procedural phase in which microembolic signals (MES) were detected differed substantially between interventional strategies. For CEA, the risk was postprocedure. For filter-protected CAS, it was throughout the procedure, which would seem to mitigate against the level of protection afforded by these systems; for flow reversal, it was before establishment of the flow-reversal circuit, implying the risks inherent in the catheterization of the arch and great vessel origins, especially with the 9-F systems that represent flow-reversal or flow-arrest technologies.

If the arch can be avoided during CAS by employing those systems that effect direct common carotid access, especially when flow reversal provides the means of neuroprotection, the procedural microembolic burden for CAS (DWMRI rate) becomes commensurate with CEA for the first time for any carotid endovascular strategy.[4,10,11]

Proximal embolic protection devices such as the MoMa system (Medtronic, Inc., Minneapolis, MN), which involves flow arrest, and the Gore Flow Reversal system (Gore & Associates, Flagstaff, AZ) have clinical utility over and above "subclinical" strengths (ie, the control of the microembolic burden of CAS). A systematic review of more than 2,000 CAS cases using proximal embolic protection highlighted a clinical event rate (all stroke/death/myocardial infarction) for a mixed population of 2,937 patients of 2.25%.[12] The ARMOUR Pivotal US IDE trial evaluating the MoMa flow-arrest device enrolled 257 patients (including the roll-in phase). There was independent neurological review and independent adjudication of outcome events. The all-stroke death rate was 2.7% (2.3% in patients older than 75 years of age), and there were no strokes in the (minority) symptomatic population.[13] The EMPIRE US IDE trial evaluating the Gore Flow Reversal system recruited 245 patients. Again, independent neurological review was mandatory, as was independent adjudication of outcome events. The all-stroke/death rate was 2.9% (2.6% in the 38 octogenarians treated and 3.8% in the 78 symptomatic patients treated).[14]

The arch can be a hostile endovascular territory (see the section on Anatomic Constraints), especially in less experienced hands. In the CAPTURE registry, 20% to 40% of strokes were related to catheterization difficulties.[15] In EVA-3S, the French national trial of CAS versus CEA for symptomatic patients, 5% of patients randomized to CAS were crossed over emergently to CEA due to access-related issues, and 15% of these had a stroke before CEA. EVA-3S was criticized for leniency regarding operator inexperience in the CAS limb of the trial.[16] One might conclude that access-related issues may be particularly problematic for novices.

Anatomic Constraints

Adverse anatomy affects CAS procedural event rates, perhaps more so than for CEA (where high bifurcation may have an impact on cranial nerve injury rather than on stroke rate)—prior radiotherapy being a clinical rather than an anatomic factor that leads to complexity with subsequent tissue dissection. Perhaps the most challenging anatomies include complex type III/bovine arches (conjoined origin of the brachiocephalic trunk and left common carotid artery). Alternative access routes (brachial, radial, direct carotid) may be useful in this circumstance. Arch atheroma, perhaps a growing concern at a time when there is an epidemic of diabetes, poses a major problem. Direct carotid access would seem to be the only valid solution.

In a Delphi consensus involving 12 geographically diverse panelists from multiple specialties, eight of 12 initial anatomic "danger zones" pertained to the arch and to great vessel access (ie, focussed on access).[17] The literature supports the impact of access difficulty on procedural hazard, even in experienced hands.[18,19]

Learning Curve

Complex interventions such as CAS are expected to have steep and/or lengthy learning curves. In an analysis of one center's first 1,000 radical prostatectomies, it was noted that the learning curve for operating time and blood loss was approximately 100 to 150 cases, but that 150 to 200 cases would be required before overall complication and incontinence rates improved.[20] In an interpretation of the operative risks of individual surgeons from the European Carotid Surgery Trialists' Collaborative Group, it was considered that analysis of an individual surgeon's endarterectomy performance was thought to require ≥ 200 cases before they could be sure of their stroke and death rates to within 95% confidence intervals.[21] An additional complexity is added by the fact that innumerable specialists perform CAS, including interventional radiologists, interventional neuroradiologists, angiologists, vascular surgeons, neurosurgeons, interventional neurologists, and interventional cardiologists. These disparate medical "species" have different baseline understandings of the disease process, physiology, anatomy, periprocedural clinical care, and bailout options, as well as high-level technical skills and attitudes. This makes the formulation and provision of multispecialty agreed-upon training guidelines for CAS difficult. CEA, on the other hand, has been part of the training portfolio requirement for all vascular surgical and some neurosurgical fellows and residents for many years.

In this issue of *Endovascular Today*, we have an excellent commentary from Drs. Willaert and Van Herzeele on the roles, strengths, and limitations of virtual reality endovascular training programs for CAS from some of the most experienced operators in the field (page 42).

CAS: ADDRESSING THE WEAKNESSES

As previously described, the remaining problems beyond the learning curve for CAS concern access, microembolization, and minor stroke excess. How can these be addressed?

Access

There are dedicated carotid access guiding catheters available in some markets for complex arches, such as the Saad catheter (Cordis Corporation, Warren NJ) and the Piton (Medtronic, Inc.); both are currently unavailable in the US). The Cordis Saad has right-sided and left-sided configurations, but these require reasonable

manipulation in the aortic arch, with potential embolic risk due to the reformation of the complex curve of these catheters.

The Piton is an 8-F (outer diameter) dedicated carotid access catheter that takes two 0.035-inch wires: the 300-cm Supra Core (Abbott Vascular, Santa Clara, CA) and the 260-cm stiff hydrophilic Glidewire by Terumo Interventional Systems (Somerset, NJ). The Supra Core exits through a sidehole in the neck of the Piton and the Terumo through the endhole. With the Supra Core against the aortic valve, acting as a wire bridge, the Terumo wire is pulled back; the tip of the Piton is thus able to form its preshaped tip, which is turned to engage the vessel to be catheterized. The Terumo wire is then advanced up the relevant common carotid artery. The Supra Core prevents prolapse of the Piton catheter into the arch. The Supra Core is then pulled back into the Piton shaft and advanced—it will only ever exit the endhole of the Piton on readvancing. Thus, access with two 0.035-inch wires into the common carotid and/or external carotid artery ipsilateral to the lesion to be treated is possible (Figures 1 through 3).

Microembolization

Both access and microembolization limitations might be addressed by proximal embolic protection combined with direct carotid access, for example the high-flow-rate flow reversal provided by the Michi Neuroprotection system (Silk Road Medical, Sunnyvale, CA), which is not yet available in the United States (Figure 4).

Direct carotid access with high-flow-rate flow reversal (6 to 7 times the rate of the Gore Flow Reversal system on the high-flow setting and 2 to 3 times the flow reversal rate of the Gore system on low-flow setting) is achieved by placement of a 10-F (outer diameter) sheath in the common carotid artery by mini surgical incision, with percutaneous femoral venous access (10-F outer diameter). A handheld flow controller allows the operator the choice of high-flow, low-flow, and no-flow settings (for the injection of contrast). The Michi system effectively provides high-flow-rate flow reversal without the need to occlude the external carotid artery ipsilateral to the lesion to be treated and achieves this by means of low-resistance, wide-bore tubing completing the circuit between the arterial and venous sheaths.

Currently, the system requires a mini (2 cm) transverse incision above the relevant clavicle. Thus, radiologists or cardiologists would have to work with their colleagues in surgery in order to offer this procedure. Vascular or neurosurgeons, however, might proceed alone. Future advances hinge on a percutaneous system, but this will require secure and reliable closure.

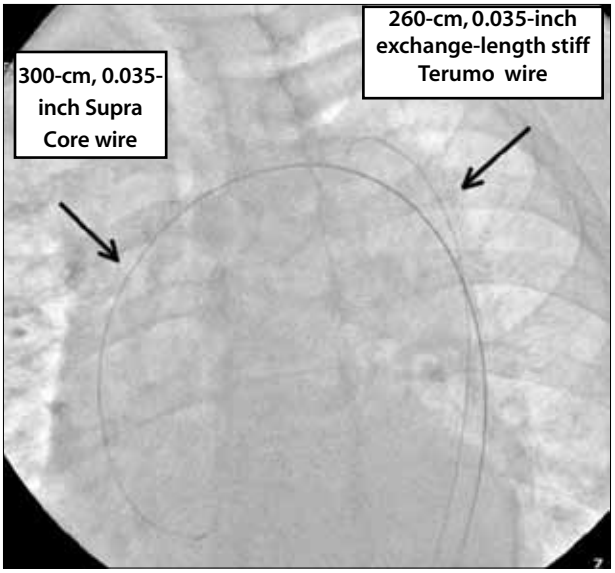

Figure 1. Two 0.035-inch wires in the aortic arch.

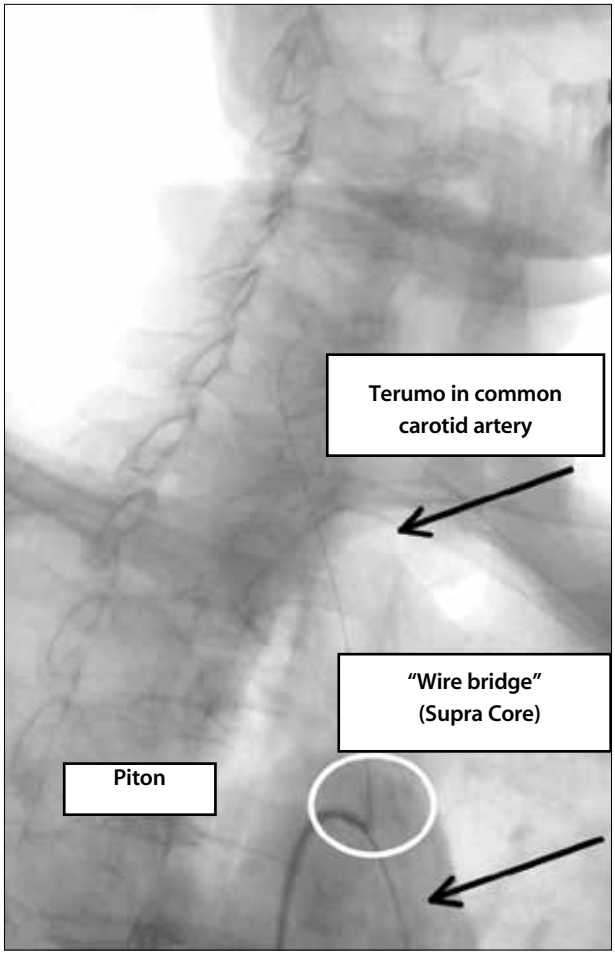

Figure 2. Piton catheter, Supra Core wire bridge, and Glidewire in the common carotid artery.

The PROOF trial detailed the first-in-man evaluation of the Michi system in Düsseldorf, Germany, and revealed a major stroke/death/myocardial infarction rate of zero in 75 patients. There was one minor stroke in the contralateral hemisphere beyond 5 days in a patient who had a negative DWMRI brain scan at 30 days as part of the DWMRI substudy.[10] As highlighted above, in a subset of 48 patients undergoing preprocedure and postprocedure DWMRI with blinded adjudication of the results by neuroradiologists in the US demonstrated a DWMRI new hyperintensity lesion count of 17% (commensurate with the CEA arm of the ICSS substudy).[4]

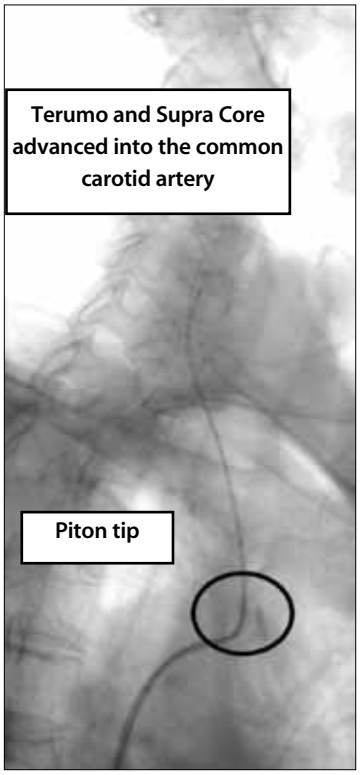

Figure 3. Two 0.035-inch wires in the common carotid artery.

Recently, in an evaluation of an in-house transcervical flow reversal system, 33 patients underwent FilterWire (Boston Scientific Corporation, Natick, MA) protected transfemoral CAS, and 31 underwent flow reversal via direct carotid access within a nonrandomized construct.[11] The DWMRI new hyperintensity rate was 33% for transfemoral filter–protected CAS and 12.9% for transcervical flow reversal (CEA in the surgical limb of the ICSS substudy being associated with a 17% new white lesion rate). Size of lesions and not just lesion count is an important consideration; there are fewer, larger lesions after CEA and more, but smaller lesions after CAS, such that the total volume of brain affected by CAS and by CEA is wholly comparable. A cognitive function analysis within the wider ICSS data set did not reveal meaningful differences between the CAS and CEA treatment limbs.[22] The persistence of DWMRI lesions and their clinical-pathological relevance require further study. Work is also ongoing with respect to categorizing the lesions by size in the PROOF study.[10] At the Freeman Hospital in Newcastle upon Tyne, United Kingdom, the ongoing LOTUS trial seeks to evaluate the Michi system in recently symptomatic patients who are deemed high risk for any intervention.

Minor Stroke

Anecdotally, these events tend to be "off-table" and less dependent on operator experience than major strokes. One might argue that they arise because of changing hemodynamics after CAS, insufficient pharmacokinetic sensitivity to one or both elements of the dual-antiplatelet regimen and/or the controversial notion of "plaque prolapse" through the stent interstices. Could carotid stent design be a relevant consideration?

Stent Design

A systematic review comprising 32 studies, including a mix of CEA and CAS cases (incorporating 1,363 carotid stenting procedures), demonstrated that closed-cell stents significantly reduced the new white lesion rate on DWMRI compared to open-cell stents.[23] A small randomized controlled trial comparing the Wallstent (Boston Scientific Corporation) and the ePTFE-covered Symbiot balloon-mounted stent (Boston Scientific Corporation) (stopped early due to excessive restenosis in the covered stent limb) demonstrated significantly

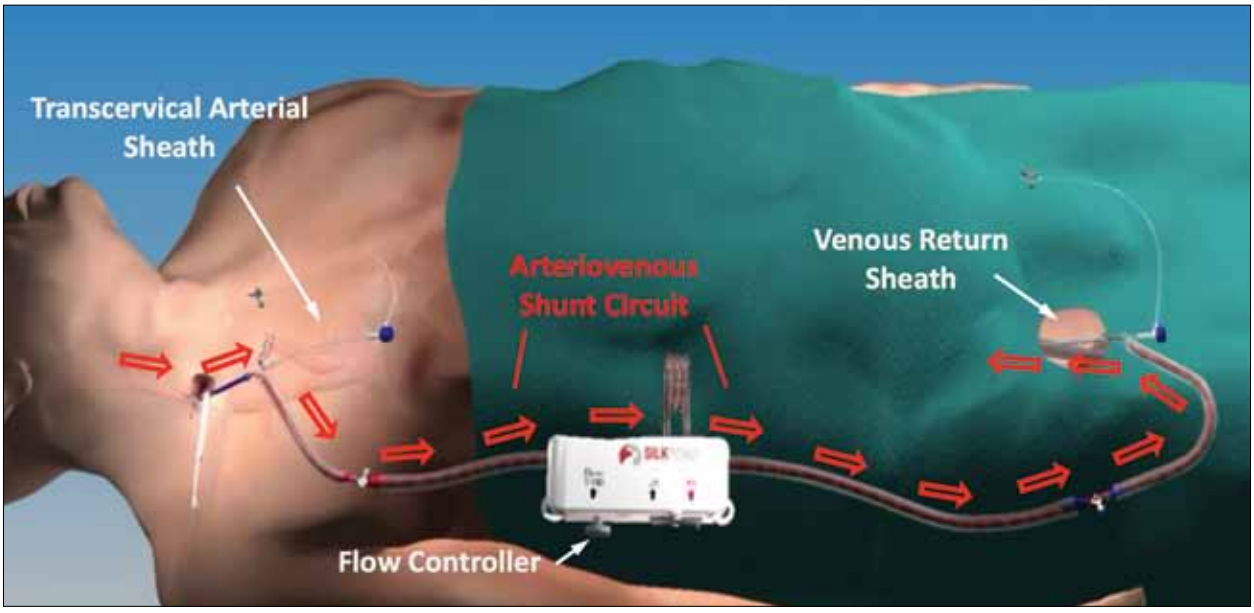

Figure 4. The Michi neuroprotection system uses the FAST-CAS method: Flow-altered short transcervical carotid artery stenting.

fewer microembolic signals on transcranial Doppler with the covered compared with the bare metal stent small free-cell-area Wallstent.[24] Conflicting data exist on the clinical correlations of definable differences between open- and closed-cell stent designs. Clinical evaluations are meaningful only by patient subset; symptomatic patients perhaps have the most to gain and the most to lose. These patients have a relatively high risk of subsequent/intermediate-term stroke if untreated and a higher procedural hazard than asymptomatic patients. Stent design might be a peculiarly important message in this population.

The Bosiers Belgian/Italian registry detailing the outcomes of 3,179 procedures in a mixed population (large majority asymptomatic) stent "free-cell area" had an impact on stroke/death outcome for CAS. There was a statistically significant benefit for the Xact (Abbott Vascular), the Wallstent (majority use), and the NexStent (Boston Scientific Corporation) compared with the open-cell Precise (Cordis Corporation), Protégé (Covidien/ev3, Plymouth, MN), Acculink (Abbott Vascular), and Exponent (Medtronic, Inc.).[25] A "rival" EU multicenter registry sought to refute these findings but eventually demonstrated a similar trend, with lower adverse procedural events when a closed-cell stent was used in symptomatic patients.[26] In the SPACE trial—a one-to-one randomized comparison of CEA versus CAS in a purely symptomatic population—use of the closed-cell Wallstent was associated with significantly better outcomes than use of the open-cell Acculink or Precise.[27] In the most recent nonrandomized comparison of transfemoral filter-protected CAS and transcervical flow reversal, a mulitvariate analysis (albeit in 64 consecutive patients) revealed that age (relative risk, 1.022; $P < .001$), symptom status (relative risk, 4.109; $P < .001$), and open-cell versus closed-cell stent design (relative risk, 2.01; $P < .001$) were associated with higher risk in the transfemoral but not the transcervical group.[11]

In a sizeable registry, the Society for Vascular Surgery sought to compare outcomes for 4,377 patients undergoing CAS with variable use of closed-cell (N = 886) and open-cell (N = 3,451) designs. This registry is, of course, prone to selection bias but nonetheless, provides food for thought. Although the majority of the patient population was asymptomatic, the authors concluded that open-cell stents were associated with a (nonsignificantly) higher all-stroke/death/myocardial infarction rate at 30 days as compared to closed cell, "suggesting the benefit of closed-cell stents at later follow-up."[28]

Membrane/mesh covered stents might represent the next advance and are anticipated soon. These might meaningfully combine nitinol open-cell conformability with scaffolding by means of bonded, permeable membranes.

"When all you have is a hammer, everything looks like a nail."

—Abraham Maslow, 1966

I suppose the counterargument to this sentiment is that if you find an effective hammer, everything becomes a nail. Direct carotid access with high-flow-rate flow

reversal in my practice has expanded the limits of those complex patients to whom CAS may or may not be offered. Advances in stent technology hold promise but are yet to be proven. ■

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