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Carotid artery disease: stenting, endarterectomy or medical therapy?

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Abstract

Carotid artery disease is a major cause of stroke. Carotid endarterectomy when performed with a low complication rate in patients with severe lesions has been shown to reduce the subsequent risk of stroke in a series of randomised controlled trials in both symptomatic and asymptomatic populations. The CAVATAS trial demonstrated that simple balloon angioplasty of carotid stenoses was as good as endarterectomy in terms of stroke prevention and was associated with a lower complication rate. Carotid stenting performed with the use of distal protection devices has been shown to be superior to endarterectomy in patients considered to be at increased perioperative risk as assessed by a variety of clinical and angiographic parameters. Comparisons of carotid stenting and endarterectomy in patients considered to be of normal perioperative risk are ongoing. Optimal medical therapy is mandatory for all patients with carotid artery disease.

Key words: stroke, carotid stenting, carotid endarterectomy, distal protection.

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Introduction

Stroke is the third commonest cause of death in the UK. Treating and managing patients with the consequences of cerebrovascular disease consumes at least 4% of the NHS budget. Approximately 25% of strokes can be causally related to extracranial carotid disease, and the need for carotid revascularisation has been estimated to be around 150 procedures per million per year.[1]

Carotid endarterectomy (CEA)

The superiority of CEA over standard medical management was established following a series of large randomised studies.

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Symptomatic patients

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) randomised patients with symptomatic ipsilateral carotid artery disease to medical therapy or to CEA plus medical therapy. The first phase of the study revealed convincing benefits of CEA in patients with high-grade stenosis (70% to 99%)[2] whilst the second phase revealed more modest benefits in patients with moderate stenosis (50% to 69%).[3]

The Medical Research Council European Carotid Surgery Trial (ECST) was designed to investigate the benefits of CEA in patients with symptomatic carotid artery disease of any severity. The results revealed that the benefit was restricted to patients with a stenosis of more than 80%.[4]

This finding is further illustrated by a meta-analysis of the available randomised CEA trials.[5] The pooled data revealed that: CEA increased the five-year risk of ipsilateral ischaemic stroke in patients with < 30% stenosis (absolute risk reduction -2.2%, p=0.05); had practically no effect in patients with 30–49% stenosis (absolute risk reduction 3.2%, p=0.6); was of marginal benefit in those with 50–69% stenosis (absolute risk reduction 4.6%, p=0.04); and was highly beneficial in those with > 70% stenosis without near-occlusion (absolute risk reduction 16.0%, p<0.001).

It is worth emphasising that there is an appreciable peri-operative morbidity and mortality associated with CEA, even within strict trial conditions and with experienced surgeons. The risks of stroke or death at 30 days in the surgical groups of NASCET and ESCT were 6.5% and 7%, respectively.

Asymptomatic patients

A meta-analysis of the available trials in asymptomatic patients, including the largest study – Asymptomatic Carotid Artery Stenosis (ACAS) – has been performed.[6] In patients who underwent CEA (n=1,215), there was a significant reduction in the odds of ipsilateral stroke plus perioperative stroke or death (odds ratio 0.62; 95% confidence interval 0.44 to 0.86), corresponding to a 2% absolute risk reduction over about 3.1 years.

Recently the five-year results of the single largest trial comparing CEA and medical therapy in asymptomatic patients have been published.[7] For all strokes, including perioperative events, the five-year risks were 6.4% with CEA *vs.* 11.8% for patients initially randomised to medical therapy alone (95% CI for net gain 3.0–7.8%, p<0.0001). There were similar relative risk reductions for fatal or disabling stroke and for fatal stroke alone.

As with all interventions, the benefits will be dependent on the operators and institution being able to carry out the procedure concerned, in this case CEA, with a peri-procedural compli-

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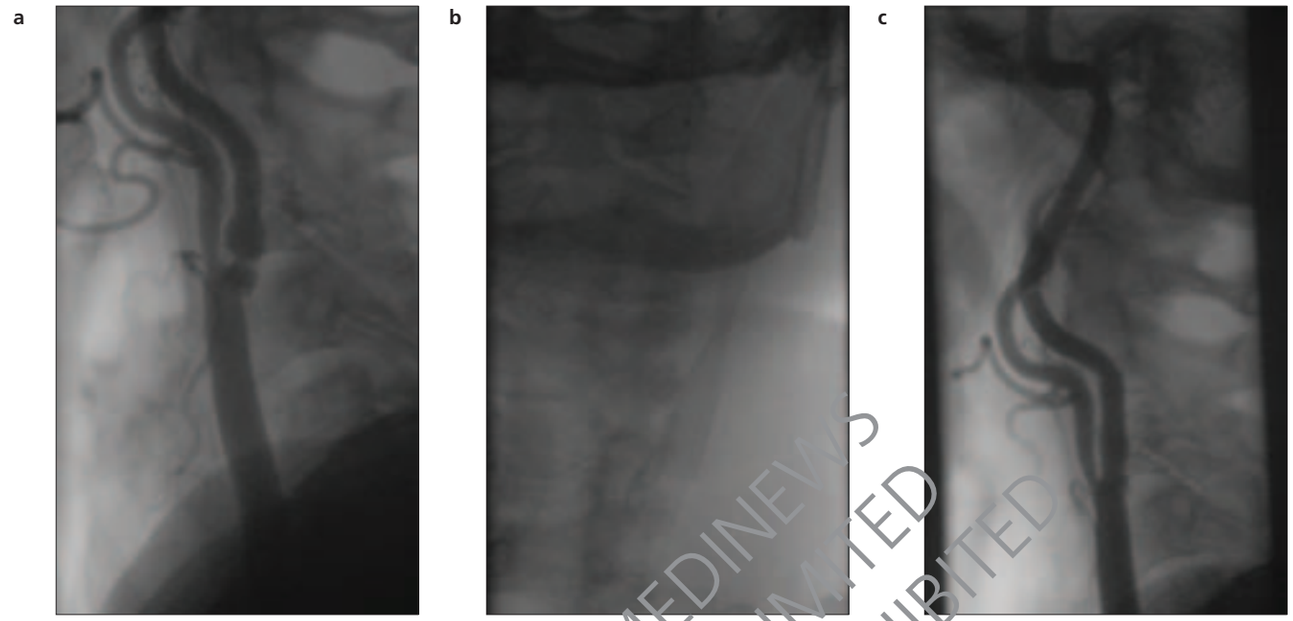
Figure 1. **a**: Selective carotid angiography at baseline, showing a severe ICA stenosis; **b**: self-expanding stent deployed with distal protection filter device (two radio-opaque markers); **c**: final result after post-dilatation



Key: ICA = internal carotid artery

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Table 1. Results of the CAVATAS trial

	Angioplasty	Surgery	p value
Disabling stroke/death	6.4%	5.9%	NS
Any stroke > 7 days/death	10.0%	9.9%	NS
Cranial neuropathy	0	22 (8.7%)	<0.002
Major haematoma	3 (1.2%)	17 (6.7%)	<0.001

Table 2. CAFE-USA primary end point: 30-day hierarchical event rates

Death	3 (1.4%)
Neurologic death	2 (0.9%)
Ipsilateral stroke	11 (2.4%)

cation rate no higher than that reported in the trials providing the evidence base for that intervention. Careful and continuing audit is therefore essential.

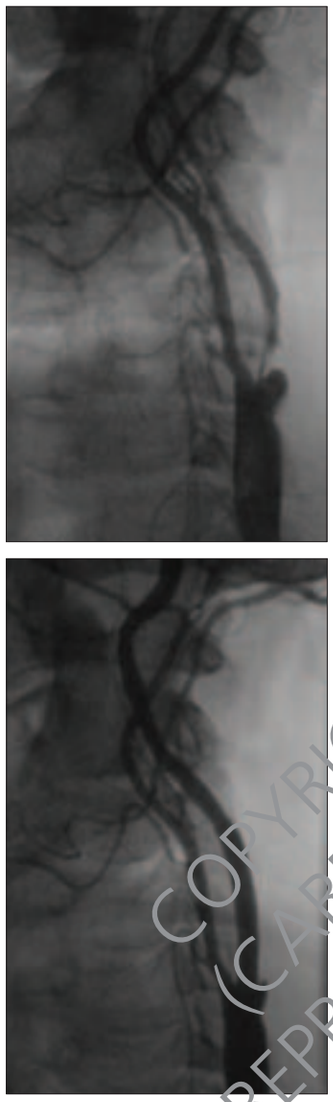
Carotid angioplasty

The first carotid angioplasty was performed in 1980. Since then, in parallel with advances in technology and expertise in coronary intervention, carotid intervention has also progressed. Many small carotid angioplasty trials and registries have been published, but the first important randomised study was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).[8] This was a multi-centre trial involving 22 centres from Europe, Canada and Australia. In total, 504 patients with high-grade symptomatic carotid artery stenosis were randomised to treatment with either CEA or balloon angioplasty (bailout stenting was performed in 26% of patients). Follow-up was carried out by independent neurologists. The trial showed no difference in long-term outcomes and fewer complications with the percutaneous technique (table 1).

Carotid stenting

In parallel with coronary intervention, balloon angioplasty was superseded by stenting. However, some of the initial studies utilising carotid stents reported disappointing results. This was probably due, at least in part, to operator inexperience but also to the occurrence of distal embolisation during stent delivery and deployment. As with CEA, the main risk of carotid stenting is the potential for neurological events, most of which are caused by embolisation of micro- and macro-particles of thrombotic or atherosclerotic material during the intervention. This problem has been addressed by the development of a number of distal protection devices which can be broadly classified into guidewire-based filters, balloon occlusion catheters and flow reversal systems. Examples of carotid stenting are shown in figures 1 and 2.

Figure 2. **a**: Selective carotid angiography at baseline showing a severe ICA stenosis – guidewire already across the lesion; **b**: final result after post-dilatation of a self-expanding stent



Key: ICA = internal carotid artery

Table 3. SAPPHIRE study: end points at one year

	Stenting (n=159)	CEA (n=151)
Death	6.9%	12.6%
MI	2.5%*	7.9%
All strokes	5.7%	7.3%
Major ipsilateral strokes	0.0%*	3.3%
Composite	11.9%*	19.9%
TLR	0.6%	4.0%
Cranial nerve injury	0.0%*	4.6%

Key: * = statistically significant difference *vs.* CEA; CEA = carotid endarterectomy; TLR = clinically driven target lesion revascularisation; MI = myocardial infarction

CAFE-USA

The first available evidence of the efficacy of distal protection devices in carotid intervention came from a prospective registry called Carotid Artery Intervention Free of Emboli (CAFE-USA).[9] This registry demonstrated that the use of an occlusive balloon distal protection device (Percusurge, manufactured by Medtronic Inc.) was technically feasible, well tolerated by most patients, and resulted in retrieval of embolic material from every patient undergoing carotid stenting. In this early learning curve experience in a high-risk patient cohort, disabling stroke and death were rare (table 2).

The role of carotid artery stenting with distal protection has subsequently been examined in numerous registries, and several large studies are ongoing.[10] So far, the results of two of these studies have been presented.

SAPPHIRE

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study was a randomised multicentre trial comparing CEA against carotid artery stenting with distal protection in high-risk surgical patients.[11] Patients with symptomatic carotid stenosis of > 50% or asymptomatic stenosis of > 80%, with one or more predefined co-morbidity criteria, were randomised to CEA or to stenting with distal protection using the Precise stent and the Angioguard XP distal protection device (both manufactured by Cordis).

A team, including a vascular surgeon, a neurologist and an interventionalist, then screened eligible patients. Consensus was required prior to randomisation. If the patient was thought ineligible by the surgeon, the patient was enrolled in a stent registry and *vice versa*. The co-morbidity criteria delineated a high-risk population and included New York Heart Association (NYHA) grade III/IV heart failure, recent myocardial infarction (> 24 hours and < 4 weeks), the need for cardiac surgery within six weeks, unstable angina (CCS III/IV), severe pulmonary disease, contralateral carotid occlusion, tandem lesions, high cervical lesions, CEA with recurrent stenosis and age > 80 years.

In all, 307 patients were randomised, 409 patients were enrolled in the stent registry following surgical refusal, and seven patients were entered in a surgical registry following refusal by the interventionalist. The major primary end point in the randomised cohort was a composite of death/MI/stroke at 30 days.

There was a technical success rate in excess of 90% for stent placement and 98% for successful delivery of the distal protection device. The 30-day composite end point was significantly lower in the stented cohort (5.8% *vs.* 12.6%). This benefit was maintained across all subgroups and sustained to 12 months. Although a large component of the reduction in the composite end point was driven by a reduction in myocardial infarction, there were also statistically significant reductions in

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Key messages

- Carotid endarterectomy has been shown to be an effective, durable procedure in patients with severe carotid artery disease
- Percutaneous carotid intervention can potentially provide similar benefits to surgical revascularisation
- The CAVATAS trial demonstrated no difference in death or stroke between carotid balloon angioplasty and CEA, with lower complications in the angioplasty group
- Carotid artery stenting with distal protection, used in conjunction with dual antiplatelet therapy, is currently the gold standard for percutaneous carotid intervention
- Recent studies suggest that carotid stenting with distal protection may be superior to, and more widely applicable than, CEA in high-risk surgical patients
- The role of percutaneous carotid intervention with distal protection needs further confirmation in large randomised controlled trials

major ipsilateral stroke, clinical restenosis and cranial nerve injury (table 3).

In the stent registry of 408 patients rejected by the vascular surgeons due to complexity of their anatomy or high risk co-morbidity, results were also excellent with stenting with a 30-day major adverse event rate of 7.8%). This further illustrates the wider clinical utility of stenting in comparison to surgery. Only seven of 7,171 patients screened were thought to be unsuitable for percutaneous intervention compared to 408 who were thought to be ineligible for surgery.

ARCHER

The Acculink for Revascularisation of Carotids in High Risk Patients (ARCHER) was a single arm prospective registry using the Acculink carotid stent system and the Accunet distal protection system (both manufactured by Guidant).[12] Inclusion criteria consisted of a symptomatic carotid stenosis of $\geq$ 50% or an asymptomatic stenosis of $\geq$ 80%. In addition, patients had to meet pre-defined high-risk criteria. The primary end points were a composite of death, stroke or MI at 30 days, the incidence of ipsilateral stroke from 31 days to one year, and the success of the distal protection device.

Preliminary 30-day results are available for 437 patients. The procedural success rate was 92.7%. The composite end point occurred in 7.8% of the patients, compared to a rate of 14% in a historical surgical control group.

Antiplatelet therapy in carotid artery stenting

In addition to the technological advances in carotid artery intervention, there have been equally important advances in adjunctive therapy. It is now routine practice to administer dual antiplatelet therapy with aspirin and clopidogrel before and after carotid stent implantation. This practice was not uniformly followed in the early randomised trials and may account for some of their discrepant outcomes.

There are no large randomised studies comparing antiplatelet regimes and our current practice arises from an extrapolation from the convincing benefits of dual antiplatelet therapy seen in coronary intervention. However, some smaller registry data exist to support this practice. Bhatt *et al*. have reported 162 patients in a consecutive single centre registry and shown that dual antiplatelet therapy with clopidogrel plus aspirin in patients receiving carotid artery stents is associated with a low rate of ischaemic events in comparison to single therapy with aspirin or dual therapy with aspirin and ticlopidine.[13] Chaturvedi *et al*. reported two cases of fatal carotid stent thrombosis.[14] Neither patient was treated with combination antiplatelet therapy, either before or after stent placement.

Conflict of interest

None declared.

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References

1. Ferris G, Roderick P, Smithies A *et al*. An epidemiological needs assessment of CEA in an English health region. Is the need being met? *BMJ* 1998;**317**:447-51.
2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of CEA in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;**325**:445-53.
3. Barnett HJM, Taylor DW, Eliasziw M *et al*. for the North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefits of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;**339**:1415-25.
4. European Carotid Surgery Trialists' Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379-87.
5. Eliasziw M, Gutnikov SA, Fox AJ *et al*. for the Carotid Endarterectomy Trialists Collaboration. Analysis of Pooled Data from the Randomised Controlled trials of Carotid Endarterectomy for symptomatic Carotid Stenosis. *Lancet* 2003;**361**:107-16.
6. Benavente O, Moher D, Pham B. Carotid endarterectomy for asymptomatic carotid stenosis: a meta-analysis. *BMJ* 1998;**317**:1477-80.
7. Halliday A, Mansfield A, Marro J *et al.* MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004; **363**:1486-7.
8. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;**357**:1729-37.
9. Roubin G, Mehran R, Diethrich E *et al*. Carotid stent-supported angioplasty with distal neuro-protection using the Guardwire™: 30 day results from the carotid angioplasty free of emboli trial (CAFÉ-USA). *J Am Coll Cardiol* 2001;**37**:38A.
10 Roubin GS, Hobson RW, White R *et al*. CREST and CARESS to evaluate carotid stenting: time to get to work! *J Endovasc Ther* 2001;**8**:107-10.
11. Stenting and angioplasty with protection in patients at high risk for endarterectomy. (SAPPHIRE study). Presented by Dr JS Yadav. Transcatheter Therapeutics (TCT) Meeting, Washington DC, USA, September 2003.
12. Acculink™ for revascularisation of Carotids in High Risk patients. (ARCHER) study. Presented by Dr Mark Wholey. American College of Cardiology 52nd Annual Scientific Session, Chicago, USA, March 2003.
13. Bhatt DL, Kapadia SR, Bajzer CT *et al*. Dual antiplatelet therapy with clopidogrel and aspirin after carotid artery stenting. *J Invasive Cardiol* 2001;**12**:767-71.
14. Chaturvedi S, Sohrab S, Tselis A. Carotid stent thrombosis: report of two fatal cases. *Stroke* 2001;**32**:2700-02.