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Carotid artery stenting in the elderly:
the time has come

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Introduction

Affecting over half a million people per year, stroke is the third leading cause of death in the United States. Approximately 30% of strokes are caused by carotid occlusive disease. The traditional methods of treating carotid stenosis have included medical or surgical therapy. Classically, those with symptomatic moderate or severe cervical carotid arterial stenosis have been treated with carotid endarterectomy (CEA). Medical therapy with aspirin and more recently with Clopidigrel (Plavix) has been reserved for mild to moderate (asymptomatic) carotid arterial stenosis or non-cervical carotid arterial stenosis.

First performed nearly 26 years ago, carotid arterial stenting (CAS), until recently, has been performed only at a few centers of excellence for very select indications (Fig. 1). Coupled with the recent development and improvement of distal embolic protection devices (EPD), CAS has become a viable option for the treatment of carotid artery occlusive disease (Fig. 2). However, in high-risk patients, CAS may actually offer similar if not better results when all of the data, trials and results are reviewed. When evaluating CAS versus CEA and “the controversy”, it is important to look at the history of CEA and CAS, the landmark trials, and future directions.

Surgical trials

Doctors Cooley, De Bakey, and Eastcott are credited with the first surgical treatment of carotid artery occlusive disease in the 1950’s. The procedure gradually gained acceptance with approximately 100,000 procedures performed annually in the 1980’s. Lack of clinical trial data, however, led to confusion as to the role of CEA in the treatment of carotid artery disease. Forty years after the first carotid artery endarterectomy was successfully performed randomized trials were designed to evaluate the indications and efficacy of CEA.

The first large-scale trials to evaluate CEA in symptomatic patients with carotid arterial stenosis were:

- North American Symptomatic Carotid Endarterectomy Trial (NASCET),
- European Symptomatic Carotid Trial (ESCT), and
- Veterans Administration Symptomatic Trial.
The NASCET trial began enrolling patients in 1988 and was first published in 1991. The initial trial included 659 symptomatic patients with severe carotid artery disease (70-99% stenosis) which compared surgical therapy to the best medical therapy at that time which included aspirin or warfarin (Coumadin). Clearly, in this group, surgical therapy was superior to medical therapy in ipsilateral stroke rates (26% to 9%) and death rates (13.1% to 2.5%) over 2 years. This accounted for a relative risk reduction with surgical therapy of 65%.

The second part of the trial enrolled 2,226 patients dividing them into two groups:
- Moderate stenosis (50-69%)
- Mild stenosis (30-49%).

In 5 years, the moderate stenosis group also demonstrated a moderate decrease in the risk of ipsilateral stroke. Importantly however, CEA did not demonstrate any benefit in symptomatic patients with mild stenosis.

ESCT enrolled 3,024 symptomatic patients in 12 European countries with similar results to NASCET. The Veterans Administration trial was terminated prematurely after NASCET and ESCT were released because of the overwhelming benefit of surgery over medical treatment in these groups who were symptomatic.

In the Asymptomatic Carotid Artery Study (ACAS) 1,662 patients were randomized to either CEA or aspirin. Despite only 9% of patients following up at 5 years, the authors concluded CEA decreased the risk of stroke or death (5.1%) as compared to aspirin (11%). Although a benefit from surgical therapy was identified, this should still not have provided adequate data collection so as to clearly elucidate the long-term clinical benefit of one therapy over another. Patients over the age of 79, a life expectancy less than 5 years, or a disorder that could “seriously complicate surgery,” were excluded from the study. As noted by many clinical trials to date exclusion of certain subsets can distort the eventual perceived clinical outcomes of those trials.

In these trials as reported, the patient’s perioperative risk of any stroke or death was 6% in the symptomatic group whereas it was only 2.3% in the asymptomatic group. It is possible that several factors could explain these numbers.

First, these trials evaluated low risk patients excluding those with major coronary artery disease, severe pulmonary disease, congestive heart failure, and patients over the age of 80.

Second, the surgeons in these trials were high volume operators at large centers. Medicare analysis has shown that lower volume centers have a higher mortality than high volume centers (2.5% vs 1.7%).

Finally, difficult carotid artery disease scenarios were not included in the study such as:
- High anatomical cervical bifurcation
- Contralateral carotid artery occlusion
- Restenotic lesions s/p endarterectomy
- Individuals who are post radiation for head or neck cancer
- Individuals with severe intracranial stenosis.

Therefore, these numbers represent low risk patients in high volume centers with experienced surgeons, thus they may reflect the true state of carotid artery endarterectomy as it existed at that time (Fig 3a, 3b).

Endovascular therapy initial experience – pre-distal protection devices

The first carotid artery angioplasty was performed by Mathias in 1979 followed a decade later by the first stent deployment in 1989. Until recently, carotid artery stenting was performed in very few centers in patients who were not surgical candidates whether anatomically or from a medical perspective. This included the use of large 7-8 Fr. iliac angioplasty balloons, 8-9 Fr. balloon expandable stents and equipment unacceptable by today’s cardiovascular standards. Therefore, early series reports were made of small cohorts or case reports.

The largest review of carotid arterial stenting prior to distal protection comes from the Global Carotid Artery Registry collected from 12 countries and 53 centers beginning in 1997. This registry includes 12,254 CAS procedures. Approximately 66% of the patients had no cerebral distal protection used in their endovascular procedures. The technical success rate was 98.9%.

From this bi-yearly report one can see that CAS performed with cerebral protection yielded a significantly less event rate than without protection. This can be demonstrated in both the symptomatic and asymptomatic patient populations. Furthermore, as in the surgical cohorts, symp-
tomatic patients also fared better than those who were actively symptomatic. Restenosis rates were approximately 2% per year over 3 years (Fig.4).

The Carotid Artery and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) published in 2001 compared percutaneous angioplasty (not necessarily stenting) to CEA. Randomization of 504 patients in the endovascular arm included mainly angioplasty. High-risk surgical patients were excluded from the trial including those with recent myocardial infarction, uncontrolled hypertension, diabetes mellitus, severe respiratory disease, cervical spondylosis, or inaccessible carotid stenosis. The results demonstrated no difference in disabling stroke or death in the endovascular versus CEA group (6.4% vs 5.9%) and no significant difference in ipsilateral stroke rate at 3 years.

One of the criticisms of the endovascular treatment group was the restenosis rate of 14% versus 4% in the CEA group. However, a closer analysis demonstrates that only 23% of patients received a stent. Also to be mentioned is the fact that the stents employed were the older generation of safety and futility in the CAS arm. One significant difference between EV A-3 and SPACE was the utilization of distal protection devices. At the end of the study only 27% of the CAS arm employed EPDs. The clinical relevance of this study is therefore questionable given the small difference in primary endpoint events combined with a lack of EPD utilization.

The multicenter EVA-3S study was similar in both design and outcome. It was a multicenter trial that evaluated the noninferiority of CAS relative to CEA in the setting of patients with severe symptomatic carotid disease. It also excluded patients with restenosis. This French trial randomized 527 patients to CAS or CEA and used a composite endpoint of stroke or death at 30 days as its primary endpoint. This study also failed to show the noninferiority of CAS and furthermore was stopped prematurely for perceived lack of safety and futility in the CAS arm.

The event rate for the primary endpoint was 3.9% after CEA and 9.6% after CAS with most of the difference arising from a greater incidence of nonischemic stroke in the CAS arm. One significant difference between EVA-3 and SPACE was the utilization of distal protection devices. At the onset of EVA-3S, systematic use was not recommended but this was changed during the course of the study and 227 of the 261 patients in the CAS arm utilized these devices. The 30 day incidence of stroke was 7.9% in the patients that received EPD and 25% in those that did not.

One of criticisms of this trial (acknowledged by the authors) includes the fact that premature termination may have led to an overestimation of the treatment effect. Also, and possibly more significantly, there may have been a significant lack of operator experience in this trial. It employed five different stents and seven different EPD with the only requirement being that the operator should have performed at least two procedures with any device used in the trial.

In 2001 Medicare, the primary payor in the USA for physicians treating elderly patients, announced that it would reimburse hospitals and physicians involved in CAS but only under an FDA (Food and Drug Administration) Investigational Device Exemption (IDE). With this landmark decision came the birth of SAPHIRE (The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Trial). This was the first FDA sanctioned trial involving CAS with the simultaneous usage of EPDs. The aim of this trial was not to show that stenting is superior to surgery but that it was not inferior by a delta of 3%...
(EVA-3S and SPACE used a delta of 2%). A total of 747 patients were enrolled in this trial. The study protocol randomized high-risk patients defined as:

- Age greater than 80,
- Severe pulmonary disease,
- Severe congestive heart failure,
- Concomitant severe coronary artery disease
- Contralateral cervical carotid artery occlusion
- Unstable angina
- Inaccessible carotid stenosis to vascular surgeons
- Previous radiation therapy in the carotid stenosis site
- This trial was somewhat unique in that it also included asymptomatic patients as well as patients with restenosis. To enter this randomized trial symptomatic patients with >50% luminal stenosis or asymptomatic patients with >80% luminal stenosis were accepted. Cardiologists, radiologists, surgeons and neurologists all participated in the decision making of whether to allow the patients into the trial or not. The non-randomized stent arm (NRSA) of this trial was defined by the surgeons themselves. The EPD used in SAPPHIRE was the Angioguard or Angioguard XP system (Cordis Endovascular), a filter with a 100 micron pore size, coupled with the Precise (Cordis Endovascular), Nitinol self-expanding stent.

The study had 3 arms:
- Randomized CEA vs CAS with EPD (334 patients)
- Non-randomized stent arm for patients who were refused for surgery (406 patients)
- Non-randomized surgical arm for those patients who were refused CAS (7 patients)

At 1 year CAS with EPD fared significantly better than CEA in the composite endpoint of death, stroke and myocardial infarction (12.0% vs 20.1%, \(P < 0.05\)). However, this was driven primarily by myocardial infarction with no significant difference in death or stroke (trend still favored CAS). In symptomatic patients, no statistical difference existed between the CAS and the CEA group (16.8% vs 16.5%) (Fig 5). Again in asymptomatic patients, no difference existed between the CAS and CEA groups (5.4 vs 10.2, \(P = 0.20\)). The trial therefore concluded that in high risk patients (with significant comorbidities) CAS is not inferior to CEA when EPD are employed. By recent communication, at up to 3 years it appears that the results of both CEA and CAS approach equivalence.

The Acculink for Revascularization of Carotids in High-Risk Patients (ARCHeR) was a prospective trial with CAS and EPD using the Acculink stent and Accunet Embolic Protection Device (Guidant) in high risk surgical patients.\(^{14}\) It was not a randomized trial and employed a historical CEA control. The study enrolled 581 patients in three single arm trials, who met the following criteria: 50% symptomatic stenosis or 80% asymptomatic stenosis with one of the following:

- Two or more coronary lesions
- Severe pulmonary disease
- End stage renal disease
- Neck radiation
- Contralateral carotid occlusion
- Myocardial infarction in the previous 30 days
- Uncontrolled diabetes mellitus.

The primary endpoint of death, myocardial infarction, and stroke at up to 2 years in ARCHeR 1 and 2 were 8.3 and 10.2%, respectively. ARCHeR 1 used the Acculink Nitinol stent but without cerebral protection, whereas ARCHeR 2 used a cerebral protection device. ARCHeR 3 was similar in the usage of the stent and EPD; however the monorail system was used exclusively during this phase of the trial. For regulatory approval, each phase tested the hypothesis of noninferiority separately, but all of the data was pooled for the analysis. The composite endpoint (30 day death, stroke, MI and one year ipsilateral stroke) for the CAS phases was 9.6% which was lower with the historical control rate of 14.4% for CEA and satisfied the prespecified criteria for noninferiority. The study was not powered to detect a difference in outcome with and without EPDs and no significant difference was detected. Almost 60% of filters used in the trial, however, were retrieved with debris.

Another recently published registry, The Carotid RX Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE), evaluated CAS with EPD in symptomatic and asymptomatic patients.\(^{15}\) One of the primary goals of this multicenter prospective registry was to evaluate if the carotid stent and EPD could be used by community based physicians from different specialties and of varying levels of experience. Physicians were stratified to three levels (Level 1-3) based on experience and the primary endpoint was again a composite of death, stroke, or MI, within 30 days of the procedure.

The registry enrolled 3,500 patients at 144 sites with baseline differences from previous studies. The CAPTURE patients (relative to the ARChEr registry) were significantly older (23.7% > age of 80 as compared to 15.5% in ARChEr), and had a higher prevalence of hypertension, hypercholesterolemia, but had less symptomatic patients, fewer patients with previous MI, and contralateral ICA lesions. The overall combined endpoint for CAS with EPD in this registry was 6.3% and did not differ significantly from the 8.3% found in the ARChEr registry. Interestingly, there was a statistically significant higher event rate in the Level 3 physicians
With regard to CAS risk and advanced age, the study noted a difference in outcomes across the physician experience levels in patients younger than 80 but no difference among patients greater than 80 (Tab.1). The relative risk of advanced age was not evaluated in this study.

Currently, a new large study is underway, Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), to compare CAS and CEA in low risk symptomatic and asymptomatic patients. This trial will also compare relative efficacy to four years post-procedure. The results are eagerly awaited to further define the role of CAS. As this publication appears, a second trial in the USA is underway randomizing asymptomatic low risk patients to either CEA or CAS with EPD (ACT I, Abbott).

Conclusions

Carotid endarterectomy (CEA) has been a mainstay in the treatment of carotid occlusive disease. Unfortunately, in the CEA trials they have only looked at low risk patients and extrapolated the results to high-risk patients in clinical practice. Based on recent trial data it is fair to state that in high-risk patients, CAS appears to be the procedure of choice. In the future, as endovascular therapy becomes further refined, with better EPDs, better stents (drug eluting) and more experienced operators, mortality and morbidity associated with the procedure will continue to decline. Endovascular therapy is now the moving target with innovation while surgical therapy has had minor changes. Just as medical therapy has a role in mild to moderate lesions, the final role of endovascular therapy in this huge population remains to be seen.

References