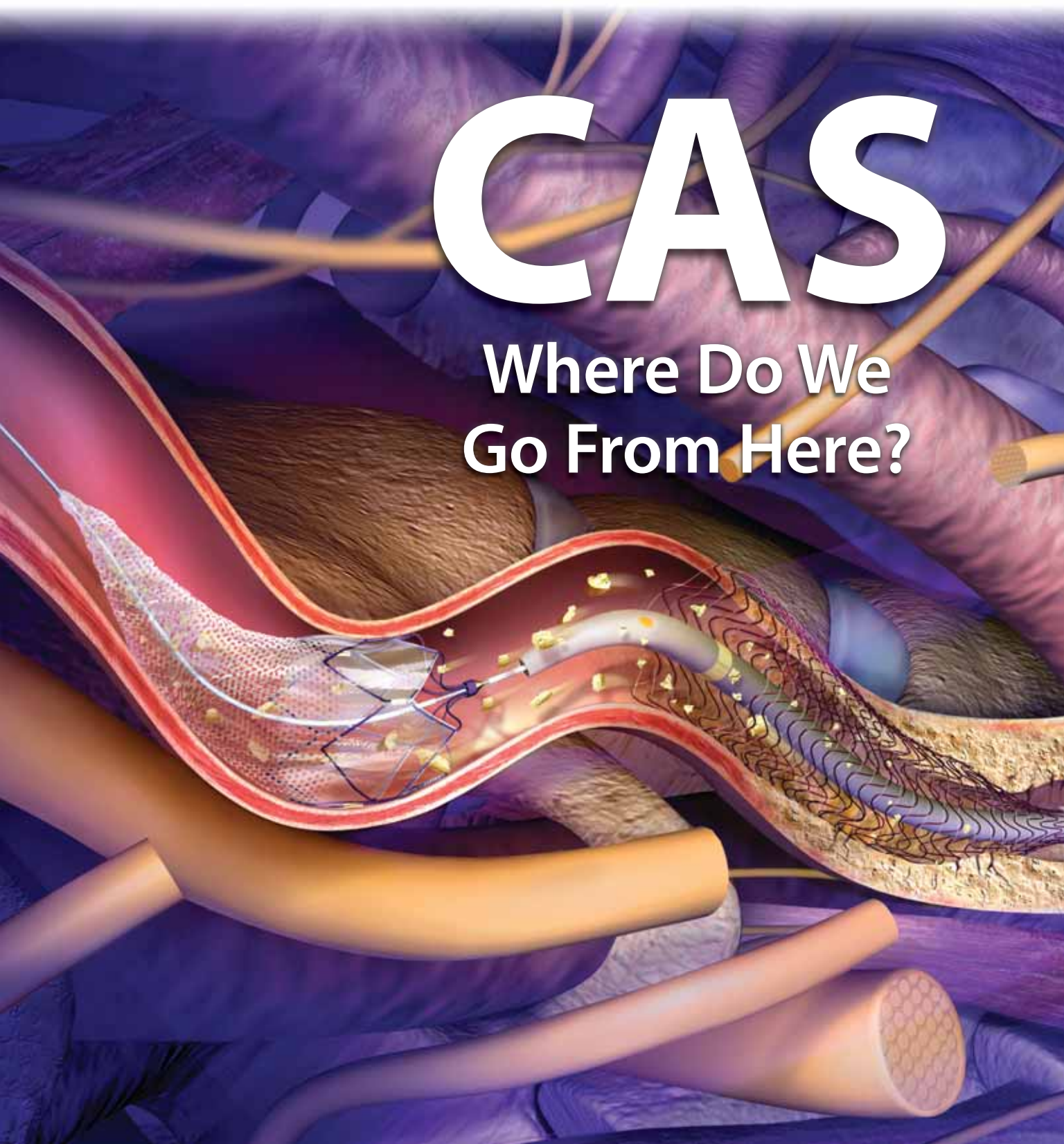


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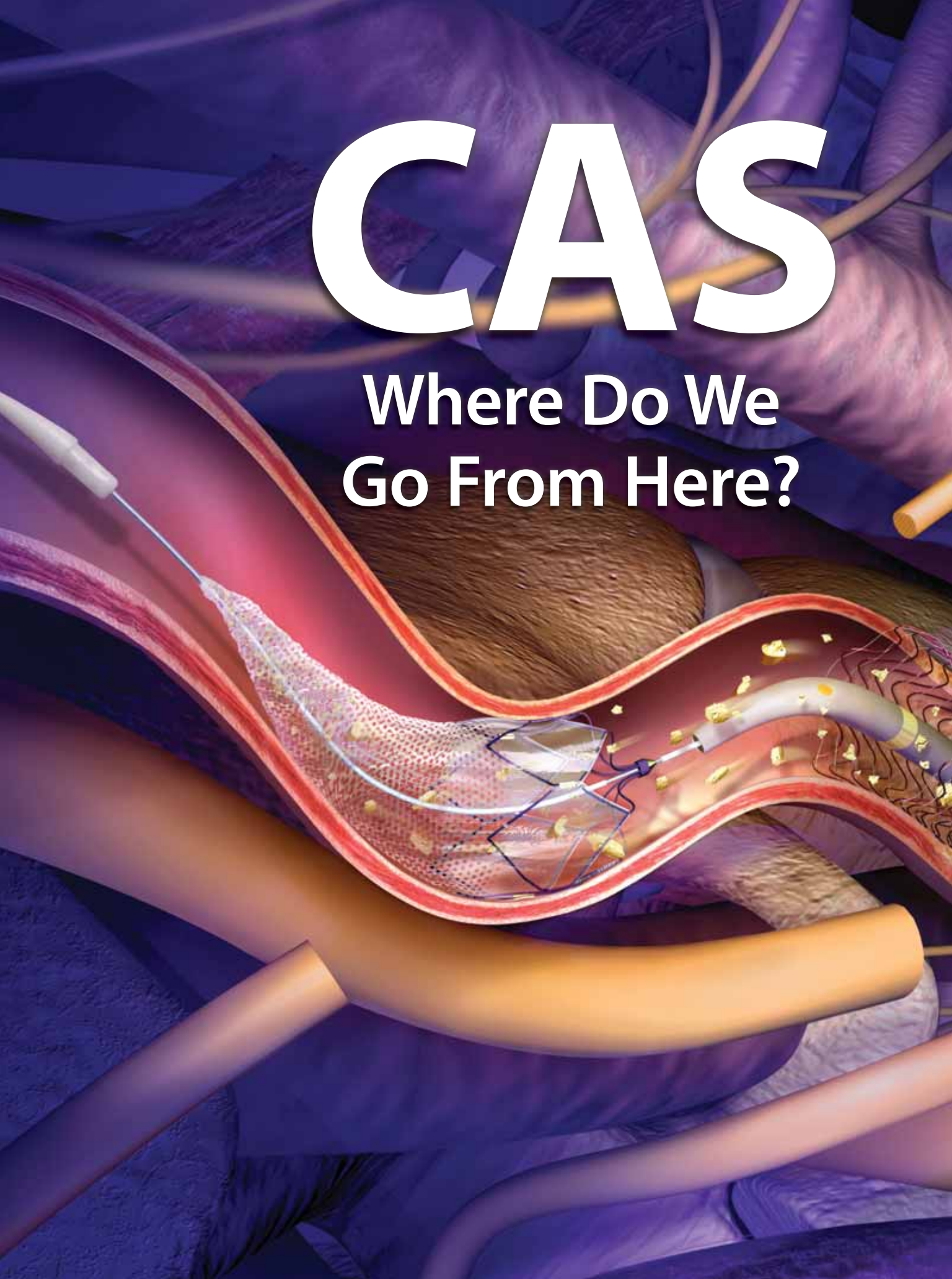
CAS

Where Do We Go From Here?



CAS

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What Can We Learn From CREST?

Highlighting the data and take-home points of this landmark carotid revascularization trial.

BY MARIUS HORNING, MD; STEFAN BERTO, MD, FACC, FSCAI; JENNIFER FRANKE, MD; NINA WUNDERLICH, MD; AND HORST SIEVERT, MD, FESC, FACC, FSCAI

The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) was initiated under the support of the National Institutes of Health and the National Institute of Neurological Disorder and Stroke to compare the efficacy of carotid artery stenting (CAS) to carotid endarterectomy (CEA) for the revascularization of extracranial stenoses of the internal carotid artery in patients with standard surgical risk. CREST was the largest study of its kind and was adequately powered to uncover significant differences in the results of both procedures. This prospective, randomized, parallel, two-arm, multicenter trial included 2,502 patients and examined the composite primary endpoint of myocardial infarction (MI), stroke, or death during the periprocedural period plus any ipsilateral stroke within 4 years after randomization.

Both symptomatic and asymptomatic patients were enrolled. Patients with symptomatic stenoses were included if the stenosis severity was > 50% angiographically (based on NASCET [North American Symptomatic Carotid Endarterectomy Trial] criteria) or > 70% measured by ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA). Patients with asymptomatic stenoses were included if the stenosis severity exceeded 60% by angiography, 70% by ultrasonography, or 80% by CTA or MRA.¹ The primary endpoint occurred in $7.2\% \pm 0.8\%$ of patients treated with stenting and in $6.8\% \pm 0.8\%$ who underwent surgical revascularization ($P = .51$). The mean follow-up period was 2.5 years.²

There was no significant difference in the composite secondary endpoint defined as periprocedural (30 day) death, stroke, or MI ($5.2\% \pm 0.6\%$ for CAS vs $4.5\% \pm 0.6\%$ for CEA; $P = .38$). Likewise, there was no significant difference in overall mortality (0.7% vs 0.3% ; $P = .18$). However, whereas strokes were more frequent after CAS (4.1% vs 2.3% ; $P = .01$), MI was more common in patients treated surgically (2.3% vs 1.1% ; $P = .03$). There was a trend toward a higher incidence of major ipsilateral stroke at 30 days in the CAS group (CAS

$0.9\% \pm 0.3\%$ vs CEA $0.3\% \pm 0.2\%$; $P = .09$). However, there was no difference in major ipsilateral stroke at long-term follow-up (CAS $1.4\% \pm 0.3\%$ vs CEA $0.8\% \pm 0.3\%$; $P = .28$).

Does It Matter Whether Patients Are Symptomatic or Asymptomatic?

Following international definitions, a stenosis was defined as symptomatic if it had caused any neurological symptoms within 180 days of enrollment and randomization. There was no difference between CAS and CEA in the primary endpoint for patients with symptomatic stenoses ($6.7\% \pm 1.0\%$ vs $5.4\% \pm 0.9\%$; $P = .30$).³ The combined stroke and death rate in symptomatic patients, however, was higher in the endovascular group ($6.0\% \pm 0.9\%$ vs $3.2\% \pm 0.7\%$; $P = .02$). Importantly, there was no difference in asymptomatic subjects ($2.5\% \pm 0.6\%$ vs $1.4\% \pm 0.5\%$; $P = .15$). The rate of MI was lower after CAS compared to surgery in symptomatic patients ($1.0\% \pm 0.4\%$ vs $2.3\% \pm 0.6\%$; $P = .08$) as well as in asymptomatic patients ($1.2\% \pm 0.3\%$ vs $2.2\% \pm 0.6\%$; $P = .20$). CREST was the first trial to show stroke and death rates for both procedures within a range recommended in the current American Heart Association guidelines for the prevention of stroke (< 6% in symptomatic and < 3% in asymptomatic patients).⁴

A subgroup analysis, which excluded patients older than 80 years of age, was performed to allow better comparison of CREST to previous clinical trials that generally excluded octogenarians. The 30-day stroke and death rate for the symptomatic cohort younger than 80 years was $5.6\% \pm 1.0\%$ for CAS and $2.6\% \pm 0.7\%$ for CEA. The corresponding rates in patients with asymptomatic stenoses were $2.4\% \pm 0.7\%$ for CAS and $1.5\% \pm 0.5\%$ for CEA.³

Are Octogenarians at High Risk for Carotid Intervention?

In 2004, Hobson et al presented a subgroup analysis of the CREST lead-in phase analyzing the association of age

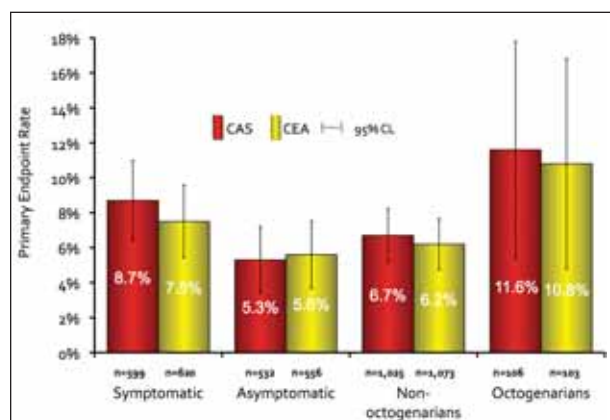


Figure 1. Primary composite endpoint of CAS and CEA by symptomatic or octogenarian status.

and periprocedural stroke and death.⁵ In total, 749 patients randomized to CAS were divided into four groups according to age. The rate of complications was higher with increasing age. The stroke and death rate by age category was 1.7% ($n = 2$ of 120) in those younger than 60 years, 1.3% ($n = 3$ of 229) in those 60 to 69 years old, 5.3% ($n = 16$ of 301) in those 70 to 79 years old, and 12.1% ($n = 12$ of 99) in octogenarians. In octogenarians, the stenoses were more severe (73.5% vs 71.5%), with more residual stenoses after stenting (12.6% vs 11.5%).

Higher complication rates in elderly patients appear to be a consistent finding, as this has been reported in a number of previous studies. Age and comorbidities may be less important reasons than the more frequently associated unfavorable anatomy due to carotid tortuosity⁵ and hostile arch related to an unfavorable takeoff of cranial vessels, as well as more pronounced atherosclerotic disease. Therefore, technical challenges could have a more pronounced impact on outcomes in elderly patients in the lead-in phase because difficult anatomy may be compounded by more limited operator experience and familiarity with the equipment used in the trial (RX Accunet for distal protection and RX Acculink stents [Abbott Vascular, Santa Clara, CA]).

Importantly, adverse events were more common in octogenarians regardless of the revascularization mode, and unlike some previous studies, there was no difference in the primary endpoint between CAS and CEA in octogenarians (Figure 1). Invariably, strokes are the result of distal embolization caused by catheter manipulation within the aortic arch, wiring of the lesion, and stenting. Our distal protection devices offer only limited protection due to larger pore sizes than a significant amount of the embolic debris and suboptimal filter-to-vessel wall apposition, particularly in tortuous vessels more frequently encountered in octogenarians. In elderly patients with tortuous carotid arteries,

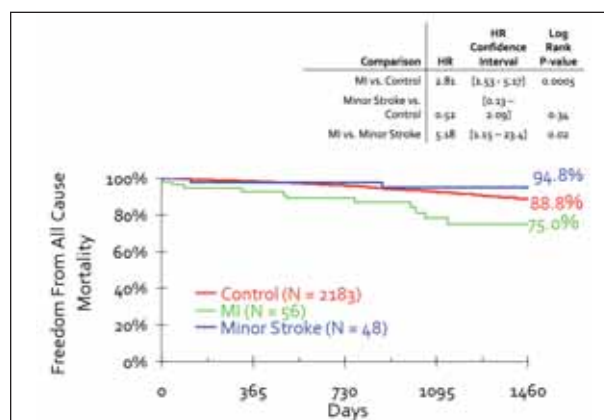


Figure 2. Association of minor stroke and MI with long-term mortality.

proximal protection may have advantages in periprocedural stroke prevention.

Does Sex Have an Influence on CAS and CEA Outcomes?

The influence of sex on an increased perioperative risk of stroke and death during carotid revascularization has been well described for CEA. The Asymptomatic Carotid Atherosclerosis Study (ACAS) was the first study showing a nonsignificant trend toward increased stroke and death risk in women ($P = .12$).⁶ The European Carotid Surgery Trial (ECST) found an increased periprocedural risk for women with symptomatic stenoses (11.1% vs 6.4%; $P = .002$).⁷ Schulz and Rothwell postulated that this effect may be caused by the female carotid anatomy.⁸ Women's internal carotid arteries can be up to 40% smaller in diameter than men's, making CEA technically more challenging.

In 2009, Howard et al presented an analysis of the lead-in phase of CREST comparing the results of 1,564 patients undergoing CAS by sex (26.5% of all stenoses were symptomatic).⁹ There was no significant difference in the periprocedural stroke and death rate for women (4.5%; $n = 26$ of 579) compared to men (4.2%; $n = 41$ of 985). Taking symptomatic status into account, the difference between symptomatic and asymptomatic women (5.6% vs 4.1%) was smaller than it was for men (5.9% vs. 3.5%). After adjustment for demographic factors (age or race), vessel characteristics (reference diameter, lesion length, percent stenosis, or symptomatic status), or cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, or smoking), the differences driven by gender were not significant.

In 2011, Howard et al presented the results of CREST comparing CAS and CEA according to gender. The composite primary endpoint of MI, stroke, or death during the periprocedural period or ipsilateral stroke within 4 years did

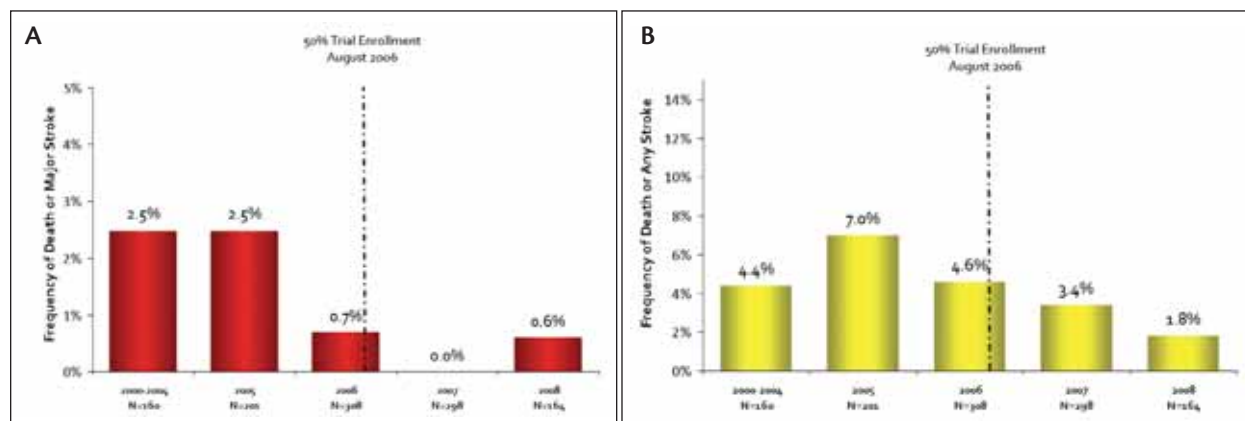


Figure 3. The effect of interventionists' learning curves during CREST. Death or major stroke rates for CAS over the period of CREST enrollment (A). Death or any stroke rates for CAS over the period of CREST enrollment (B).

not differ significantly by sex ($P_{\text{interaction}} = .34$). The primary endpoint occurred in 6.2% of men treated with CAS compared to 6.8% treated with CEA (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.57–1.41; $P = .94$).¹⁰ The rates for women were 8.9% in the stenting group versus 6.7% in the surgical group (HR, 1.35; 95% CI, 0.82–2.23; $P = .24$). Regarding periprocedural events only, the rate of complications was 4.3% in the male CAS group compared with 4.9% in the male surgical group (HR, 0.9; 95% CI, 0.57–1.41; $P = .64$). Among women, the rate in the CAS group was 6.8% compared with 3.8% in the CEA group (HR, 1.84; 95% CI, 1.01–3.37; $P = .064$).

What Is the Role of MI After Carotid Revascularization?

Periprocedural MI was one component of the composite primary endpoint. Cardiac biomarkers and electrocardiography were performed before and 6 to 8 hours postprocedure. The level of cardiac biomarkers was followed, and serial electrocardiography was performed in case of pathological postprocedural elevation of biomarkers, chest pain lasting for more than 15 minutes, or if other symptoms suggested myocardial ischemia. MI occurred in 14 patients undergoing CAS (1.1%) and 28 patients treated with CEA (2.3%; HR, 0.5; 95% CI, 0.26–0.94; $P = .032$).¹¹

In addition, an increase in cardiac biomarkers only was seen in eight CAS patients (0.6%) and 12 in CEA patients (0.97%; HR, 0.66; 95% CI, 0.27–1.61; $P = .36$). Importantly, mortality was higher in subjects with a periprocedural MI than in those without after 4 years of follow-up (HR, 3.4; 95% CI, 1.67–6.92; $P < .001$). Similar results were found in patients in whom only increased biomarkers were detected (HR, 3.57; 95% CI, 1.46–8.68; $P = .005$). Multivariable analysis showed that the only independent predictor of periprocedural myocardial infarction was a history of previous cardio-

vascular disease ($P = .02$). Baseline creatinine clearance of < 30 mL/min and a history of cardiovascular disease were predictors for the composite endpoint of MI and isolated biomarker release. The inclusion of periprocedural MI or biomarker release in the primary endpoint for trials examining a procedure's efficacy in stroke prevention has been debated with controversy. However, the impact of periprocedural MI on long-term mortality appears to be more important than that of periprocedural minor strokes and therefore should not be discounted (Figure 2).¹²

QUALITY OF LIFE AFTER CAROTID REVASCLARIZATION

Overall, CREST demonstrated fewer strokes in the endarterectomy group and a lower risk of MI in the stenting group. Although there was no difference in major strokes (0.9% for CAS vs 0.6% for CEA; $P = .52$), the incidence of minor strokes was significantly higher in the CAS group (4.1% vs 2.3%; $P = .01$). How does this translate into quality-of-life (QOL) measures? QOL studies suggest that the effect of a minor stroke is more severe than that of MI at 1-year follow-up.² However, many deficits related to minor strokes after CAS diminish or completely resolve. For example, in the Acculink Carotid Stent System for Revascularization "of Carotids in High-Risk Patients (ARCHER) trial, most deficits were no longer apparent after months of follow-up.¹³ Cranial nerve injury, a complication seen primarily after CEA, was not included in the QOL analysis. The appearance of cranial nerve palsies with CAS was 0% compared with 5.3% in the endarterectomy cohort ($n = 62$ of 1,176; $P < .0001$), of which 3.6% persisted for 1 month ($n = 42$ of 1,176; $P < .0001$) and 2.1% for at least 6 months ($n = 25$ of 1,176; $P < .0001$).¹²

As demonstrated in the ECST trial, the overall risk of permanent cranial nerve injury was 0.5%, and 5.1% of the

patients experienced at least a temporary motor nerve palsy (36 hypoglossal, 31 mandibular branch of the facial nerve, 17 recurrent laryngeal nerve, and one accessory nerve palsy).¹⁴

Most health care providers who have followed patients with cranial nerve palsies as a result of carotid surgery would probably agree that these deficits affecting sensation, appearance, swallowing, and speech are not minor and can significantly affect QOL. Given these important neurological deficits, similar to those reported with minor strokes, patients with cranial nerve palsies should be taken into account when assessing the impact of procedure-related adverse neurological events on QOL. Finally, local access complications may affect postprocedural QOL. In the endovascular group, 1.1% had access-site complications requiring further treatment compared with 3.7% in the surgical group ($P < .001$). Although two patients treated with CAS needed a surgical intervention due to postinterventional hematoma, the corresponding number of reoperations needed among CEA patients was 17.

What Is the Importance of Operator Experience?

In CREST, the majority of deaths and major strokes appeared within the first half of patient enrollment. This underlines the importance of experience and the impact of the interventionists' learning curves on patient outcomes (Figure 3) and confirms findings of a number of previous studies suggesting better outcomes with more experience.

What Is the Role of Medical Management?

One limitation of this largest trial comparing CAS and CEA to date is the poor knowledge of patients' medications. This information may have been useful for the analysis of cerebrovascular and cardiovascular events. All patients were required to continue aspirin therapy, but no data were available regarding the use of dual-antiplatelet, statin (except in patients with hyperlipidemia), or β -blocker therapy, all of which may affect the periprocedural rate of MI or long-term risk of cerebrovascular and major adverse cardiac events.

To allow better comparison between CAS and CEA, all subjects participating in future trials should be treated with the best medical treatment, and their medication should be documented. Importantly, very little data are available on stroke risk in patients with optimal medical therapy. Given the significant but relatively small benefit seen with surgical revascularization in asymptomatic patients in an era when statins, angiotensin-converting enzyme inhibitors, and thienopyridines were not routinely used, optimally, any mode of revascularization, even in the absence of symptoms, should occur with optimal medical management and be compared with a control arm of patients treated with medical management only.

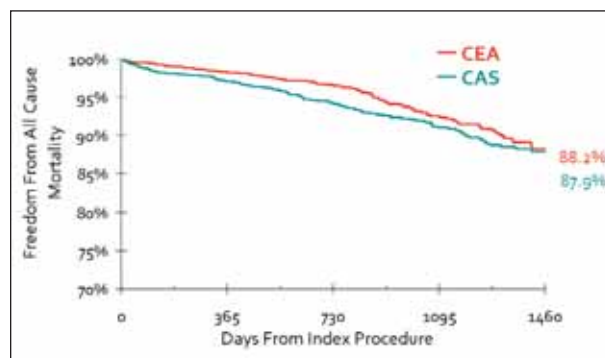


Figure 4. Similar mortality rates after CAS and CEA up to 4 years.

LESSONS LEARNED FROM CREST

The most important lesson to be learned from CREST is that CAS was noninferior to CEA in the treatment of extracranial stenoses of the internal carotid artery in patients at standard risk for surgery. The risk of major stroke or death did not differ significantly between both groups regardless of whether patients were symptomatic or asymptomatic. Although in the endovascular group, the rate of minor strokes was higher than in the group treated with surgery, CEA was associated with a higher rate of periprocedural MI, cranial nerve palsies, and vascular access complications. The composite primary endpoint of periprocedural MI, stroke, or death and ipsilateral stroke within 4 years within randomization was well balanced between both groups (Figure 4). Therefore, the long-term results are equivalent.

The following observations merit attention. First, the observed composite major event rates of stroke and death are low, equal to, or lower than the expected event rates seen in historical controls and equal to those recommended by the American Heart Association whether CAS or CEA was used. Second, although periprocedural events were more common in octogenarians regardless of revascularization mode, there was no difference in event rates between revascularization modes. Third, sex did not have a significant impact on long-term outcomes. Fourth, although minor strokes appear to have a differing impact on patients' QOL than MI (in patients who survive the infarctions), other adverse events such as the neurological deficits caused by cranial nerve injuries or access-related complications need to be taken into account when analyzing patients' QOL. Finally, operator experience clearly affects outcomes.

FUTURE PERSPECTIVES

Despite a 40-year history, the benefits of carotid surgery have only become evident during the past 2 decades. As with any medical technology, CAS is constantly undergoing modifications aiming to improve procedural safety. In the

past 2 decades, this has resulted in a steady decline in adverse events. Similar to surgery, it is unlikely that a standard procedural technique and equipment are best suited for all patients because the anatomy is highly variable. Although interventionists taking part in CREST were limited to the use of only one stent system (RX Acculink) and one distal filter system (RX Accunet) for embolic protection, there were no restrictions in surgical techniques in the CEA group. Meanwhile, newer embolic protection devices and stents have become available, which could be associated with lower stroke rates, thus potentially improving outcomes for CAS. In future trials, interventionists should be allowed to tailor the approach, technique, and equipment according to the patients' anatomy.

Further, the impact of optimal medical management on stroke risk in patients with carotid disease is worth reinvestigating. To allow better comparison between CAS and CEA, all subjects participating in future trials should be treated with best medical treatment, and their medication should be documented. Importantly, very little data are available on stroke risk in patients with optimal medical therapy. Given the significant but relatively small benefit seen with surgical revascularization in asymptomatic patients in an era when statins, angiotensin-converting enzyme inhibitors, and thienopyridines were not routinely used, optimally, any mode of revascularization in the absence of symptoms should occur with optimal medical management and be compared with a control arm of patients treated with medical management only.

Finally, although major stroke rates are low after both types of revascularization, events continue to occur. Therefore, both surgeons and interventionists must continue their quest to eliminate the risk of stroke whether caused by carotid disease itself or by its revascularization. ■

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Advances in Embolic Protection Devices

Will improvements in EPD design lead to safer carotid artery stenting procedures?

BY SAMIR K. SHAH, MD; NAVEEN BALASUNDARAM, MD; AND DANIEL G. CLAIR, MD

Internal carotid artery stenting (CAS) has become an increasingly tenable alternative to carotid endarterectomy for occlusive disease in high-risk patients. Although CAS is advantageous in several respects relative to endarterectomy, both show risk for embolic stroke.^{1,2} Despite the absence of any form of embolic protection during initial CAS experiences, the potential for embolism during wire manipulation of the plaque with continuous antegrade blood flow is intuitively evident.³ In fact, one would expect that the number of emboli produced during CAS would be substantially higher than that produced by carotid endarterectomy, and indeed, this has been shown in several studies.^{4,5} Although the clinical significance of emboli remains to be clarified (patients appear to tolerate some emboli as documented by transcranial Doppler or diffusion-weighted imaging [DWI] without sequelae^{6,7}), it is likely that a reduction in distal embolization would improve the safety of CAS.

EMBOLIC PROTECTION DEVICES

Since the initial description of an embolic protection device (EPD) in 1990 by Theron et al, there have been numerous technological advances.⁸ Currently, three broad categories of EPDs exist: proximal occlusion devices, distal occlusion devices, and filters (Table 1).

Proximal Occlusion Devices

Proximal occlusion devices represent the most recent evolution in EPDs and include the Mo.Ma Ultra (Medtronic Invatec, Frauenfeld, Switzerland) and the GORE® Flow Reversal System (Figure 1), which produce flow stasis and flow reversal, respectively. The Mo.Ma device uses balloon occlusion of the common carotid and external carotid arter-

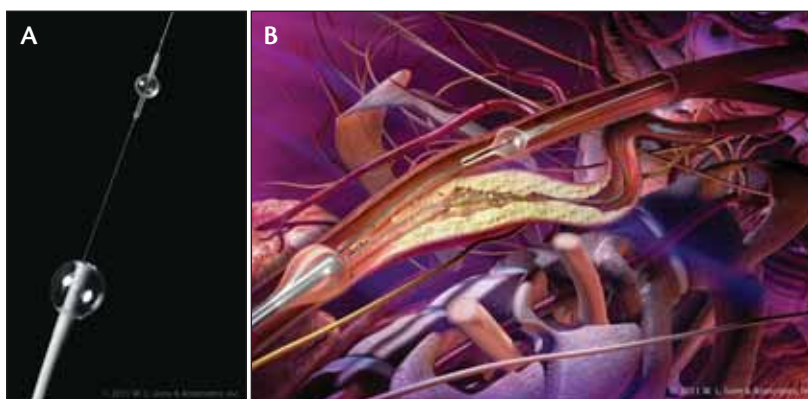


Figure 1. GORE® Flow Reversal System (W. L Gore & Associates [Gore], Flagstaff, AZ). Ex vivo view (A). The larger proximal balloon occludes the common carotid artery, while the distal balloon occludes the external carotid artery. In situ depiction of common and external carotid occlusion and flow reversal (B).

ies to achieve cessation of blood flow before angioplasty and stenting. The GORE® Flow Reversal System additionally establishes a filtered arteriovenous shunt between the common carotid and femoral vein to produce flow reversal.

The principal advantage of proximal occlusion devices is the avoidance of plaque disruption (provided the lesion begins distal to the origin of the external carotid artery) during EPD placement. The GORE® Flow Reversal System has the added benefit of actively removing particulate matter. Given that these devices sit proximally to the target lesion, there are no relevant landing zone requirements. Disadvantages include the need to separately place two balloons, a slightly larger 9- to 9.5-F compatibility, and potential intolerance to flow cessation.

Distal Occlusion Devices

Distal occlusion devices attempt to prevent embolization via balloon occlusion of the internal carotid artery distal to the lesion. The only currently available device is the GuardWire system (Medtronic, Inc., Minneapolis, MN). The device is 6-F compatible and is available with two balloon

TABLE 1. TECHNICAL DETAILS OF SELECTED EPDs

Type of Protection Device	Device Name	Manufacturer	Landing Zone (mm)	Pore Size (μm)
Proximal occlusion	Mo.Ma Ultra	Medtronic Invatec	–	–
	GORE® NPS	W. L. Gore & Associates	–	–
Distal filter	FilterWire EZ	Boston Scientific Corporation	13.4	110
	Emboshield Nav ⁶	Abbott Vascular	19–22.5	140
	RX Accunet	Abbott Vascular	15.1	150
	SpiderFX	Covidien	17.3	50–300
	FiberNet	Medtronic, Inc.	15	< 40
	GORE® Embolic Filter	W. L. Gore & Associates	9 ^a	100
	Angioguard RX	Cordis Corporation	5.9	100
Distal occlusion	GuardWire	Medtronic, Inc.	–	–

^aNo landing zone recommendation provided in the Instructions for Use.

sizes to occlude vessels with 2.5- to 5-mm and 3- to 6-mm diameters; crossing profiles are 0.028 inches and 0.036 inches, respectively.

The balloon is equipped with a 2.5-cm nitinol distal tip and is advanced past the lesion and inflated using a 0.014-inch wire inflation system. The inflation device is then detached from the balloon and wire, which are used to complete the intervention. After stent placement, an aspiration catheter is advanced over the wire to evacuate debris before balloon retrieval. The aspiration catheter can also be used to flush debris from the “dead end” of the internal carotid artery below the inflated balloon into the external carotid artery, but this risks embolism via external to internal carotid collaterals.

Clear advantages of distal occlusion devices include a low crossing profile and a minimal 4.5-mm landing zone for the occlusion balloon. The need to traverse the lesion before intervention, mandatory use of aspiration, risk of embolism past the balloon, interference with visualization of the lesion, injury to the distal carotid artery, and intolerance to flow occlusion constitute its principal disadvantages.

Filter Devices

Filter devices are the most common EPD type and are available in a broad variety of specifications (Figure 2). Many filter EPDs come attached to a moldable wire tip and wire body, whereas some may be advanced over a 0.014-inch wire that has traversed the lesion. Filter details range widely with regard to several specifications: crossing profile, landing zone length, and pore size. Crossing profile ranges from 1.7 F (FiberNet, Lumen Biomedical, Inc., Plymouth, MN) to 3.9 F (Angioguard Rx, Cordis Corporation, Bridgewater, NJ). The majority of filters can be primarily advanced past the lesion without angioplasty; if needed, the lesion can be predilated

with a low-profile angioplasty balloon, although this risks embolism. In addition to the smallest crossing profile, the FiberNet filter also has a short landing zone (15 mm). Although pore size typically ranges from 100 to 140 μm, devices with substantially smaller (FiberNet, 40 μm) and larger pores (SpideRX [Covidien, Mansfield, MA], 167–209 μm) are available.

Assessment of flow before filter retrieval is mandatory, as diminished flow may indicate clogging of the device with embolized debris. This requires aspiration of the debris and reassessment of flow to avoid embolism during retrieval. Persistent flow limitations may be due to arterial spasm, which can be treated with injection of a vasodilator (eg, nitroglycerin). Filter devices are easy to deploy, do not interfere with lesion visualization, and maintain antegrade blood flow. However, they also suffer from some disadvantages: the need to cross the lesion before implementation of protection, embolism through the filter both during the intervention and during recapture, and the need for a nontortuous landing zone. Absence of the latter may make performance of the procedure impossible and can allow embolism between the vessel wall and the filter when coaptation of the filter to the vessel wall is inadequate.

EFFECTIVENESS

There have been numerous studies establishing the safety of individual devices (Table 2). Nonetheless, it is difficult to arrive at any robust conclusions regarding the relative effectiveness of particular EPDs because of differences among studies with respect to patient comorbidities, degree of carotid stenosis and symptomatology, carotid stents, operator experience, and other factors that could feasibly affect outcomes. The ideal test to determine EPD effectiveness would be a comprehensive comparative randomized trial involving multiple EPDs;

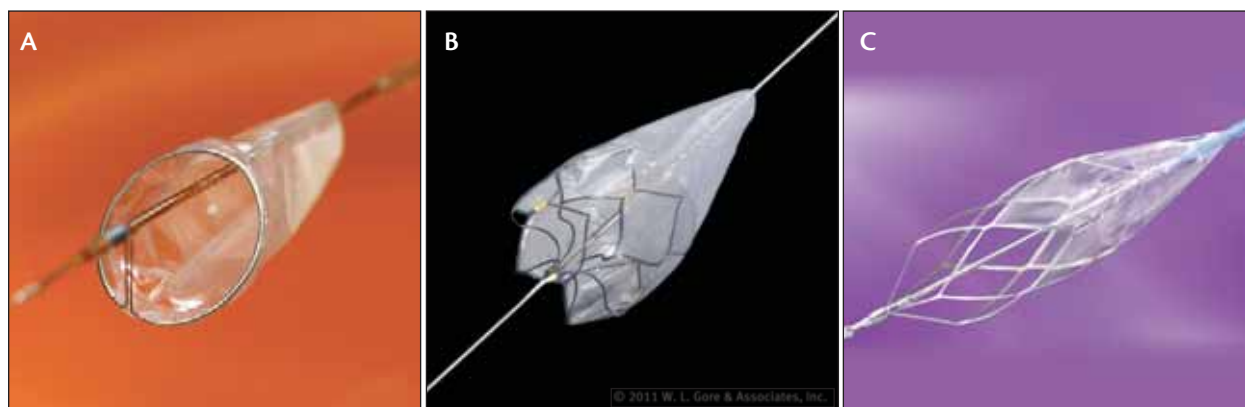


Figure 2. Filter EPDs. FilterWire EZ (A), GORE® Embolic Filter (B), and RX Accunet embolic protection system (C).

regrettably, there is no such study. To make matters worse, as stated previously, knowledge regarding the number and size of emboli required to produce clinical sequelae is lacking.

More problematic is the absence of clear evidence of the general effectiveness of EPDs. No clinical trial has shown improved outcomes from EPD use despite the instinctive sense that they must improve safety. Macdonald et al compared 15 CAS patients who underwent treatment with the Emboshield filter (Abbott Vascular, Santa Clara, CA) with 15 patients who underwent unprotected CAS, using DWI magnetic resonance imaging and transcranial Doppler signals as surrogates for stroke.⁷ There was a statistically greater number of signals consistent with embolism on transcranial Doppler in patients with filter placement than in those without. Similarly, there was an increased, but statistically nonsignificant, number of new white lesions indicating emboli on DWI in patients with EPD. The increased number of emboli in EPD patients was generated during filter installation and retrieval.

A similar randomized study by Barbato et al using the RX Accunet embolic protection system (Abbott Vascular) in 35

patients found that there was no statistical difference in the number of lesions detected by DWI between the EPD and non-EPD cohorts.⁶ Both of these studies have a number of weaknesses—most importantly, the small sample size and the use of proxy imaging measurements instead of actual clinical stroke. The latter point cannot be overemphasized, and one must be cautious when interpreting the clinical significance of these findings. Whether or not these potential drawbacks are limited to filter devices or extend to all current EPDs is unknown. Some studies have suggested reduced embolism with distal occlusion⁹ or proximal occlusion devices relative to filters.¹⁰

It is important to be mindful that filter use may not be as protective as once thought and has the potential to paradoxically increase embolic phenomena. Despite these issues, most agree that the use of embolic protection is mandatory, and evidence for this comes from several sources. First, the capture rate for visible debris in filters is very high and has been noted at 60% when evaluated by Sprouse et al.¹⁶ Second, experimental ex vivo assessments of

TABLE 2. SELECTED EPD TRIALS

Device	Trial	Number of Patients	30-Day Stroke	30-Day MI/Stroke/Death
Mo.Ma Ultra	ARMOUR ¹¹	262	2.3%	2.7%
GORE® Flow Reversal System	EMPIRE ¹²	245	2.9%	3.7%
Angioguard/Angioguard XP	SAPPHIRE ²	167	3.6%	4.8%
Accunet	ARCHER ¹³	581	5.5%	8.3%
GuardWire	MAVERIC I/II ¹⁴	498	4.2%	5.4%
FiberNet	EPIC ¹⁵	237	2.1%	3%

Abbreviations: MI, myocardial infarction.

EPDs reveal that they all trap debris typically released during CAS.^{17,18} Finally, large registries that have compared outcomes with and without protection have found significant reductions in neurologic events among patients who were treated with EPDs.¹⁹⁻²¹ It is unclear whether data that do not support the use of these devices reflect a failure of the device, some problem with the devices inducing embolization, or the inability of the devices to trap microparticles. In this regard, the use of proximal protection has the distinct advantages of protected lesion crossing, trapping of debris of all sizes, and no injury beyond the area being protected.

A thoughtful paradigm for choosing EPD type has been outlined by Schneider and Ansel.²² Briefly, these authors recommend the use of proximal protection in the setting of complex lesions and in those with limited cerebral reserve, filters in the setting of poor collaterals, and a device of the interventionist's choice in situations that do not fall into any of these categories. What is perhaps most important in the performance of CAS is the understanding that adequate experience with every available device is unattainable, and each interventionist should choose one proximal protection system and one distal protection system (filters most commonly) to achieve familiarity and develop a procedural routine. This will limit intraprocedural complications related to deployment and use problems.

CONCLUSION

Embolic stroke remains one of the principal risks of CAS. EPDs attempt to reduce this risk via proximal or distal occlusion or filtration. Although seemingly obvious, evidence regarding the effectiveness of EPD use and of the superiority of one EPD over another is lacking, and we are unlikely to ever see randomized data regarding the use of these devices. Further study is needed to clarify the role of EPDs during CAS. For example, what are the implications of embolic debris below the threshold of filter trapping? Are symptomatic and elderly patients more susceptible to microembolic debris (as an explanation for increased neurologic events in these patient groups)?

Advances in CAS are likely to continue and will be related to the systems used to introduce equipment into the carotid artery, embolic protection, and stent design. Of all of these areas, the majority of advancements to date have been in the design of EPDs, which are now specifically engineered for CAS. I believe that CAS has been made safer because of these advances, and further iterations of these devices will likely lead to continued improvements in the safe performance of this procedure. One can easily envision the day when performance of CAS will be the primary method of treating carotid disease because of successful efforts to limit neurologic sequelae as is already being seen in the development of EPDs. ■

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Debate: Current Stent Design Is Inadequate and
Contributes Significantly to Procedure-Related Stroke

Why Should Stent Design Not Have an Impact on Procedural Outcomes?

BY SUMAIRA MACDONALD MBChB (COMM.), FRCP, FRCR, PhD, EBIR

When faced with a debate such as this, against a more-than-worthy opponent, one feels the need to point out that the debate really ought to pivot solely on an exposé of the influence of stent design on outcomes for carotid artery stenting (CAS) and not on nonstent-related causes of adverse outcomes, which are, of course, myriad.

It is accepted that patient factors such as age, sex, and precategorized presenting complaint significantly affect CAS outcomes, as does patient sensitivity to the prerequisite dual-antiplatelet regimen (sensitivity being largely variable even when exact dose, dosing schedules, and named drug are explicitly described in the inclusion criteria of either a randomized trial or independently audited registry). The well-recognized influence of operator experience on outcomes also cannot be easily overlooked. Lastly, it should be accepted that while the European Union has been in somewhat of a “comfort zone” regarding the use of a bewildering array of CE Marked carotid stent and embolic protection devices, the United States has been subject to a relatively controlled environment enforced by federal regulatory restrictions. This means that United States datasets are not geared to compare stent systems and their possible differential influence on outcomes, but rather, by necessity, sizeable United States cohorts evaluate a single stent (and often the same manufacturer’s embolic protection device).

I would like to frame my argument based on a number of considerations that I hope the *Endovascular Today* readership might see as at least thought provoking.

WHY ARGUE AGAINST DEDICATED CAROTID STENT DESIGNS?

I would like to turn the question on its head for Dr. Gray: Why should stent design *not* have an impact on outcomes?

Individual arterial territories demand individualized solutions. The inexorable drive to improve aortic stent graft parameters (profile, conformability, and the use of novel materials that better mold a rigid structure to a compliant major vessel that has undergone expansion as a result of weakness in the arterial wall) is intended to improve outcomes with respect to length of stay and late interventions to better secure aneurysm exclusion from the circulation (the 30-day mortality benefit over open repair being already well documented).

The superficial femoral artery, a traditionally hostile territory for stent placement on account of unique hemodynamics (a relatively low-flow, high-resistance circuit) and exacting standards regarding the ability of any endovascular stent to rise to the challenge of unparalleled mechanical forces, has benefited from advances in stent design. Dedicated third-generation systems show significantly improved intermediate-term patency compared with generic balloon-mounted historical stents and second-generation models adapted from iliac platforms.

The carotid bifurcation lesion presents a unique endovascular challenge, requiring that a stent couples conformability with scaffolding properties sufficient to “brace back” friable plaque.

DEDICATED DATASETS

Studies specifically formulated to evaluate differences in outcomes relating to stent design are few and far between. These are largely of European origin and, when specifically formulated to examine differences, exclusively use surrogate markers of stroke and death—namely diffusion-weighted (DWI) magnetic resonance imaging new hyperintensities or procedural transcranial Doppler (TCD) microembolic signals. Secondary datasets also exist—sizeable real-world registry data outcomes that enable us to retrospectively explore differences in outcomes based on stent type, although none of these sources were powered to answer this seminal question. Under these circumstances, the inevitable confounding variables can only be partially accounted for, if at all. Having acknowledged this, the European data (that allow liberal use of CE Marked systems, resulting in registries in which many different stents are included) indicate that stent design significantly affects outcomes in the symptomatic population.

The Bosiers Belgian-Italian registry, which included more than 3,000 patients, clearly indicates the benefit of closed-cell over open-cell designs for symptomatic patients (there being no such relationship in asymptomatic patients).¹ As a stand-alone piece of evidence, this is perhaps of esoteric interest only. However, the Schillinger registry, subsequently published, with the specific aim of refuting any relationship between stent design and outcomes (and into which data from my own unit were entered) showed, if not statistical significance, a clear trend toward improved outcomes in symptomatic patients when closed-cell stents were used.²

Stent design issues were further evaluated as a prespecified analysis within the SPACE trial (German/Austrian/Swiss 1:1 randomized trial of carotid endarterectomy versus stenting in an exclusively symptomatic population). The ipsilateral ischemic stroke/stroke death rates were significantly lower when closed-cell systems (Wallstent, Boston Scientific Corporation, Natick, MA) were used compared to the Precise (Cordis Corporation, Bridgewater, NJ) or the then-Guidant Acculink (now Abbott Vascular, Santa Clara, CA) systems.³

There is a clear common thread running through the available datasets, suggesting that in symptomatic patients, closed cell-stents are associated with better procedural outcomes.

The key is the definition of those populations in whom stent design is a crucial consideration and those in whom it is of secondary relevance.

MEANINGFUL POPULATIONS

There exists a sizeable discrepancy in the differential magnitude of benefit when one compares a symptomatic patient with an asymptomatic patient. Based on NASCET and ESCT pooled data, the numbers needed to treat for symptomatic patients in order to prevent one subsequent stroke are an order of magnitude different.⁴ We perhaps need to treat approximately seven unselected symptomatic patients to prevent one stroke compared to approximately 20 unselected asymptomatic patients.

In health care environments that are increasingly constrained around the globe, we will be forced to justify our procedural expenditure. Furthermore, it is known from enumerable datasets that symptomatic patients incur a higher procedural hazard than their asymptomatic counterparts.^{5,6} In a population that has so much to gain from carotid intervention and in whom the procedural risks could be modified, why should we not focus diligently on these risks and try to evaluate the procedural variables that may affect patient outcomes?

MEANINGFUL SURROGATES

The use of surrogate markers of clinical endpoint (stroke and death) allows a more convenient comparison of outcomes stratified by stent design (compared with stroke and death) owing to the simple fact that new hyperintensities on DWI magnetic resonance imaging of the brain and microembolic signals on TCD during/after CAS are florid by comparison with stroke and death. Although there are differences in these parameters based on stent design, an important limitation is that these surrogates may be dismissed as clinically dubious or irrelevant, and it is true that both the clinical relevance and fate of new DWI lesions require further elucidation.

However, if one were to suspend disbelief for even a short while, it is clear that closed-cell systems are associated with significantly fewer new brain lesions than open-cell systems for both symptomatic and asymptomatic lesions (regardless of embolic protection),⁷ and a prototype of a covered stent system (Symbiot, Boston Scientific Corporation) was associated with significantly fewer TCD-measured embolic signals than an uncovered closed-cell stent (Wallstent) in a mixed patient population.⁸

Although pilloried in some circles, surrogates, such as those described, may serve as valid endpoints for the scientific community who wish to advance medical science without practicing on thousands of patients. Furthermore, I would like to ask the readership what

they would prefer: Would they like a reduced microembolic burden to their brains (or to the brains of their loved ones) regardless of the fact that we still cannot determine the longer-term consequences of these subclinical events?

ADEQUATE POWER

When the overall event rates for CAS fall to 2.7% or 2.9%, all stroke/death in independently reviewed registries with independent adjudication of adverse events (ARMOUR and EMPIRE registries evaluating proximal embolic protection systems such as Mo.Ma [Medtronic Invatec, Frauenfeld, Switzerland] and the GORE® Flow Reversal System [W. L. Gore & Associates, Flagstaff, AZ], respectively),^{9,10} it becomes a statistical challenge to derive any meaningful difference in outcomes between open-cell and closed-cell carotid stents unless there are several thousand patient outcomes to compare. It goes without saying that any such comparison should also be separately powered for asymptomatic and symptomatic patients because the procedural hazards and the net gain for carotid intervention in these two populations is markedly discrepant. Anyone attempting to embark on such an endeavor will find that the United States registry data comprise a majority asymptomatic population—a conservative estimate reflecting that asymptomatic patients represent perhaps 60% to 80% of all carotid interventions.

CLOSING ARGUMENT

Dr. Gray might argue that in the EXACT (closed cell)/CAPTURE 2 (open cell) combined registry⁵ and, for example, the EMBOLDEN registry, in which a variety of stent designs were used with a single-filter-type embolic protection device, stent design did not have an impact on outcomes. True. However, the majority of these patients were asymptomatic (87.9% and 85%, respectively). The lesion demands for symptomatic and asymptomatic patients are wholly different. Furthermore, these registries were simply not powered to answer the question inherent in the title of this debate.

And so I rest my case. When we deal with the most deserving population (patients with symptoms attributable to a significant carotid lesion) in whom procedural hazard is substantial, if there is a recurring theme

in the world literature in favor of closed-cell stents, why would we not want to tentatively endorse current findings, to further explore, and to refine our procedural paradigms to improve outcomes by focusing on specific technical parameters?

The jury may still be out, but I hope that I have provided enough fodder for the intellectually curious to at least sit on the fence, if not quietly accept that more work needs to be done. ■

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Debate: Current Stent Design Is Inadequate and
Contributes Significantly to Procedure-Related Stroke

Stent Design Is Not a Major Factor Leading To Stroke

BY WILLIAM A. GRAY, MD

As the practice of carotid artery stenting (CAS) has grown over the past decade, along with a greater acquired experience with the procedure and equipment, and rapid improvement in outcomes, the natural progression of the field is to look for further opportunities to refine the technique and improve the technology so as to create an even safer and therefore more effective stroke-preventative procedure.

Among the possible improvements suggested as critical to reducing procedural stroke is in stent design. This discussion has come about for a variety of reasons, which have been well described by my opponent in this debate. I will submit here, however, that an analysis of the data—without the requirement to suspend disbelief—will lead away from the concept of the stent as being *significantly* responsible for procedure-related stroke in CAS. This determination is important because it means that we will not hang our hat on the advancement of technology in stents, but rather spend our efforts on more productive and effective pursuits.

For those of you unfamiliar with my opponent, she is not someone to be trifled with. She is well educated, having earned a PhD in embolic protection, highly experienced in complex carotid stenting, and exceptionally articulate in both spoken and written forms. Nevertheless, I will humbly offer my most reasoned arguments in hopes of dissuading you from this siren's song.

The premise of this debate, in a nutshell, revolves around the concept that open-cell stents (which are made that way to increase flexibility and conformability) are too porous, and that, as compared to closed-cell stents, open cells are too large and permit emboli more readily. However, the physical basis of this argument is in question because the minimal circumferential unsupported area (MCUSA, the biggest circle that one can fit

through a cell) does not materially differ based on cell structure, ranging between approximately 0.90 and 1.10 mm in diameter. Moreover, the filters that are used with these stents have pore sizes approximately one-tenth of this diameter, such that any liberated procedural debris this size should be adequately retrieved by a well-functioning filter.

LOOKING BEYOND INTUITIVE SENSE

Before presenting my perspectives on stent design in CAS, let's deconstruct my worthy opponent's arguments and see if they hold water. The first argument is that specialized stents for specific vascular territories make intuitive sense. In defense of this argument, stent grafts for endovascular aortic aneurysm repair are paired with superficial femoral artery stents, and the unique design requirements inherent in each are offered as de facto proof of specialized device requirements. The problem with this line of reasoning is that, in each case, an irrefutable failure mode and mechanism (device migration and stent fracture, respectively) was identified before the iterative improvements of these devices, such that the design goal was clear from the outset.

The topic of this debate and the arguments that follow will be evidence enough that no such unassailable proof of the failure mode of carotid stents exists on which to base design changes or subsequent testing. In other words, what shall we tell our engineers we want from their next design? What specifications shall we require based on what data, and what mechanism of failure can we test to?

FLAWED STUDIES AND INSUFFICIENT DATA

The second argument offered is frankly not very robust, and although my adversary acknowledges this up front, she presents it anyway. The various publications

positing that stent design has any influence on CAS outcomes are so methodologically weak so as to be dismissed *res ipsa loquitur*, that is, as speaking for itself. Specifically, all of the data sets that are referenced by my opponent are not randomized, are retrospective, with only one being prespecified. Therefore, they are subject to profound operator stent selection bias. Selection bias can take several forms, such as using open-cell stents in more complex and tortuous anatomy, which could be compounded by the fact that such anatomy is found in older patients. Because these data were not controlled or corrected for such issues, it is easy to see how quickly confounded the outcomes and conclusions can be. Worse, in the Bosiers analysis, if one removes the non-standard component of transient ischemic attack from the composite endpoint, no significance between stent types remains.

Statistically, there are also flaws with the studies cited: an ad hoc retrospective analysis with multiple samplings no longer becomes significant at $P < .05$, but rather at a much smaller P value, something that these studies did not account for. Moreover, it would take significantly more than 5,000 patients to detect even a 1% difference in death and stroke based on stent design. If one wished to compare open-cell and closed-cell stents (which is what the cited studies purport to do), we do not have to look any further than the prospectively gathered and analyzed CAPTURE (open cell) and EXACT (closed cell) registries.¹ These had the same inclusion/exclusion criteria, many of the same operators, they represent thousands of patients, and there were no differences in 30-day death/stroke/myocardial infarction outcomes (5.7% vs 5.1%, respectively).

In addition, many of the recent US trials performed to establish the safety of new embolic protection devices (EPDs) allowed the operators to use any stent type available, and no trend toward differentiated outcomes was seen by these various stent designs. In fact, outcomes in US trials appear to have improved independent of stent type being tested (Figure 1). Lastly, several clinical trials evaluating stent design, albeit underpowered, have not found even a suggestion of differences in patient outcomes.²⁻⁴ So, as this argument is concerned, there are no unconfounded, adequately powered clinical data to support a differentiation in outcomes based on stent design.

THE TALE OF THE TAPE

The nonclinical evidence of a difference in stent design is also very weak. The surrogate outcome measures of transcranial Doppler (TCD) and magnetic resonance imaging diffusion-weighted imaging (MRI DWI) abnormalities have no proven clinical correlative value.



Figure 1. Outcomes of US trials over time according to the type of stent (open cell or closed cell) tested.

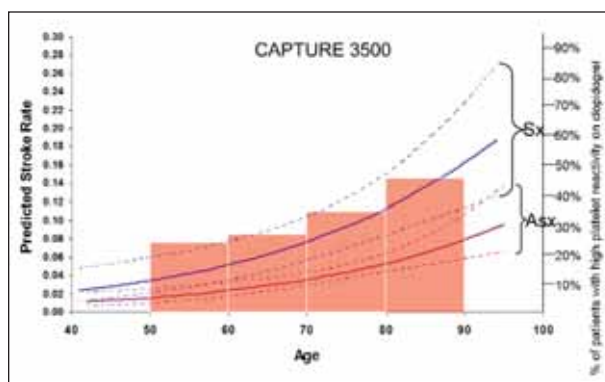


Figure 2. Outcomes in CAPTURE 3500 registry (solid lines with dashed confidence intervals) overlaid with the outcomes of clopidogrel testing for platelet reactivity (shaded bars).

Accepting that, the data cited by Dr. Macdonald do not support her argument. The trial examining TCD and MRI DWI differences between covered and non-covered stents found no differences in MRI DWI and postprocedural 90-minute TCD monitoring; even the investigators concluded they could find no differences.⁵ More importantly, the trial had to be abandoned very early in its course because an excessive degree of restenosis was noted in the covered stent group. This raises the importance of this debate: modifying the carotid stent to address an as yet unclear excess risk and unclear putative mechanism of stent design “failure” does not represent all upside, and possible unintended consequences such as were seen here may be myriad. Accordingly, the justification to do so should be solid.

If we are to take seriously an analysis adequate enough to come to the conclusion that the stent is the significant cause of stroke in CAS, we will need to take many factors into account and do our best to rank the contribution of each. An exhaustive review of possible

factors is not possible within the scope of this debate, but some important elements will be highlighted.

PATIENT AND OPERATOR FACTORS

Our internal analysis of films from some of the previous angiographically controlled US trials suggests that operator error (balloon sizing, wire misadventure, EPD errors, etc.) is not a trivial factor in the creation of strokes in CAS. Second, there are patient-related factors, many of which will be unrelated to stent design, such as vulnerable plaque with resultant iatrogenically induced rupture and acute stent thrombosis, aortic plaque leading to stroke during access manipulations, and genetics related to incomplete clopidogrel metabolism leading to inadequate platelet inhibition. This thienopyridine issue, interestingly, seems to worsen with age⁶ much as the results from CAS do (Figure 2)—a possible explanation? Certainly as plausible as the stent design. And last, intraprocedural failure of EPDs due to lack of apposition, etc., can also contribute significantly to stroke in patients who have undergone CAS.

In fact, a relatively simple calculation of the known alternative causes of stroke in CAS patients is possible from the CAPTURE registry, which is a prospective, well-studied, and characterized experience in CAS.⁷ In CAPTURE, the overall 30-day rate of stroke was 4.8% in the high-surgical-risk population. Of these strokes, several categories unrelated to the stent can be eliminated. Specifically, if the nonipsilateral (clearly not stent-related), the hemorrhagic (generally not embolic in etiology), the procedural strokes (when EPD would have been protective), etc., are discounted, then the strokes possibly related to the stent become approximately 1.0%, or about one-fifth of the total strokes. This is clearly not a significant cause of stroke in CAS as outlined in this debate's proposition. Moreover, if the same analysis is done with presumably "at-risk" plaques (symptomatic and elderly patients), which would be expected to be particularly sensitive to defects in stent design, no difference is seen in the rate of plausible stent-related strokes.

CLOSING ARGUMENT

Although it is tempting to jump to the conclusion that stent design should be improved in order to reduce strokes occurring in patients who have undergone CAS,

a critical analysis of the data does not support the stent as a significant contributor to stroke, does not reveal a specific failure mode of the stent such that specific design modifications would be a guess at best, and suggests that not only would a difference in outcomes after a change in design be difficult to ascertain, but that it is possible a negative outcome could result, as was seen in the covered stent experience. Other advances and modifications focusing on patient selection, procedural technique, access, EPD improvement, and possibly pharmacology modification are more likely to have a beneficial effect in CAS outcomes. ■

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The Journey of Carotid Stenting in Contemporary Stroke Prevention

Lessons learned during the development of carotid artery stenting and a look at where we go from here.

BY PETER A. SCHNEIDER, MD

As the concepts and technology that drive carotid artery stenting (CAS) as an option for treating extracranial carotid occlusive disease have matured, the understanding of CAS's value to our patients has followed a roller coaster pattern in recent years. The safety of CAS has improved dramatically during the past 10 years, with recent studies achieving perioperative stroke/death rates that are within recommended guidelines for carotid repair.¹⁻⁶ However, it is challenging to interpret what the available data and the existing clinical practice patterns mean. The results of CREST have left many questions unanswered, and this will be especially evident once the subanalysis is published.

During the time that CAS has developed, our approach to endovascular repair in every vascular bed has become significantly more sophisticated, and we are using and transferring those skills to all our work. The overall level of endovascular skill for all specialties is better now than it was 10 years ago, and we have become a lot smarter about managing carotid disease in the interim. In my opinion, trends are emerging from the research, clinical experience, and development in this area that show a trajectory toward establishing a major role for carotid stenting in the management of carotid occlusive disease and the prevention of stroke.

DEVELOPMENTAL PATHWAY

Anyone in the active practice of carotid endarterectomy (CEA) will attest that during the removal of carotid bifurcation plaque, one often finds friable, seemingly antibiological material that defies proper description and will cure any onlooker of interest in fast food. In

addition, carotid bifurcation stenosis causes problems through embolization, a process during which the moonscape flow surface of the heterogeneous lesion becomes unstable. Given these factors as a starting point, it makes little sense a priori that CAS would be effective in preventing stroke because it modifies the plaque in situ. This helps to explain some of the heart-felt resistance that many endarterectomists have had for CAS.

However, let's look beyond this initial impression for a moment. If the carotid stenosis were not attached to the brain, it would be ideal for successful endovascular intervention. The lesions are almost always focal, with healthier artery proximally and distally. The lesions are stenoses, not occlusions, and it is almost always possible to dilate them with standard balloon technology. Perhaps to render the lesion harmless to the patient, the stent must only modify the morphology of the flow surface. In fact, it appears that the scaffolding provided by the carotid stent is enough to maintain an adequate lumen and, at the same time, prevent the carotid lesion from becoming unstable. This is borne out by the long-term follow-up after EVA-3S, SPACE, SAPPHERE, and CREST, which all show the same level of stroke protection after both CAS and CEA once the patient is beyond the first 30 days.^{1,7-9}

The important difference between CAS and CEA in all randomized trials so far is the perioperative risk of stroke. In the CREST trial, the risk of major stroke and the risk of death were not significantly different between CAS and CEA, but there were more minor strokes with CAS. Our challenge is to make the perioperative period safer if CAS is going to be of value to our

patients in preventing stroke. One would hope that we were paying attention and honing our skills during the past decade as CAS has been developing and that we have learned something along the way: which patients, arches, and lesions can be safely considered for CAS. This is exactly what we are experiencing, and there is mounting evidence that CAS has become safer.

When perioperative morbidity rates for CAS from the early 2000s are compared with those from the end of the decade, we see that the stroke/death rates have decreased from the high single digits (eg, 8% in ARCHER) to the low single digits (3% or less range for PROTECT, EPIC, EMPIRE, and ARMOUR trials).^{2-5,10} The CREST trial also showed a steady improvement in periprocedural results for CAS. Although these data are not yet published, it is impressive to see how much the perioperative results for CAS have improved over time as the available devices, inclusion criteria for the study, and participating investigators were held constant. Information about the change in results of CAS over the course of the CREST trial is available at the US Food and Drug Administration Web site and was presented during the administration's panel on CAS on January 26, 2011.¹¹

Each of the sophisticated endovascular procedures in our repertoire is the product of a gradual building process with incremental improvements in technology, technique, and clinical skill, creating a feedback loop that leads to better results. No one expected endovascular repair of aortic aneurysm or recanalization and reconstruction of a superficial femoral artery occlusion to be a finished product on day one. In contradistinction, CAS was presented as a finished product and a replacement for CEA. Whether this was hubris, a miscalculation based on previous successes, a misunderstanding of how confounding carotid disease can be, a demand from the regulatory system (that expected a complete CAS system to be tested before any approval could be achieved), youthful enthusiasm, or all of these, is not clear.

However, if CAS were being rolled out today, it would be done differently. It would likely be introduced in the same manner as other endovascular procedures have been presented—as a partial solution that will likely grow into the new role with improvements over time. What if the regulatory apparatus, the market for medical devices, the research institutions, the physicians, and the patients had insisted that endovascular aneurysm repair had to solve all of the potential problems up front, including difficult neck anatomy and endoleak, to become a viable treatment? It would never have gotten off the ground.

Take yourself back to Y2K. The dawn of the new millennium was a rapid development phase for many of the things that we rely on now in various aspects of daily life: the dissemination of web-based information and business opportunities, digital communication, an Internet-based economy, the emergence of Google, the ability to move capital rapidly from place to place, and the realization that everyone would have a cell phone, to name just a few. This was also a time frame during which the pace of development in the endovascular field was on an amazing slope of progress. Multiple vascular beds were being treated with new techniques and new attitudes at once. Most of our current procedures have developed significantly during the past 10 years. Clopidogrel was new, and there were no drug-eluting coronary stents yet available. The top-selling endovascular aneurysm repair grafts of the time have gone by the wayside. The possibility that carotid disease could be solved using stent implantation evoked opinion from all and emotion from most. This was the era in which the CREST trial began to enroll.

In 2001, the first major randomized trial comparing CAS and CEA, the CAVATAS trial, was published.¹² Neither CAS nor CEA performed well; the stroke and death rates were > 10% in each group. Among those undergoing intervention, all received angioplasty but only one-quarter received a stent. So, without a scaffold being used in most of the patients and without any method of cerebral protection, the stroke and death rate was 10%. At the time, in my vascular surgeon's mind's eye, I imagined that the rate of complications should have been 50% because I had the experience of handling nasty plaque material for many years. This was the first indication that it would be a matter of time, technology, and case selection before carotid intervention would become a worthwhile approach. Since then, a lot of toil and trouble have gone into the development of CAS.

WHAT HAVE WE LEARNED?

Developments in the endovascular arena during recent years have facilitated the field of CAS, including a trained workforce, the broader availability of endovascular skills and techniques, a wider experience with carotid and cerebral arteriography, improvements in noninvasive duplex and axial imaging, a better understanding of vulnerable plaque, and the general appreciation of endovascular techniques and what they can do in all vascular beds. At the same time, we are chastened by some of the things that we learned the hard way with CAS. For example, CAS is not a direct replacement for CEA. In the same way that there are many factors

that make a patient a better or worse candidate for CEA, there are other factors that influence the suitability of patients for CAS. CEA will be performed for many years to come and will continue to be the best solution for a large proportion of patients with carotid bifurcation stenosis.

We also know that there is a learning curve in terms of the number of procedures performed by each operator, as well as in terms of patient selection. Trial results have been profoundly influenced by the experience and abilities of the practicing clinicians, and this is grossly evident in the randomized trials of CAS and CEA. We know that octogenarians should be managed carefully. Furthermore, we have learned about the clinically unapparent but nevertheless worrisome lesions that can be detected by diffusion-weighted magnetic resonance imaging of the brain after all forms of carotid reconstruction and that these lesions must be better understood and managed. Some type of cerebral protection is required to make CAS viable, and proximal occlusion is tolerated in most patients.

We have learned new facets of arch anatomy and cerebral physiology. Carotid lesions are more dynamic structures than previously thought and are capable of significant remodeling. We now know at least some of the factors that make a patient high risk for CAS. Events after CAS are more frequent, more often minor, and more often delayed in comparison to CEA. We must make the first 30 days as safe as possible to offer value to our patients with CAS.

What can we show for our collective efforts? We have randomized trials, recommendations for training, and the widespread practice of CAS in communities around the world. There are multiple databases, including one maintained by the Centers for Medicare & Medicaid Services. Most sophisticated hospitals have specific criteria to obtain privileges to perform CAS. We now have multiple options for cerebral protection during CAS. We have seen improving results: CAS has been performed with incredibly low risk considering conformance of both the symptomatic and asymptomatic arms of the CREST trial to American Heart Association guidelines (3% stroke and death rate for asymptomatic patients, 6% for symptomatic patients). We have multiple stents and cerebral protection devices with at least some form of approval in many countries. There are also some wounded feelings left over from interspecialty conflict, and there is exasperation among many clinicians at the slow pace of the regulatory progress.

We also have the CREST trial, of which we should be proud. CREST was a valiant, multispecialty effort in which patients, physicians, industry, and the National

Institutes of Health pursued a level of investigation and clinical science that was courageous, especially at the time it was initiated. The CREST trial was the only one among the major randomized trials that included both symptomatic and asymptomatic patients and required a high level of expertise for those performing both procedures. Ten plus years later, the results show that this endeavor has never been as simple as we all hoped. A more definitive answer is not to be had immediately, especially in light of the results for separate endpoints (ie, more minor strokes after CAS and more myocardial infarctions after CEA). Information will be made available in subsequent publications that should help us to understand which subgroups are better treated with CEA and which are better treated with CAS. By virtue of when it was planned, CREST had a lot of criteria for what makes a good CEA candidate but minimal criteria for what makes a good CAS candidate.

WHERE DO WE GO FROM HERE?

I am one of the foolish people who imagined that the role of stents in managing carotid bifurcation stenosis would be more settled by this point. We still have our work cut out for us. A well-done procedure presupposes a well-trained workforce. The quality of the endovascular skills and the number of people who possess them, from a number of fields, is dramatically better now than it was 10 years ago. However, as CAS goes through fits and starts, we will have to be resourceful in managing the staffing for these cases in an effort to maintain the proficiency of practitioners who have gone before and improve the experience of those who hope to gain proficiency.

An absolute stroke rate of 1% appears to be due to arch manipulation. What if you could take the arch out of the equation whenever there was significant tortuosity or disease by performing direct cervical access? Some strokes occur in the hours or days after the CAS procedure, presumably with embolization through the open cells of the carotid stent. What if different stent designs could be used to prevent these episodes of delayed perioperative embolization? We know that patients with recent symptoms have a higher risk of stroke after CAS. What if proximal occlusion could be used for cerebral protection in these patients? What if various stent designs and methods of cerebral protection could be customized to the needs of each individual patient taking into account the presentation, the lesion, and the anatomy to design an optimal treatment plan? The results of contemporary medical management of critical but asymptomatic carotid stenosis without mechanical repair has not yet been established, so the added value

of carotid repair cannot be fully understood in this group. Optimal management of asymptomatic stenosis is a major issue on the horizon for all clinicians that must be addressed during the next few years and will certainly influence the practice of CAS.

CONCLUSION

Trends emerging from research and clinical experience suggest a major role for CAS in the management of carotid occlusive disease. However, further development will be required. CAS and CEA will likely be complementary for the foreseeable future. We need to keep calm and keep working. Although there are issues that are yet to be fully understood, carotid stents are of value to our patients. ■

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