

# The Current Status of Carotid Artery Angioplasty and Stenting

## Background

As a result of important landmark studies such as the North American Carotid Endarterectomy trial (NASCET) and the Asymptomatic Carotid Atherosclerotic Study (ACAS), surgical intervention has been found to be beneficial in decreasing the relative risk of morbidity and mortality in patients with significant carotid artery atherosclerotic disease<sup>1-4</sup>.

However, carotid endarterectomy still carries a significant perioperative risk. The risk of perioperative stroke from carotid endarterectomy varies from 1.5% to 9% depending on the published series<sup>5,6</sup>. The perioperative stroke and death rate was 7.5% in the European carotid surgery trial (ECST), 5.8% in NASCET and 2.3% in ACAS<sup>1-4,7,8</sup>.

Also, the NASCET perioperative stroke and death rate for contralateral occlusions was 14.3%<sup>9</sup>. The risk of cranial nerve palsies occurs in 7.6% to 27% of cases and these results frequently are not recorded as morbidity in surgical publications<sup>5,8,10</sup>. As an alternative to the traditional surgical treatment of carotid artery occlusive disease, there has been much interest in the use of carotid artery stenting (CAS)<sup>7,8,10,11</sup>, an area that has a huge amount of political and public scrutiny.

## Carotid Stenting - A Review

Mathias, Theron and Kachel were the first to introduce this treatment for cervical carotid artery disease in the early 1980s<sup>12-16</sup> and with the advent of stent technology, interventional management of carotid artery disease began to develop as a practical new technique. Stents provide key improvements compared with angioplasty alone. They also help to decrease restenosis, to prevent dissections and to contain lesion surfaces so reducing the susceptibility for thromboembolism.

When the use of stenting was newly introduced only two peripheral stent systems were available: The balloon-mounted Palmaz-Stent and the Wall-Stent. According to the 1997 world carotid registry of approximately 2041 stents placed, Palmaz-Stents were used in 54% followed by Wall-Stents in 40%<sup>11</sup>. Both systems have advantages and disadvantages. The Palmaz-Stent was of shorter length, required only a two-step-process and had more precise deployment, which allowed it to be placed at the ostium of the internal carotid artery as opposed to the Wall-stent, which was frequently placed across the origin extending into the common carotid artery. However, the major disadvantage of the Palmaz-Stent was the compression and deformability issue.

When Nitinol-Stents became available in 1999, many interventionalists had changed or were in the process of changing from balloon-mounted stents to newer Wall-stents or the Nitinol-stents. In the updated 2000 world registry of 5427 stents placed, Wall-stents were placed in 57% and Palmaz in 33%<sup>17</sup>.

## Cerebral Protection Devices

Dislodgement of embolic particles during catheter manipulation and stent placement can be disastrous. Various cerebral protection devices including various filters and balloon catheter systems have been developed to prevent dislodgement of embolic particles. These devices are designed to trap, collect and remove particles distal to the lesion.

Currently three types of cerebral protective devices are used. The first type is a microcatheter, such as a Percusurge-Guardwire that has a soft, occlusive balloon

catheter at or near the distal tip which is inflated during the procedure.

This balloon catheter system was initially developed and employed by Theron in 1990<sup>12</sup>. The microcatheter is carefully advanced past the carotid lesion and inflated during the procedure. The angioplasty balloon catheter is advanced over the microcatheter and through the guiding catheter. With the microcatheter inflated, embolic debris is aspirated through the guiding catheter.

The second type is a microcatheter or wire with a filter designed to capture and retrieve embolic particles. The third type relies on an occluding guiding catheter and occluding balloon in the external carotid artery, which allows for reverse arterial flow from the targeted internal carotid artery into the guide catheter and then via the femoral vein through a special sheath system.

The filter is designed to be advanced past the lesion in a closed state and then opened during the procedure to collect embolic debris. After the procedure is completed, the filter collapses and the particles are removed from the body.

Both protection devices have advantages and disadvantages. The advantages of the balloon catheter system include the existence of clinical studies in both neurological and coronary systems, the use of soft latex and other materials that minimally damage the artery and a high rate of removal of embolic debris. The disadvantages of the balloon system include occlusion of the entire flow during the procedure in patients who frequently have compromised contralateral carotid artery and collateral flow and inability to evaluate the lesion while the balloon is inflated in the internal carotid artery.

Advantages of an embolic filter device include the ability to provide flow during the procedure while fully expanded and that it does not require flushing.

The disadvantages of the umbrella-type-microfilter-technique include the induction of spasm or damage to the vessel wall, the risk of releasing microparticles and the possibility of draped embolic particles being squeezed out the filter as it is retracted and collapsed.

## Current Evidence from Controlled Clinical Trials

Three randomised clinical trials comparing the efficacy of carotid artery stenting and CEA have been conducted. In Europe, the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) investigators were comparing surgical intervention with angioplasty for treatment of carotid and vertebral occlusive lesions. Among 504 patients randomised primarily to angioplasty alone (only 25% received stents) and considered suitable candidates for CEA, the 30-day disabling stroke and death rates were comparable: 6.3% for CEA and 6.4% for CAS. Phase II is now active and will employ CEA vs. CAS in symptomatic carotid cases<sup>17</sup>.

The influence of these recently published data on cases randomised to CEA or CAS may be blunted by the somewhat higher than expected complication rate in the CEA group.

A smaller clinical trial was halted prematurely because of a higher than expected complication rate in the CAS arm of the study<sup>18</sup>. However, concerns have been raised as to the investigators choice of an unacceptably small sample size, inadequate performance of the stenting procedure and unrealistic complications from CAS before the trial was halted.

Alberts *et al.* described the methodology of another randomised clinical trial comparing CAS with CEA in



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219 randomised symptomatic patients<sup>19</sup>. The stated aim of the trial was to determine whether or not CAS was equivalent to CEA in the prevention of ipsilateral stroke, periprocedural death (within 30 days) or vascular death within one year of treatment.

However, this trial was discontinued because of procedural and recruitment difficulties.

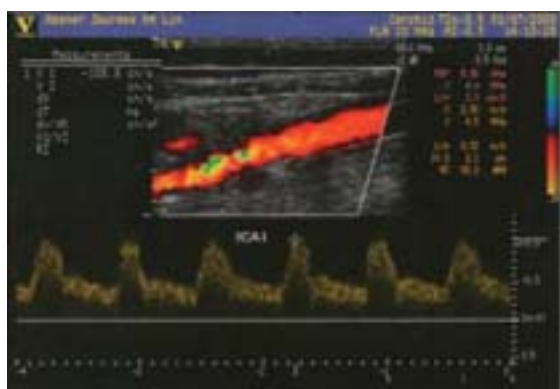
Data from this clinical series, however, demonstrated a 30-day stroke and death rate for CEA of 4.5% and for CAS of 12.1% as well as a primary end point rate of 3.6% for CEA and 12.1% for CAS<sup>20</sup>. In an equivalency analysis, this trial did not find that CAS was equivalent to CEA in symptomatic patients. Methodological flaws included limited experience with the procedure by some interventionalists, non uniformity of antiplatelet regimes, absence of supervisions by a designated principal investigator and apparent lack of input to the trialists from an independent cross data monitoring and safety board.

Conclusions regarding the results of these initial clinical trials await further review and do not provide conclusive data. However, as confirmed at a recent consensus conference, CAS can be used to treat extracranial carotid stenosis in selected subsets of patients with periprocedural complications that approach those reported for CEA<sup>21</sup>.

Nevertheless, a well designed clinical trial is urgently required, particularly for good risk patients with primary atherosclerotic occlusive disease, if we are to advise our patients about the comparative efficacy of these two new procedures.

#### Patient Selection

Careful patient selection is critical if the potential benefits of carotid stenting are to be realised. Given the proven

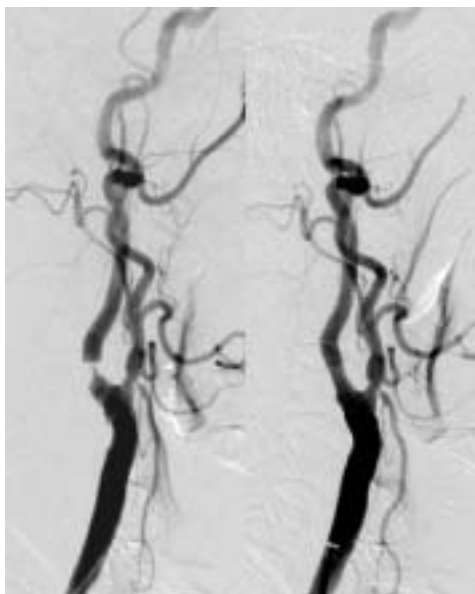


**Figure 2:** Color coded duplex sonography reveals complete hemodynamic normalisation from high velocity and turbulent jet flow (left) to regular laminar flow after stent insertion (right).

efficacy and track record of endarterectomy, carotid stenting will remain an experimental procedure until further data from clinical trials is available. Thus, all reasonable candidates for endarterectomy should either be referred for surgery or enrolled in a clinical trial randomising patients to stenting or surgery. Patients considered to be high risk for surgery should be enrolled in a stent registry, particularly if the patient is asymptomatic. This is important, not only to further define the utility of stenting but also to afford patient's access to the variety of embolic protection devices under investigational protocol. A number of risk factors have been identified that are predictive of embolic complications during carotid stenting. These include advanced age, recent symptoms or large stroke, severe disease of the aortic arch, severe lesion calcification, subtotal occlusion or "string sign", significant lesion – associated thrombus, ostial common carotid disease in conjunction with bifurcation stenosis and significant vessel tortuosity<sup>22,23</sup>. Endovascular therapy for patients exhibiting these risk factors should be avoided if possible, particularly in a physician's experience. All patients should undergo a comprehensive assessment by an independent neurologist both before and after the procedure and during the follow-up period.

#### Technical Approach and Postprocedural Management

Carotid interventions are optimally performed in a suite having technology with high-resolution imaging capability. Digital subtraction capability is essential, which enables optimisation of imaging at the carotid bifurcation, which is frequently heavily calcified. In addition, adequate imaging of the intracranial circulation requires subtraction. Patient sedatives are administered to avoid obscuring the neurological examination while maintaining patient comfort. For arterial access the femoral route is normally preferred although both the brachial and transradial approaches have been successfully employed<sup>24,25</sup>. Furthermore, equipment developed



**Figure 1:** Angiogram of high grade (90%) internal carotid artery stenosis before (left) and after (right) stent application. An Easy Wall Stent has been deployed expanding from the distal common- through the internal carotid artery.



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specifically for carotid stent deployment has been tailored to the femoral approach. Central venous access, although not required, provides a safe root for rapid pacemaker deployment and fluid resuscitation in cases of persistent procedure-related bradycardia and hypotension. Although these events occur with much less frequency than in early experience with carotid stenting, they are all still occasionally observed. Preparing for them in advance may prove to be life-saving.

After femoral access is obtained, heparin is administered to achieve an activated clotting time (ACT) of 300 seconds. This level was primarily based on safety data from coronary intervention and seems thus far to have provided a similar safety profile for carotid intervention<sup>26,27</sup>. Standard prophylactic use of glycoprotein IIb/IIIa inhibitors is not generally accepted as in coronary stenting, subgroup analysis of clinical trials of IIb/IIIa inhibitors have consistently failed to show benefit in degenerated vein grafts, presumably because of the non platelet nature of distal emboli<sup>28,29</sup>. Furthermore studies suggest that embolic debris freed during carotid intervention also consists primarily of plaque component fragments rather than platelet aggregates and thrombi<sup>30,31</sup>. Recent studies have shown no increased risk of intracranial bleeding when IIb/IIIa inhibition is used during coronary intervention<sup>32</sup>. Studies evaluating risk of intracranial haemorrhage in carotid stenting with adjuvant abciximab have shown mixed results<sup>33,34</sup>. No study of IIb/IIIa inhibition in carotid intervention has been adequately powered to assess safety or efficacy of this adjunctive pharmacological therapy. Further studies are needed before recommendations can be made.

Sheaths are removed the same day, and post procedure anticoagulation is not routinely administered. Little data is available with regard to stent thrombosis in the carotid circulation, although its incidence appears to be exceedingly rare<sup>35</sup>. Nonetheless, given the proven benefits and excellent safety profile of combination antiplatelet therapy for the prevention of stent thrombosis after coronary intervention and the devastating nature of stent thrombosis should it occur, routine practice has been to treat patients with Aspirin and Clopidogrel for at least four weeks<sup>36-39</sup>.

In uncomplicated procedures, the patient may be safely discharged the next day. Surveillance duplex ultrasound scanning should be performed after carotid stenting. The timing and intervals for these examinations is not prescribed, although a typical program might recommend duplex scanning before discharge and then at three, six and twelve months and then annually. Although a negative study is a reliable indicator of patency, the positive predictive value of an abnormal study appears to be poor. Contrast angiography should be performed to examine clinically significant restenosis detected by ultrasound.

### Ongoing Clinical Trials

Unlike with PTCA, renal or innominate artery stenting, the Federal Drug Administration (FDA) has required that randomised trials and registries be performed to assess the safety of carotid stenting. The endpoints for the carotid filter are major neurological events such as minor and major strokes and deaths. Currently, two randomised trials are underway in the USA. The carotid revascularisation endarterectomy versus stenting trial (CREST) is a randomised carotid stent placement versus surgical endarterectomy trial that has been recently approved by

**Table:**

Completed and ongoing randomised controlled trials (RCT) comparing safety and efficacy of carotid endarterectomy (CEA) versus carotid artery stenting (CAS).

RCT	STATUS	PUBLICATION	RESULTS
Alberts <i>et al</i>	Completed	1997 (20)	CEA superior to CAS
Naylor <i>et al</i>	Stopped	1998 (18)	Prematurely halted due to unexpected high complication rate in CAS arm
CAVATAS I	Completed	2001 (17)	CEA and CAS equivalent
CAVATAS II	Ongoing		
CREST	Ongoing		
SAPPHIRE	Ongoing	Preliminary data presented at AHA meeting Chicago 11/2002	CAS superior to CEA in high risk surgical subgroup
EVA II	Ongoing		
SPACE	Ongoing		

the FDA. It is currently being initiated and will eventually comprise approximately 40 centres and 2300 patients with symptomatic carotid stenosis. The 2nd randomised trial is SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy), which is studying stent placement with the Angioguard protection device versus endarterectomy in high surgical risk patients. Preliminary results have been presented at the Chicago AHA Meeting in November 2002: 307 patients were randomly assigned to either CAS or CEA. Both symptomatic ( $\geq 50\%$  ICA stenosis) and asymptomatic ( $\geq 80\%$  ICA stenosis) patients were eligible when suitable for either technique. A critical inclusion criterion was high surgical risk (NYHA III/IV, restenosis following CEA, radiation therapy etc.). 156 patients received CAS and the remaining 151 patients underwent CEA. The 30 day incidence of the primary endpoint (death, stroke, myocardial infarction) was significantly lower in the CAS group compared to the surgical group (5.8% vs. 12.6%;  $p=0.047$ ). The advantage of the stent held true in both symptomatic (4.2% vs. 15.4%;  $p=0.13$ ) and asymptomatic (6.7% vs. 11.2%;  $p=0.33$ ) patients. In addition to the randomised group, the SAPPHIRE study enrolled 409 patients into a stent registry. These were patients who required treatment but were felt by their multidisciplinary treatment team, (which included at least one vascular surgeon) to not qualify for CEA. The 30-day primary EP rate for this group was 7.8% and thereby somewhat above the study group (5.8%). This might reflect the fact that significantly more high-risk patients who did not qualify for randomisation were entered onto the registry.

European studies include EVA II, a French study, and SPACE, a German-Austrian trial. The SPACE trial (Stentprotected Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy) is a randomised multicentre study to compare safety and efficacy of CAS vs. CEA in 450 patients each. Currently, 39 centers in Germany and Austria have randomised 248 CAS and 240 CEA patients. Primary endpoint is the combined 30-day rate of vascular death and ipsilateral stroke.

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#### Speakers will include:

Dr Tim Betts - Consultant Neuro-psychiatrist from Queen Elizabeth Hospital in Birmingham - *epilepsy and women*  
 Dr Sunny Philip - Consultant Paediatric Neurologist from Birmingham Children's Hospital - *epilepsy and children - Paediatric Services*.  
 Catherine Doherty - Epilepsy Specialist Nurse for Learning Disabilities, South Birmingham PCT. *The role of the Learning Disability ESN*.

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