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## Carotid Artery Angioplasty and Stenting: Interventional Radiology Point of View

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Stroke is the third leading cause of death in the United States and affects over a half million people per year.<sup>1</sup> Coastal South Carolina is the leader of the "Stroke Belt."<sup>2</sup> Stroke is the third leading cause of death in South Carolina, accounting for 2,832 deaths or approximately 8% of the state's deaths in 2001.<sup>3</sup> Cardiovascular disease (CVD) is the leading cause of death and disability in South Carolina. In 2001, CVD accounted for approximately 34% of deaths in South Carolina. Although known as a primary cause of death in older adults, it is also the leading cause of death of South Carolinians aged 35–44.

Together, heart disease and stroke account for over 90% of all CVD deaths. According to the 2001 CDC mortality data, South Carolina had the 23rd highest heart disease death rate in the nation and the 2nd highest stroke disease death rate. The stroke related mortality rate in U.S in 1995 was 60.1/100K and in 2001 was 57.4/100K, while in SC in 1995 was 75.2/100K and in 2001 was 69.7/100K.<sup>3</sup> The economic costs of CVD in South Carolina are staggering. In 1999, the cost of CVD in South Carolina was almost \$1.4 billion in direct costs (hospital charges). Of these charges, \$629 million (45%) was for coronary

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heart disease and \$15 million (15%) was for stroke. The total hospital charges for treatment of cardiovascular disease patients increased by 330% from 1987 to 1999.<sup>3</sup> African Americans, who comprise over 30% of South Carolina's population, have heart disease and stroke death rates that are approximately 1.5 to 2 times higher than the state's white population. This difference is most prominent among African American women in South Carolina who, in 2000, were 1.3 times more likely to die of heart disease than white women.<sup>3</sup> The recognized major risk factors for heart disease and stroke are high blood pressure, high blood cholesterol, diabetes, tobacco use, physical inactivity, poor nutrition, and obesity, allowing ample prevention opportunities. It is known that more than 30% of strokes are caused by carotid occlusive disease.<sup>1</sup>

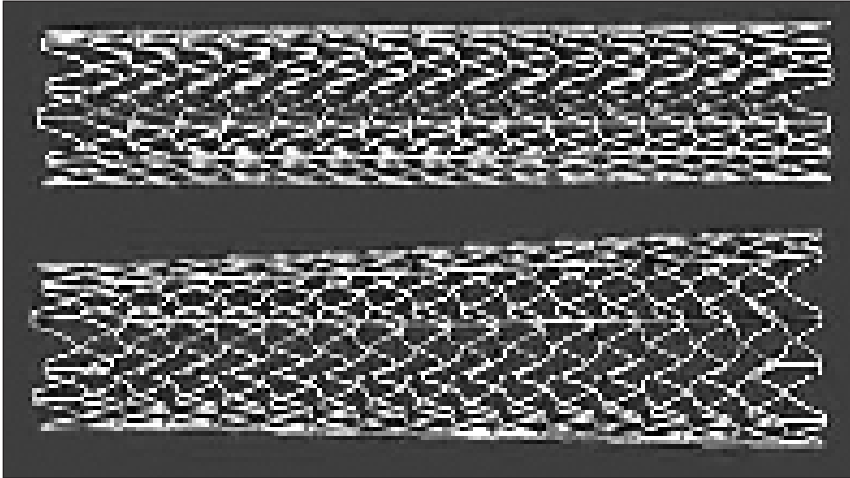
Since it is a correctable problem, carotid artery occlusive disease screening should be more widely used. The detection and treatment of carotid disease can prevent a significant number of strokes. In asymptomatic patients, one has to treat 80 patients to avoid one stroke within one year, but in symptomatic patients with stenosis greater than 70%, one has to treat only six patients to avoid one stroke within two years.<sup>12</sup> However, more than 80% of the strokes related to carotid occlusive disease will not present with red flags or recognizable symptoms before the stroke event. The traditional method of treating carotid stenosis has included medical and surgical therapy. Symptomatic patients with moderate or asymptomatic severe cervical carotid stenosis have been treated with carotid endarterectomy (CEA). Medical therapy with aspirin and

more recently with clopidogrel has been reserved for mild-to-moderate (asymptomatic) carotid stenosis or non cervical carotid stenosis.

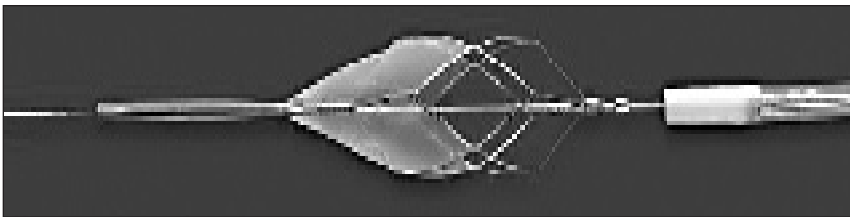
First performed about 26 years ago, carotid artery stenting (CAS) has, until recently, been only a footnote in the management of carotid artery disease, mostly because it was performed at only a few institutions, for few selected indications and was non reimbursable by insurance carriers.<sup>4</sup> The perfecting of angioplasty techniques, improvement of stent devices and more recently the development of distal embolic protection devices (EPD), CAS has become a viable alternative in the treatment of carotid artery occlusive disease. Until recently, carotid endarterectomy was the only therapy available for carotid revascularization, but with the recent developments in CAS in high-risk patients, it may actually offer similar or better results when all of the data, trials and the global carotid artery registry and results are reviewed. When evaluating CAS versus CEA and the "controversies" derived from it, it is important to look at the history of CEA and CAS, the trials and the future directions.

### Surgical Therapy

Cooley, DeBakey and Eastcott are credited with the first surgical treatment of carotid artery occlusive disease in the 1950s.<sup>5</sup> Today, approximately 180,000 surgical CEA procedures are performed annually in the United States. More than 70% of the patients undergoing CEA are asymptomatic. A great deal of confusion has ensued concerning the role of CEA in the management of carotid artery disease; it took forty years to design and perform



**Figure 1A. Carotid stent Acculink, straight and tapered.** The tapered stent is useful to bridge from the internal carotid to the common carotid, vessels with different diameters.



**Figure 1B. Embolic protection device.** “AccUNET” the first EPD device approved for carotids in United States.

the randomized trials to validate the indications and efficacy of CEA. Modern clinical practice is based on three clinical trials performed in the United States and Europe in the early 1990s: the North American Symptomatic Carotid Endarterectomy Trial (NASCET),<sup>6</sup> the Asymptomatic Carotid Artery Study (ACAS)<sup>7</sup> and the European Symptomatic Carotid Trial (ESCT).<sup>8</sup>

The NASCET trial began enrolling patients in 1988, and results were first published in 1991.<sup>6</sup> The trial developed in two parts. The first part with 659 symptomatic patients, with stenosis 70%-90% and compared CEA to aspirin and Coumadin. Surgical therapy was clearly superior to medical therapy in ipsilateral stroke rates (9% vs 26%) and death rates (2.5% vs 13.1%) over two years. The second part of the trial with 2,226 patients divided in two groups: moderate stenosis (50%-69%) and mild stenosis (30%-49%). In five years, the moderated stenosis group showed a moderate decrease in the risk

of ipsilateral stroke. CEA did not demonstrate benefit in symptomatic patients with mild stenosis. Other complications included cranial nerve palsy in 7.6%, neck wound hematoma in 5.5%, and wound infection in 3.4% of patients. In the ACAS study, 1,662 patients were randomized to CEA or aspirin. At five years, the risk of stroke or death was reduced by CEA (5.1%) compared with aspirin (11%), but only 9% of the patients were available for follow-up.<sup>7</sup> The ESCT study enrolled 3,024 symptomatic patients in twelve European countries and obtained results similar to the NASCET.<sup>8</sup>

On the various trials reported, the patient's perioperative risk of any stroke or death was about 6% in the symptomatic group, whereas it was only 2.3% in the asymptomatic group. Several explanations for those results are possible, including evaluating low-risk patients, excluding individuals over 80 years and those with major coronary artery disease, COPD or CHF. In addition, the surgeons in these

trials were high-volume operators, at large institutions. Other complex scenarios were also excluded, such as high cervical bifurcation, contralateral carotid occlusion, and restenotic lesions after CEA, intracranial stenosis and hostile necks. Therefore these numbers more likely represent low-risk patients in high-volume centers with experienced surgeons and may not reflect the true state of CEA as the time of the trials.

### **Carotid Stenting Prior-Distal Embolic Protection**

The first carotid angioplasty was performed by Mathias in 1979, followed by the first stent deployment a decade later.<sup>4</sup> Until recently, carotid artery stenting was performed in few institutions and mostly in patients who were not surgical candidates, either for anatomical or medical reasons. The procedures were performed with high profile devices unacceptable by today's interventional standards.

The Carotid Artery and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), published in 2001,<sup>9</sup> compared balloon angioplasty (not necessarily stenting) to CEA. A group of 504 (mostly angioplasty) patients were randomized into the endovascular arm. High-risk surgical patients were excluded from the study. Results demonstrated no difference in disabling stroke or death in the endovascular versus the CEA group (6.4% vs 5.9%) and no significant difference in ipsilateral stroke rate at three years. However, the restenosis rate was 14% for the endovascular group versus 4% in the CEA group, but only 23% of the patients in the endovascular group received a stent which were of older-generation not designed for carotid work.

The most comprehensive collection of data on CAS was published in 2003 with the update of the Global Carotid Artery Registry, obtained from twelve countries and 53 centers starting in 1997.<sup>10</sup> The registry included 12,254 CAS procedures, and approximately 66% of the patients did not have the benefit of cerebral em-

bolus protection. The technical success rate was 98.9%. The update report indicates that CAS performed with cerebral embolic protection yielded a significantly lower event rate than without protection, both in the symptomatic and asymptomatic population. As in the surgical trials, asymptomatic patients fared better than those who were symptomatic. Restenosis rate was approximately 2% per year over three years.

### **Carotid Stenting Post-Distal Embolic Protection**

The highest risk of the CAS is peri-procedural stroke from the liberation and migration of debris during balloon angioplasty of the carotid stenosis. In theory, prevention of intracranial embolism would allow to perform CAS with lower risk. The first attempt for distal protection was performed by Theron in 1990 using an occlusion balloon to avoid distal migration of clots or plaque fragments.<sup>11</sup>

More recently, a number of technical refinements and materials enabled the development of a variety of embolic protection devices, which can be used with CAS. In 2001, Medicare decided to reimburse for CAS procedures, as long as performed under a FDA Investigational Device Exemption (IDE). Soon after the announcement, the industry designed a trial for comparing the state of the art carotid stenting technology with conventional carotid surgery, called Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial, also known as the SAPHIRE study.<sup>12</sup> This was the first comparative trial of CAS with an embolic protection device versus CEA. The aim was to demonstrate that stenting is not inferior to CEA by a difference of 3%.

A group of 747 high risk patients were enrolled in a randomized fashion. The patients were symptomatic with a >50% luminal narrowing or asymptomatic with >80% stenosis. The study using the "Angioguard" embolic protection device had three arms: (1) Randomized CEA vs CAS

**Table 1. Importance of learning curve in carotid angioplasties.** Clinical experience over a period of 10 years with 924 patients (independent neurologic evaluation).<sup>16</sup>

<b>Year</b>	<b>Angioplasties</b>	<b>Complications</b>
1989/1991	111	8.8%
1992/1994	196	4.8%
1995/1999	617	2.0%

with embolic protection device (N=334), (2) Nonrandomized stent arm for patients who were refused surgery (N=406), and (3) Nonrandomized surgical arm for patients who were refused CAS (N=7).

At two years, the patients treated with CAS with protection devices overall fared significantly better than those receiving CEA in the observed endpoints of death, stroke and MI (12.0% vs 20.1%, p<0.05). The difference was mostly due to MI. There was no significant difference between death and stroke, but with a trend favoring stenting with protection. The symptomatic group did not show a statistically significant difference in freedom of major adverse events between CAS and CEA (16.8% vs 16.5%). The same happened in the asymptomatic group of patients (5.4% vs 10.2%, p=0.20), but with a trend in favor of CAS. However, at 30 days CAS patients had a significantly lower incidence of adverse clinical events in comparison with those who underwent CEA for both groups, symptomatic and asymptomatic. Cranial nerve injury was about 5% in surgical patients and none in the CAS group. The data of this trial showed that the outcomes of CAS are not

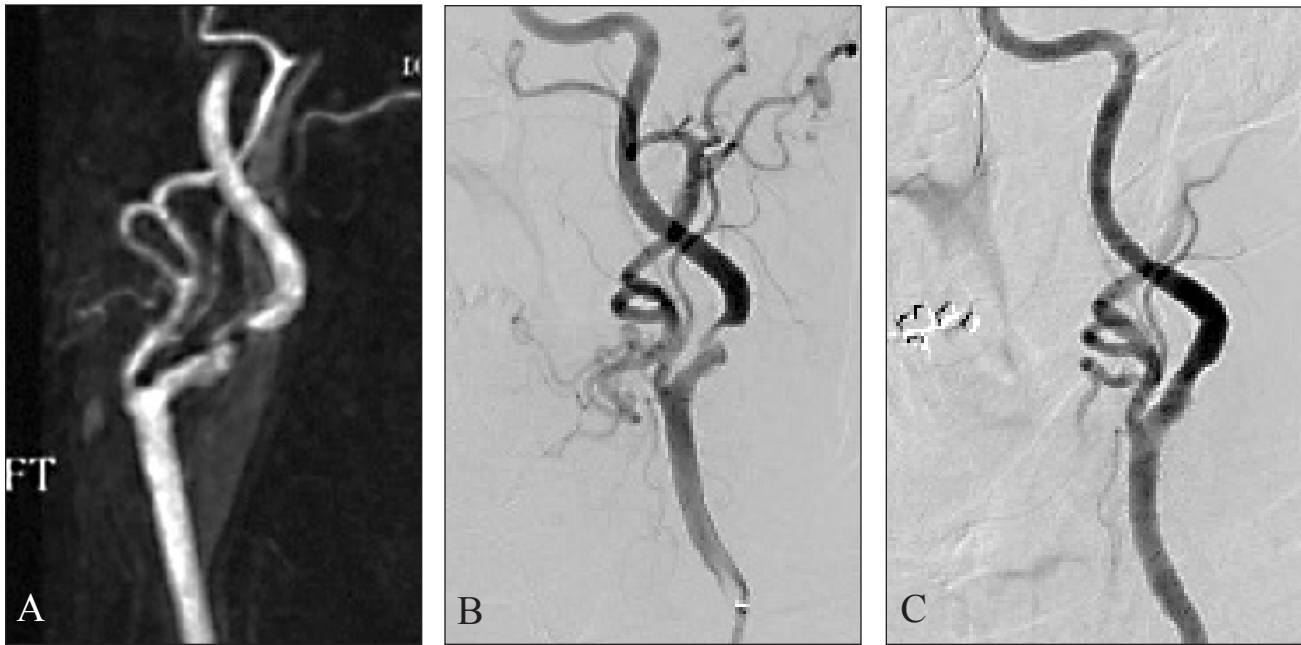
inferior to the outcomes of CEA and the benefits of stenting were clearly durable. In April of 2004, the FDA approved carotid artery stenting, and gave permission to Cordis/Johnson & Johnson to market a carotid stent and an embolic protection device.

The other trial was the Acculink for Revascularization of Carotids in High-Risk Patients study (ARCHEr) by Guidant (Figure 1). It was a prospective trial, or a registry, with CAS without embolic protection in one arm, and in the two other arms the use of a refined stent system and embolic protection, using the AccuLink carotid stent and the Accunet embolic protection device in high-risk surgical patients. There were three arm trials, enrolling 581 patients who had >50% symptomatic stenosis or 80% asymptomatic luminal blockage with some specific risk-factors.<sup>13</sup> The primary endpoints of death, MI and stroke at up to two years in ARCHEr II and II were 8.3% and 10.2%. At one year, the incidence of major stroke and death was 2.5% in ARCHEr II (with distal protection) and 3.8% in ARCHEr I (without cerebral embolic protection). The results of this trial were presented

**Table 2. Overall complication rates** after carotid artery stenting with and without embolic protection devices according to several experts.<sup>13</sup>

	<b># Cases</b>	<b>S/D rate - No Embolic Protection</b>	<b>S/D rate - With Embolic Protection</b>
Henry, M.	315	4.9%	2.2%
Roubin, G.	1276	6.9%	1.8%
Wholey, M H	10653	5.3%	2.3%
Mathias, K	405	3.0%	1.3%
German Registry	1353	2.8%	2.0%

\*Global Registry. S/D rate = Stroke/Death rate



**Figure 2 A.** MRA of the carotids showing a tight stenosis of the left carotid artery with ulceration. **B.** Left carotid angiogram confirmed the MRA, showing a  $>70\%$  stenosis of the left internal carotid associated with a deep and wide ulceration. The patient was having repeated TIAs with motor symptoms and amaurosis. **C.** Left carotid angiogram showing the result of the stenting with enlargement of the stricture and coverage of the ulcer. The patient became totally asymptomatic as verified at the 6 months follow up.

to the FDA and in November 2004 the federal agency approved the “AccuLink Carotid Stent” and the “Accunet Embolic Protection System.”

There are several other trials, such as SE-CuRITY, BEACH and CABERNET,<sup>14</sup> showing basically the same results, with similar rates of major adverse cardiac events and the rate of complications similar or better to those found in the SAPPHIRE and ARCHER trials. So far, carotid stenting has been shown to be a safe, effective and durable method of treatment for carotid disease.

As of this writing, another randomized trial comparing CAS and CEA in low-risk patients, (ACT I, Abbott) has been closed and the results presented to the FDA, generating approval (September 2005) for the “XACT carotid stent” and the “EmboShield” embolic protection device. The results of this trial are still to be published. Currently another large study, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), is under way, comparing CAS and CEA in

low-risk patients. The results are anxiously awaited.

In the United States, CMS decided to cover only high-risk, symptomatic patients with  $>70\%$  carotid stenosis,<sup>15</sup> different from the inclusion criteria for the, above mentioned, trials. Asymptomatic patients are not covered regardless of the severity of the carotid disease.

### **Recent Advancements in Carotid Stenting**

Since 2001, there have been major technological advances in carotid stenting. The current devices are specifically designed for use in carotid arteries. The advent of cerebral protection devices has significantly reduced the incidence of cerebral embolic events. There are several embolic protection devices, although only two currently available in the United States. These are very low profile devices which allow passage through the carotid stenosis with minimal disturbance of the plaque or ulceration, causing minimal high intensity transient signals (HITS) as observed by transcranial Doppler studies. The stent

delivery system profile is in general, below 5.0Fr size and the stents are made of nitinol, and are more flexible. The main advantage of nitinol is the increased flexibility and continuous expansion to the pre set size due to the temperature of the blood. An additional advancement in the stent technology was the development of the tapered stents which allow the treatment of carotid arteries with greater discrepancy in size between the common carotid and internal carotid arteries. Drug eluting stents are not available yet for carotids, but research is under way.

The learning curve of the procedure is also very important. Mathias showed that experience with carotid angioplasties and high volume of procedures increases the success and reduces dramatically the complication rates, even without embolic protection devices (Table 1).<sup>16</sup> However, the experience of individual authors and the available registries show dramatic reduction in the complication rates with the use of the embolic protection devices (Table 2).<sup>9</sup>

## The MUSC Experience

The Division of Vascular and Interventional Radiology at the Medical University of South Carolina has been working with revascularization of supraaortic, cervical branches and carotid artery angioplasty and stenting for more than ten years and accumulated expertise in managing carotid artery obstructive disease, particularly in high-risk patients (Figure. 2).<sup>17-21</sup> Our outcomes are comparable or better than the above-mentioned trials. In a group of 54 symptomatic patients with stenosis greater than 70%, treated by carotid stenting, in the past five years, no stroke, myocardial infarction or death were observed within 30 days of the procedure. Stent placement was successful in 100% of the patients and in only one patient, we failed to place the protection device. Only one stent occlusion and one restenosis developed at one year follow up, and the latter was treated by new angioplasty and stenting. Since 2002, we have been using embolic protection devices, which increased significantly the safety of the procedure (Figure 2). Currently we use the FDA approved devices for high risk, symptomatic patients, and we are starting to participate in the EXACT trial which will include high-risk, asymptomatic patients with stenosis greater than 80%, as well as the symptomatic patients with stenosis greater than 50%. Participation in this trial will open a window of opportunity for treating other patients in need, who are not covered by the CMS reimbursement rules.

## Conclusions

Carotid endarterectomy is still the mainstream treatment for carotid obstructive disease, and many critics have viewed carotid artery stenting as a niche procedure, which will not withstand the test of time; however, a lot of data and experience has been accumulated in the last several years, which appear to be proving otherwise.<sup>12-14</sup>

Why should we consider recommending carotid stenting? With carotid stenting, we can avoid general anesthesia, avoid a

neck incision, and avoid the risk of post-operative infection, cranial nerve injuries, and other surgical complications. CAS is a shorter, less invasive procedure, with less blood loss, a shorter length of hospital stay, and a shorter recovery period. Lesions that are difficult to treat with CEA such as high cervical lesions, behind the mandible, and lesions that are below the clavicle can also be treated by stenting. As it has been recently demonstrated,<sup>12-14</sup> the less invasive stenting procedure may offer an alternative treatment to open surgery with low morbidity and low mortality rates. The paradigm is definitely changing.

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