



# Past, present and future of carotid artery stenting: a critical review of randomized studies and registries

Carotid endarterectomy (CEA) has been the standard of care in primary and secondary stroke prevention following the publication of seminal trials comparing CEA to medical therapy for both symptomatic and asymptomatic patients determined to require revascularization. In recent years, carotid artery stenting (CAS) has emerged as a potential alternative to CEA, as it is less invasive and associated with less surgically related morbidity and the potential for an accelerated convalescence. A large body of literature, including randomized clinical trials and real-world registries, has attempted to compare the safety and efficacy of CAS with that of CEA. Unfortunately, despite the wealth of data, studies have been, for the most part, conflicting and inconclusive. What appears clear is that CAS provides long-term stroke prevention equal to surgery at least to 4 years, and is a reasonable alternative to CEA in patients regardless of surgical risk or symptomatic status in the hands of experienced operators. After the publication of the most recent randomized trials, we can further conclude that outcomes in CAS continue to improve and may be a better alternative for younger patients

**KEYWORDS:** carotid endarterectomy ■ carotid stenosis ■ carotid stent ■ embolic protection device ■ randomized clinical trial ■ registry ■ stroke

Dimitrios Bliagos<sup>1</sup> & William A Gray<sup>1</sup>

<sup>1</sup>Columbia University/Center for Interventional Vascular Therapy, New York, NY, USA

<sup>1</sup>Author for correspondence:

161 Ft. Washington Avenue, 5th floor, New York, NY 10032, USA

Tel.: +1 212 3057060

Fax: +1 212 342 3660

wg2131@columbia.edu

Cerebrovascular disease is the leading cause of adult disability and the third leading cause of mortality in the developed world, with the vast majority of strokes being ischemic in etiology, 20% of which are caused by atherosclerotic disease of the intracranial and extracranial arterial circulation [1]. Therefore, the prevention and treatment of atherosclerosis in this vascular bed is an important public health imperative.

Carotid endarterectomy (CEA) has been the standard of care for the treatment of symptomatic and critical asymptomatic internal carotid stenosis determined to require revascularization rather than medical therapy for almost 60 years [2,3]. In multiple large, randomized studies of CEA as compared with medical therapy, CEA has been shown to significantly reduce stroke in the years following the operation [4–7]. For symptomatic patients with recent ocular or hemispheric symptoms, the benefit of CEA accrues quickly and in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) produced an absolute stroke reduction of 17% at 2 years compared with no revascularization. In asymptomatic trials (Asymptomatic Carotid Surgery Trial and Asymptomatic Carotid Atherosclerosis Study), stroke reduction was also achieved with revascularization compared with the contemporary medical treatment of the era, but the stroke reduction was less profound (~6% absolute

reduction, ~50% relative reduction) and took 5 years to achieve, with benefit not appearing for at least 2 years.

As technology and experience advanced in the field of carotid artery angioplasty and stenting (CAS), this technique has become an attractive alternative to CEA owing to the potential for a nonoperative revascularization to result in decreased morbidity and a shorter time to recovery. There have been a number of randomized clinical trials and registries comparing the safety and efficacy of CAS with CEA. Results from these studies have been conflicting, and often controversial. In addition, there have been multiple confounders, such as heterogeneity in the patient populations treated, operator qualification and the frequency of embolic protection devices (EPDs) to name a few.

## Randomized clinical trials

The first studies to compare CEA and carotid angioplasty (but not stenting) were performed in the 1990s and found that angioplasty was inferior to CAS with respect to periprocedural stroke and death [8,9]. Initial single-center randomized comparisons of CAS to CEA were reported in relatively small trials. These early attempts at comparing outcomes between the two therapies had mixed results: some showed no differences between revascularization methods [10,11] while others were stopped early due to excess events in the CAS arm [12]. It should be noted that the

future  
medicine part of fsg

technique employed in the CAS arm was rudimentary and in its infancy, as was patient selection. There was no embolic protection used nor dedicated stent for comparison purposes.

The first large, multicenter trial was CAVATAS, randomizing 504 symptomatic patients to CEA versus carotid angioplasty, with only 26% of the angioplasty patients receiving a stent toward the latter stages of the study [13]. The results showed no difference between the two groups in the primary end point of disabling stroke or death at 30 days, with no substantial difference in the rate of ipsilateral stroke noted up to 3 years after randomization. Cranial neuropathy was reported much more commonly in the CEA group and ipsilateral carotid stenosis at 1 year was more common in the angioplasty arm. It is important to note, as compared with the predicate NASCET outcomes, that the CEA group had higher death and stroke rates.

In the Wallstent (Boston Scientific, MA, USA) trial, 219 patients with symptomatic carotid artery stenosis were randomized to CEA versus CAS using no embolic protection and a nondedicated (tracheobronchial) version of the Wallstent, with inadequately trained operators (given the early era in which the trial was run). The trial was terminated early as it was determined that at the originally projected study size, the primary hypothesis of noninferiority at 1 year (death/stroke) would not be satisfied due to an early excess of stroke in the CAS group [14].

In the era of embolic protection CAS, the SAPPHERE trial was a landmark trial [15], in that it was the first trial to use distal embolic protection as well as identifying a specific patient population to test the possible benefits of CAS. A total of 334 symptomatic and asymptomatic, high surgical risk patients were randomized to either CEA or CAS. High surgical risk was defined as significant cardiac or pulmonary disease, hostile necks with anatomic challenges (post-irradiation, post-tracheostomy, post-neck exploration), high carotid bifurcations and contralateral carotid occlusion. This was the first trial of its kind to include mandatory embolic protection in the CAS arm. The study showed that CAS was noninferior to CEA with respect to the primary end point: the cumulative incidence of a major cardiovascular event at 1 year – a composite of death, stroke or myocardial infarction (MI) within 30 days after the intervention plus death or ipsilateral stroke between 31 days and 1 year (12.2% in CAS vs 20.1% in CEA;  $p = 0.004$  for noninferiority). The trend favors CAS owing to a reduction in MI. At 3-year follow-up there was still no significant

difference between the two groups in death, MI and stroke [16]. Despite encouraging results for CAS, there was criticism of the results. First, the trial was halted early due to poor enrollment over its last 6 months. Almost 25% of the patients had recurrent stenosis after CEA; this increases the risk of repeat CEA but was felt to favor CAS, although this could not be known *a priori*. In addition, only 30% of the patients were symptomatic, raising doubt as to how the results could be extrapolated to this subgroup. Moreover, outcomes by symptomatic status were not published and although they would have been too small to draw conclusions, they would have nevertheless been hypothesis generating.

The next large, multicenter, randomized trial in the embolic protection era to be published comparing CEA and CAS was EVA-3S [17]. This study enrolled standard surgical risk symptomatic patients with carotid stenosis of  $\geq 60\%$  and randomized them to CEA or CAS. Only 527 of the 872 patients were randomized, as the trial was terminated early due to both safety and futility concerns. The primary end point of the study was the combination of stroke and death 30 days after treatment. A significantly higher risk of stroke or death in the CAS group than in the CEA group was observed (9.6 vs 3.9%;  $p = 0.01$ ; relative risk: 2.5; 95% CI: 1.2–5.1). There was also a significantly higher risk of disabling stroke in the CAS group at 30 days (3.4 vs 1.5%; relative risk: 2.2; 95% CI: 0.7–7.2). At 4-year follow-up, the risk of periprocedural stroke or death and subsequent ipsilateral stroke were higher in the CAS group than in the CEA group (11.1 vs 6.2%;  $p = 0.03$ ). This observation was due to the number of periprocedural events but with no differences noted in stroke events between the two therapies after 30 days. In fact, stroke prevention following the periprocedural period is equally effective for CAS and CEA, a finding which has been validated in both long-term follow-up SAPPHERE data as well as others. Since the periprocedural event rate in the CAS group was higher than in prior studies, the results of EVA-3S were very controversial, and plausible explanations were offered. Specifically, requirements for CAS operator training were meager by today's standards and clearly inferior to CEA operators in the trial. Remarkably, randomization was allowed during tutelage; this is tantamount to recruiting general surgeons who have a good experience with cholecystectomy and having them perform endarterectomy under randomized conditions. Evidence of poor training beyond the overall death/stroke outcomes was found in the

5% of CAS patients who went to emergent surgery, a rate not seen before or since in multicenter CAS trials. It is axiomatic in procedural medicine that volume and experience are associated with improved outcomes, as has been shown with CEA and other operations. The 'reverse learning curve' supposedly shown by Mas and Schatellier [18] in a subsequent *ad hoc* analysis was too small to demonstrate meaningful outcome differences, and in any event compared three groups of operators all with unacceptable outcomes for stroke and death, probably due to the era in which the trial was run (early 2000s decade) and relatively poor training as compared with other trials (i.e., Carotid Revascularization Endarterectomy Versus Stenting Trial [CREST]). A lack of uniform equipment use/training also has been raised as problematic; five different stents and seven different EPDs were used, without requiring the use of the device in the first 80-plus patients. In an analysis of those first 80 patients, the use of embolic protection reduced the absolute risk of stroke in the CAS group by 17.1% (7.9 vs 25%;  $p = 0.03$ ). There was also no identification/selection of unfavorable CAS anatomy/patient such as those with unfavorable arch and carotid bifurcation anatomy. Most importantly, CAS operators were not required to be as experienced as their surgical colleagues, and were, by most standards, poorly trained. All of the aforementioned concerns call into question the validity and applicability of the results drawn from EVA-3S. Nevertheless, its publication was influential.

CAS was next studied as a safe alternative to CEA for the treatment of carotid stenosis in the SPACE trial. This was a large, international, multicenter, randomized trial that enrolled 1200 moderate surgical risk, symptomatic patients with carotid artery stenosis  $\geq 50\%$ , comparing CEA to CAS [19]. Unfortunately, embolic protection was not mandated and used in only 27% of the CAS patients. The proposed trial design called for the interval assessments of the total enrollment number needed to achieve noninferiority, but after 1200 patients and analysis determined over 1000 more patients would be required, funding was withdrawn and the trial halted; therefore, the study was underpowered to detect noninferiority. Nevertheless, there was no difference between CAS and CEA with respect to the primary end point, defined as death and ipsilateral stroke at 30 days (6.84% CAS vs 6.34% CEA;  $p = 0.09$ ). Moreover, there was no significant difference between the two groups in the composite end point of death or ipsilateral stroke from day 30 to 2-year follow-up [20].

Within the past year, two large, multicenter, randomized trials have been published comparing CEA and CAS.

The International Carotid Stenting Study (ICSS) randomized 1713 recently symptomatic patients, the majority of which had carotid stenosis  $\geq 70\%$ , to either CEA or CAS [21]. The primary end point of the study was the rate of fatal or disabling stroke at 3 years, and has not yet been published. In the interim intention-to-treat analysis, the incidence of stroke, death and procedural MI in the CAS group was 8.5 versus 5.2% in the CEA group at 120 days (hazard ratio [HR]: 1.69; 95% CI: 1.16–2.45;  $p = 0.006$ ). The risk of any stroke and all-cause death was also higher in the CAS group, while the risk of a cranial nerve palsy and hematoma was higher in the CEA group. The 30-day per-protocol rate of disabling stroke or death, however, was not different between the therapies (3.1 vs 2.2%;  $p = 0.23$ ). Important caveats regarding the ICSS study include the inexperience of the CAS operators (many of whom were being supervised during randomized cases) especially in relationship to a reasonably well-vetted surgical group, and that embolic protection was used at the discretion of the proceduralist, totaling only 72% of the CAS group. In addition, periprocedural/operative MI was not routinely surveyed in ICSS and as a result the investigators under-reported this important safety end point due to a lack of ascertainment. Given these and other issues, definitive conclusions about the safety of CAS relative to CEA are difficult to ascertain from ICSS.

Data from the CREST trial were published shortly after the ICSS trial results and with different outcomes and conclusions. This NIH funded, multicenter trial of 2502 symptomatic (carotid stenosis  $\geq 50\%$ ) and asymptomatic (carotid stenosis  $\geq 70\%$ ) cases randomized patients to CEA or CAS in a 1:1 ratio [22]. The primary composite end point was stroke, MI or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. Over a median follow-up period of 2.5 years, there was no significant difference in the primary end point between the CAS group and the CEA group (7.2 and 6.8%, respectively; HR: 1.11 with stenting; 95% CI: 0.81–1.51;  $p = 0.51$ ). Secondary analyses include a 4-year rate of stroke or death of 6.4% with CAS and 4.7% with CEA (HR: 1.50;  $p = 0.03$ ). Periprocedural rates of individual components of the end points differed between the CAS group and the CEA group: for stroke, 4.1 versus 2.3% ( $p = 0.01$ ) and for MI, 1.1 versus 2.3% ( $p = 0.03$ ).

The increase in stroke rate in the CAS group was primarily driven by minor ipsilateral stroke (HR: 2.16; 95% CI: 1.22–3.83;  $p = 0.009$ ). In addition, the rate of cranial nerve palsies was less frequent during the periprocedural period with CAS than with CEA (0.3 vs 4.7%; HR: 0.07; 95% CI: 0.02–0.18). In contrast to the prior randomized controlled trials, one stent and one embolic protection system were used, the RX ACCULINK stent (Abbott Vascular, CA, USA) and RX ACCUNET (Abbott Vascular) EPD. Embolic protection was used in 97% of the CAS patients; this combined with significantly more experienced operators likely led to stroke rates in the CREST trial lower than those in EVA-3S, SPACE and ICSS. In fact, although there were few patients who did not receive EPDs in CREST, a subsequent analysis of outcomes [101] according to the presence or absence of EPD demonstrated markedly worse outcomes when EPD was not employed. It should be noted that such an analysis is fraught with selection bias and is grossly underpowered, but nevertheless supports EPD use as a meaningful determinant of outcomes in CAS. The authors concluded that, when performed by experienced surgeons and interventionalists, carotid revascularization was safe and effective in the combined population of symptomatic and asymptomatic patients studied. Because the end points were powered for these combined populations of patients, conclusions as to the outcomes of CAS and CEA according to symptom status should be made with caution. Also of interest in the CREST results is the finding that the events that differentiated the therapies, minor stroke and MI, had differentiated effects on longer-term outcome. As presented to the US FDA panel, minor stroke had no effect on mortality over the longer term, but MI was associated with a significant and substantially worse mortality outcome compared with either minor stroke or the population in CREST that did not sustain any event. This not only validates the inclusion of MI as an end point in CREST (which had initially been criticized) but also calls into question the previous trials (EVA-3S, SPACE and ICSS) that either did not include MI as an end point or did not routinely survey for the occurrence of MI. Other important findings of the FDA analysis include outcomes of patients according to age. The FDA analysis demonstrated no differences among the octogenarians (HR: 1.01), even though the initial publication of these data in the NIH analysis was skewed not by better outcomes in CEA among the octogenarians but rather by a remarkably

low (HR: 0.37) rate of complication in the CAS cohort under the age of 60 years. If that group is eliminated, the best-fit line becomes horizontal without differentiation between the therapies by age. Last, the FDA analysis demonstrated an in-trial learning curve in CREST such that the last half of the trial population outcomes in CAS were significantly better than the first half, so much so that the trial would have met all of its prespecified analyses with only these 1250 patients.

### Long-term outcomes in CAS & CEA

Several trials have published extended follow-up of their randomized cohorts. The CAVATAS study published 11-year follow-up data demonstrating slightly more stroke events for the angioplasty (but largely not stented) group that did not reach statistical significance [23]. The SAPPHIRE trial showed no differences between the therapies at 3 years [16], as did CREST at 4 years (mean 2.5) and the SPACE trial at 2 years [20]. Although EVA-3S had disparate 30-day outcomes between the therapies, it demonstrated that events after 30 days to 4 years were not different between the treatments [17]. Therefore, while mid-term outcomes in CAS appear to demonstrate both stroke reduction efficacy on par with CEA and durability of revascularization, nothing definitive can be said beyond 4 years as to the comparative outcomes for CAS and CEA.

### Meta-analyses

It is not surprising to find that meta-analyses in this field demonstrate conflicting results and conclusions. This is due to the heterogeneity of patient populations (e.g., high surgical risk, symptomatic vs asymptomatic, age) between trials, the variability of equipment used (including the presence or absence of mandated embolic protection), operator experience and ascertainment bias, among other factors. In a meta-analysis combining five major clinical trials of 2122 symptomatic patients (SAPPHIRE, SPACE, EVA-3S, Wallstent and Kentucky Symptomatic Trial) [24], the authors found no significant difference between the CEA and CAS patients with respect to the following 30-day end points: death, stroke, disabling stroke, death and stroke, death and disabling stroke. Along the same lines was another meta-analysis including ten randomized trials [25] showing no difference between CAS and CEA in death, MI or stroke and a trend towards a reduction in death and MI with CAS. Conversely, a meta-analysis performed by the Society of Vascular Surgery, including 2985 patients, found that CAS was associated with a higher rate of death or stroke

at 30 days (OR: 1.38) [26]. Suffice to say, meta-analyses in this field should be interpreted with circumspection.

### Single-arm carotid studies

Although prospective, single-arm studies provide a level of evidence lower than randomized clinical trials, they can offer important information as to the safety and efficacy of 'real world' use of CAS, especially because all major registries are multicenter, adjudicated by an independent clinical events committee and operators are well chosen and generally highly experienced. With the exception of CARESS, these studies are divided into two broad categories: those performed for device approval in the USA, and those performed post-market approval that gather data in real-world settings. Some of these studies have not been published, and are not included in this discussion. It is noted that the outcomes of CAS have steadily and consistently improved throughout the decade, in keeping with an early stage technology adoption. Therefore, discussion regarding CAS outcomes must include most recent data sets.

The CARESS Phase I trial was a nonrandomized, prospective study that enrolled 397 symptomatic and asymptomatic patients to undergo CEA and CAS in a 2:1 ratio [27]. The cohort's surgical risk varied from high to low and treatment decisions were made by the physicians and their respective patients. Patients with prior CEA were more likely to undergo CAS. There was no significant difference in death or stroke at 30 days and at 1 year: 3.6% CEA and 2.1% CAS, and 13.6% CEA and 10% CAS, respectively. The rate of periprocedural events in the CAS group was the lowest among all major CAS trials and meets the American Heart Association (AHA)/American College of Cardiology (ACC) standard of <3% (asymptomatic) and <6% (symptomatic) 30-day risk of stroke or death. This is probably due to careful patient selection, paying special attention to vascular anatomy and medical comorbidities.

The ARCHER registry was a series of three prospective studies totaling 581, high-risk, symptomatic and asymptomatic patients who received the ACCULINK stent and ACCUNET EPD – the embolic protection was used in the latter two studies, but not the first [28]. The primary end point of 30-day death, stroke or MI was 8.3% and that of stroke and death was 6.9%. The primary composite end point of 30-day death/stroke/MI plus ipsilateral stroke at 1 year was 9.6%, well below that of the historical comparator. Accordingly, these study results ultimately led to the first CAS device approval in the USA.

The BEACH registry enrolled 480 surgical high-risk, symptomatic and asymptomatic patients, who received the carotid Wallstent and FilterWire EX/EZ (Boston Scientific) embolic protection system [29]. The 30-day composite major adverse event rate for the entire cohort was 5.8% (all death 1.5%, all stroke 4.4% and all MI 1.0%).

The MAVERIC registry enrolled 399 high-risk asymptomatic patients who received the AVE stent (Medtronic, MN, USA) and Percusurge embolic protection system (Medtronic) [30]. The stroke and death rate at 30 days was 4.3% and stroke, death and MI was 6.3%.

The CABERNET registry enrolled 454 high-risk, symptomatic and asymptomatic (76% asymptomatic) patients who received the EndoTex NexStent (MA, USA) and FilterWire EX/EZ EPD [31]. The 30-day rate of death or stroke in the entire cohort was 3.9%, 2.7% for asymptomatic and 6.4% for symptomatic patients, while the 1-year rate of adverse events was 11.6%, comparable to that of historical controls.

The CAPTURE registry was the first post-market approval study and prospectively enrolled 3500 high-risk symptomatic and asymptomatic patients who received the ACCUNET/ACCULINK stent and embolic protection system [32]. The primary end point of death, stroke or MI at 30 days was 6.3%. This was an important study outcome since it bested the predicate trial (ARCHER) and provided proof that the technology and technique could be transferred safely outside the clinical trial setting with the same or better results. This proof was largely due to a standardized training program mandated according to a previous level of carotid stent experience.

The CASES-PMS post-market approval registry demonstrated a 5% 30-day rate of death, stroke or MI in 1493 high-risk, symptomatic and asymptomatic patients who were treated with the PRECISE Nitinol stent and the ANGIOGUARD XP (Cordis/Johnson and Johnson, NJ, USA) EPD [33], also representing an improvement in the landmark SAPPHERE trial that preceded it.

Two recently published registries came to decidedly different conclusions regarding the safety and efficacy of CAS, and demonstrate some of the pitfalls of carotid outcomes analysis. The first was an analysis of 6320 patients, from two post-market surveillance CAS studies of high-risk surgical patients, EXACT and CAPTURE 2 [34]. Both studies had pre- and post-procedure neurologic assessments and

independent adjudication of neurologic events. The overall 30-day death and stroke rate was 4.1% (95% CI: 3.3–5.0) for EXACT and 3.4% (95% CI: 2.9–4.0) for CAPTURE 2. In the population less than 80 years of age (which best correlates with the long-established AHA guidelines recommendations), the combined 30-day death and stroke rate was 5.3% (95% CI: 3.6–7.4) for symptomatic patients and 2.9% (95% CI: 2.4–3.4) for asymptomatic patients, independent of unfavorable anatomic or physiologic risk factors. The authors concluded that CAS is indeed a safe and efficacious alternative to the treatment of carotid artery stenosis. By contrast, an analysis of the Society of Vascular Surgery registry came to a different conclusion [35]. This was a prospective collection of data from 287 providers at 56 centers in the USA on 2763 CAS patients and 3259 CEA patients from 2005 to 2007. The registry reports an unadjusted 30-day risk of death, stroke or MI of 7.13% in symptomatic patients who underwent CAS and 3.75% who underwent CEA, while in the asymptomatic group the 30-day outcome was 4.6% for CAS and 1.97% for CEA. After risk adjustment for age, history of stroke, diabetes and ASA grade the CAS group had a higher likelihood of reaching the 30-day end point (HR: 1.965;  $p < 0.001$ ). The authors concluded that CEA is superior to CAS in the treatment of carotid stenosis. There are several problems with this registry analysis and with the authors' conclusions. Specifically, the population undergoing CAS was very different to that undergoing CEA, demonstrated by a statistically significant difference between the CAS and CEA patients with respect to symptomatic carotid stenosis, prior stroke, diabetes, MI, congestive heart failure, hypertension, transient ischemic attack, COPD, cancer and New York Heart Association scale  $>2$ . Despite propensity scoring risk adjustment, there are unknown confounders that can contaminate any conclusions in this kind of analysis. But probably of greater importance than the aforementioned selection bias is the presence of an ascertainment bias, since most patients undergoing CAS in the time period studied were examined by neurologists before and after the procedure as they were largely treated within research protocols that mandated such evaluation; CEA patients had a very low rate of such stroke ascertainment, skewing the outcomes reporting significantly.

Other analyses have attempted to combine the large multicenter studies previously mentioned (EVA-3S, SPACE, ICSS and CREST)

[36]. The authors do not believe this meta-analysis is valid owing to the lack of poolable trial data. Given the differentiated operator experience, EPD use and MI inclusion as an end point, the trials are substantially different (and thus largely invalidated) enough so as not to warrant inclusion. Last, CAS outcomes have demonstrably improved since the time of this survey, so that the reporting of many of these outcomes is largely of an historical nature.

## Conclusion

Although there is a multitude of registry and randomized clinical trial data available on the efficacy and safety of CAS, the differences in the populations studied, biases in ascertainment, differences in operator experience, differences in devices used and in the temporal relation to the evolution of CAS have led to conflicting results, and furthermore polarized interpretations have occasionally made it difficult to draw definitive conclusions regarding the comparative safety of the procedures. The CREST trial is reasonably unencumbered by many of these issues and suggests that CAS and CEA are both safe and effective therapies for stroke prevention in the patient with severe carotid stenosis. When these results are taken with the large and well-collected data available for CAS in high surgical risk patients, for which similar multicenter data for CEA do not exist in this high-risk population, certainly not with the same ascertainment of neurologic end points and adjudication of events, it appears that CAS has become a reasonable option for many patients. Accordingly, these two therapies should be considered as complementary and selected on an individualized basis for patients depending on multiple considerations such as anatomy, and medical and anatomic comorbidities. In this way, patients will have the lowest possible stroke and death risk from the procedure, and therefore the greatest benefit of revascularization. Further studies are ongoing and will hopefully help elucidate the best application of these therapies.

## The future of CAS

The conduct of the CREST trial and outcomes, and the attendant realization of European trial issues, which limit their utility in comparative analysis with CEA, has put CAS on a much firmer footing as a safe and effective alternative to CEA, certainly for the high surgical risk patients, and now for standard surgical risk as well.

Further questions remain both for revascularization of either variety, and for each modality separately. Is it possible to further reduce minor stroke risk in CAS by virtue of either improved or selective EPD (e.g., proximal vs distal), stent modification, pharmacologic means, plaque characterization, access improvement or patient selection? Is it possible to reduce the MI rate in CEA with screening or adjunctive pharmacology? And for both CAS and CEA, the question as to whether medical therapy can be optimized to the point where revascularization no longer has a relevant place in the management of patients with severe bifurcation carotid disease remains an open one. Until it is more completely studied, however, the data to date suggests revascularization carries a significant benefit. The management of the octogenarian patient with either therapy also remains ill-defined without randomized data for guidance.

Two recent events will almost certainly influence the method of carotid revascularization in the future. The first was the publication of a multisociety consensus document assigning both CEA and CAS as reasonable treatment options

for patients with carotid disease, although for the asymptomatic patient the recommendations for both were less definitive. The second was the presentation of further CREST data to the FDA Circulatory Advisory Panel as part of Abbott Vascular's application to extend the current approval of their stent system to include standard surgical risk patients. After deliberation, the FDA panel voted 7–3 in support of that application, and granted approval May 6 2011.

In broad terms, the future of CAS will be focused on continuing the marked improvement in outcomes over early results, and on understanding which population is most appropriate for endovascular revascularization.

#### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

*No writing assistance was utilized in the production of this manuscript.*

#### Executive summary

- Carotid endarterectomy (CEA) has been established as the standard of care for patients with critical carotid stenosis with or without symptoms.
- Carotid artery stenting (CAS) has been tested in patients with excessive risk of complication following CEA and found to be at least as safe.
- The long-term data for CAS demonstrates equivalent stroke prevention in several trials, and at least out to 4 years.
- European trials comparing CAS and CEA have been confounded by several issues including: lack of qualified operators, lack of routine embolic protection, lack of myocardial infarction (MI) inclusion as an end point or adequate surveillance for it. As a result, these European studies provide conflicting results.
- The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) addressed these issues and serves as the most definitive assessment of the comparative outcomes of CAS and CEA to date.
- In CREST, CAS and CEA demonstrated no differences in the primary composite end point of 30-day death, stroke and MI plus ipsilateral stroke to 4 years.
- Within this composite end point, individual components demonstrated differences between the two therapies: CAS had more minor strokes and CEA had a roughly equivalent excess of MI.
- Patients with MI demonstrated a significantly worse long-term mortality compared with patients without any procedural event; minor stroke showed no long-term effect on mortality.
- As has been noted during the last decade with high surgical risk CAS outcomes, outcomes during the 8-year CREST trial also showed significant improvements, likely related to better operator experience, better patient selection and a continuous refinement of technique.

#### Bibliography

- 1 White H, Boden-Albala B, Wang C *et al.*: Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 111(10), 1327–1331 (2005).
- 2 Biller J, Feinberg WM, Castaldo JE *et al.*: Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 97(5), 501–509 (1998).
- 3 Moore WS, Barnett HJ, Beebe HG *et al.*: Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the ad hoc Committee, American Heart Association. *Stroke* 26(1), 188–201 (1995).
- 4 Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 351(9113), 1379–1387 (1998).
- 5 Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 273(18), 1421–1428 (1995).
- 6 Barnett HJ, Taylor DW, Eliasziw M *et al.*: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N. Engl. J. Med.* 339(20), 1415–1425 (1998).

- 7 Rothwell PM, Eliasziw M, Gutnikov SA *et al.*: Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 361(9352), 107–116 (2003).
- 8 Golledge J, Mitchell A, Greenhalgh RM, Davies AH. Systematic comparison of the early outcome of angioplasty and endarterectomy for symptomatic carotid artery disease. *Stroke* 31(6), 1439–1443 (2000).
- 9 Theron JG, Payelle GG, Coskun O, Huet HF, Guimaraens L. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. *Radiology* 201(3), 627–636 (1996).
- 10 Brooks WH, McClure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery* 54(2), 318–324; discussion 324–325 (2004).
- 11 Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J. Am. Coll. Cardiol.* 38(6), 1589–1595 (2001).
- 12 Naylor AR, Bolia A, Abbott RJ *et al.*: Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J. Vasc. Surg.* 28(2), 326–334 (1998).
- 13 Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 357(9270), 1729–1737 (2001).
- 14 Alberts MJ. Results of a multicenter prospective randomized trial of carotid artery stenting vs. carotid endarterectomy. *Stroke* 32, 325 (2001).
- 15 Yadav JS, Wholey MH, Kuntz RE *et al.*: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N. Engl. J. Med.* 351(15), 1493–1501 (2004).
- 16 Gurm HS, Yadav JS, Fayad P *et al.*: Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N. Engl. J. Med.* 358(15), 1572–1579 (2008).
- 17 Mas JL, Trinquart L, Leys D *et al.*: Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol.* 7(10), 885–892 (2008).
- 18 Mas J-L, Schatellier G. Endarterectomy versus stenting for carotid stenosis: Authors reply. *N. Engl. J. Med.* 356, 306–307 (2007).
- 19 SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H *et al.*: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368(9543), 1239–1247 (2006).
- 20 Eckstein HH, Ringleb P, Allenberg JR *et al.*: Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol.* 7(10), 893–902 (2008).
- 21 International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL *et al.*: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 375(9719), 985–997 (2010).
- 22 Brott TG, Hobson RW 2nd, Howard G *et al.*: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N. Engl. J. Med.* 363(1), 11–23 (2010).
- 23 Ederle J, Bonati LH, Dobson J *et al.*: Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomized trial. *Lancet Neurol.* 8(10), 898–907 (2009).
- 24 Gurm HS, Nallamothu BK, Yadav J. Safety of carotid artery stenting for symptomatic carotid artery disease: a meta-analysis. *Eur. Heart J.* 29(1), 113–119 (2008).
- 25 Murad MH, Flynn DN, Elamin MB *et al.*: Endarterectomy vs stenting for carotid artery stenosis: a systematic review and meta-analysis. *J. Vasc. Surg.* 48(2), 487–493 (2008).
- 26 Ringleb PA, Chatellier G, Hacke W *et al.*: Safety of endovascular treatment of carotid artery stenosis compared with surgical treatment: a meta-analysis. *J. Vasc. Surg.* 47(2), 350–355 (2008).
- 27 Carotid revascularization using endarterectomy or stenting systems (CARESS): Phase I clinical trial. *J. Endovasc. Ther.* 10(6), 1021–1030 (2003).
- 28 Gray WA, Hopkins LN, Yadav S *et al.*: Protected carotid stenting in high-surgical-risk patients: the ARChER results. *J. Vasc. Surg.* 44(2), 258–268 (2006).
- 29 White CJ, Iyer SS, Hopkins LN *et al.*: BEACH Trial Investigators. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc. Interv.* 67(4), 503–512 (2006).
- 30 Ramee S, Higashida R. Evaluation of the Medtronic self-expanding carotid stent system with distal protection in the treatment of carotid artery stenosis: the MAVeRiC Trial Phase II 30-day update. *Am. J. Cardiol.* 94, 61E (2004).
- 31 Hopkins LN, Myla S, Grube E *et al.*: Carotid artery revascularization in high surgical risk patients with the NexStent and the Filterwire EX/EZ: 1-year results in the CABERNET trial. *Catheter Cardiovasc. Interv.* 71(7), 950–960 (2008).
- 32 Gray WA, Yadav JS, Verta P *et al.*: The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv.* 70(7), 1025–1033 (2007).
- 33 Katzen BT, Criado FJ, Ramee SR *et al.*: Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. *Catheter Cardiovasc. Interv.* 70(2), 316–323 (2007).
- 34 Gray WA, Chaturvedi S, Verta P. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. *Circ. Cardiovasc. Interv.* 2(3), 159–166 (2009).
- 35 Sidawy AN, Zwolak RM, White RA *et al.*: Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. *J. Vasc. Surg.* 49(1), 71–79 (2009).
- 36 Carotid Stenting Trialists' Collaboration; Bonati LH, Dobson J, Algra A *et al.*: Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet* 376(9746), 1062–1073 (2010).

## ■ Website

- 101 2011 Meeting Materials of the Circulatory System Devices Panel  
[www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm](http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm)