Current Status of Carotid Stenting

Bahaeddin Shabaneh, Neil Strickman and Zvonimir Krajcer

Department of Cardiology, Texas Heart Institute at St Luke's Episcopal Hospital

Abstract

Carotid stenting has significantly evolved over the last decade as techniques and equipment have continued to improve. Several phases of waxing and waning enthusiasm have occurred that have started to settle in favour of carotid stenting in select patients. Carotid stenting is being performed more frequently in community hospitals with reasonable results, as seen in multiple registries. The most recent randomised trials that have compared carotid stenting versus carotid endarterectomy have shed considerable light on the safety and efficacy of stenting, but also have created controversy over the methods and design of many of these trials. The results of the most recent trial, Carotid revascularization endarterectomy versus stenting (CREST) and other registry studies have lifted considerable fog from the scene and confirmed the safety and efficacy of stenting. We are optimistic that future trials will involve better methods and equipment and will help to establish carotid stenting as a standard therapy for carotid artery stenosis.

Keywords

Carotid stenting, carotid stenosis, carotid angioplasty, carotid endarterectomy

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Correspondence: Zvonimir Krajcer, 6624 Fannin St., Suite 2780, Houston, TX 77030, US. E: ZvonkoMD@aol.com

Carotid stenting has been introduced for the treatment of carotid artery stenosis as a potentially less invasive therapy than carotid endarterectomy, because carotid stenting does not require general anaesthesia and does not lead to local surgical complications. Despite major technical progress in decreasing the risk of embolisation, this risk continues to be a hurdle in the acceptance of carotid angioplasty and stenting. Several phases of waxing and waning enthusiasm have occurred that have started to settle in favour of carotid stenting in select patients. Initially, the evidence for carotid stenting came from registries, single-centre experiences and non-randomised trials. These trials differed in their methods, design, technical aspects, sponsorship, method of neurological evaluation and definitions of outcomes, which led to conflicting results.

The results of several registry studies of different stents and protection devices include 30-day rates of stroke, myocardial infarction (MI) or death that range from 3.8 to 8.5%.[1] Early randomised trials were discouraging and some were discontinued early because of high complication rates, including high rates of stroke.[2] However, since then several randomised trials have been conducted that have shed considerable light on the safety and effectiveness of carotid angioplasty and stenting.

CAVATAS

The Carotid and vertebral artery transluminal angioplasty study (CAVATAS), published in 2001,[3] was a multicentre randomised trial in which 504 patients were assigned to either carotid angioplasty or endarterectomy. At 30 days, the risk of stroke or death was approximately 10% in both groups, which was higher than the risk seen in earlier surgical trials. Embolic protection devices were not used in this trial. Patients in the angioplasty arm had more carotid restenosis because stenting was used in only a minority of cases (26%) and the surgical arm had a higher incidence of neck haematoma and cranial nerve palsy.

SAPPHIRE

In the Stenting and angioplasty with protection in patients at high risk for endarterectomy (SAPPHIRE) trial,[4] 334 patients were randomly assigned to carotid stenting with mandated distal protection by the AngioGuard device (Cordis Corporation, Miami, FL, US) versus carotid endarterectomy. Because of slow enrolment, the study was stopped prematurely. It included high-risk patients (from a surgical standpoint) who either had >50% stenosis and were symptomatic or had >80% stenosis and were asymptomatic. The primary end-point was the cumulative incidence of death, stroke or MI within 30 days after the procedure, or death or ipsilateral stroke between 31 days and one year after the procedure. The incidence of the primary end-point was 12.2% in the stenting group and 20.1% in the surgical group ($p=0.004$ for non-inferiority and $p=0.053$ for superiority). The 30-day incidence of MI, stroke or death was 4.8% after stenting and 9.8% after surgery ($p=0.09$). This difference was not fully attributed to the inclusion of more asymptomatic patients in the SAPPHIRE trial but also to methodological differences compared with earlier studies. The three-year incidence of the composite end-point was similar in both groups.[5]

Although the SAPPHIRE trial created enthusiasm for carotid stenting in high-risk patients, several aspects of the study were criticised. First, many patients were screened but not randomised in the trial. Second, patients in the trial were considered high-risk from a surgical standpoint but not in terms of their stroke risk. Third, some authors opined that aggressive medical therapy could have been

a better choice to treat these patients, underlining the importance of including a medical therapy arm in carotid angioplasty and stenting trials.[6]

In 2009, the outcomes of the SAPPHIRE worldwide registry were announced. Approximately 4,000 patients were included. The 30-day incidence of the composite end-point of death, MI or stroke was remarkably low (4.5%).[7]

EVA 3S

The Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA 3S) trial was a publicly funded French study designed as a multicentre, randomised non-inferiority trial.[8] It included patients with symptomatic carotid stenosis of 60–99% and at overall low risk. The recruitment started in autumn 2000; after 527 of the 872 intended patients had been recruited, the study was stopped prematurely in 2005 by the safety committee for safety and futility reasons.

The primary end-point of the trial (the incidence of stroke or death at 30 days) was 3.9% after endarterectomy (95% confidence interval [CI] 2.0–7.2) and 9.6% after stenting (95% CI 6.4–14.0). At six months, the incidence of stroke or death was 6.1% after endarterectomy and 11.7% after stenting (p=0.02).[9] The study favoured carotid endarterectomy over carotid stenting in average-risk patients, but it was criticised for several reasons. The 9.6% incidence of major adverse events observed in the stenting patients in the EVA 3S trial seemed excessive compared with the lower incidence seen in the earlier SAPPHIRE trial.[4,10] Furthermore, compared with the SAPPHIRE trial, in which only one system was used, the EVA 3S trial operators used five different stents and seven different neuroprotection devices. Neuroprotection was mandated only halfway through the trial, resulting in a 92% frequency of use at the end of the trial. In addition, EVA 3S operators had variable experience, with the requirement of performing only two procedures with each specific device before the trial. Operators could perform carotid stenting with the supervision of an experienced tutor, who had to have placed 12 stents in the carotid artery or, alternatively, 35 stents in the supra-aortic trunk, including five in the carotid artery. Although the learning curve was an issue in this trial, the investigators stated that there was no difference in outcomes among various operators. The failure rate of device deployment was about 5%. Additionally, the use of dual antiplatelet therapy in the trial was suboptimal; a small percentage of patients received single antiplatelet therapy with no defined dose of clopidogrel loading.[11]

The four-year results of EVA 3S were published in 2008.[12] The incidence of stroke or death was higher with stenting than with endarterectomy (11.1 versus 6.2%; p=0.03). The stroke risk was predominantly peri-procedural and both groups had a low incidence of post-procedural stroke.

SPACE

The Stent-supported percutaneous angioplasty of the carotid artery versus endarterectomy (SPACE) trial was a multicentre, randomised trial performed in Germany, Austria and Switzerland. This trial included patients with symptomatic carotid stenosis of at least 70% according to the European Carotid Surgery Trial (ECST) criterion (diameter of the vessel at the lesion compared with the total vessel diameter at the same level), or of at least 50% according to the North American symptomatic carotid endarterectomy trial (NASCET) criterion (diameter of the vessel at the lesion compared with the vessel diameter in the reference segment).[13]

Recruitment for the SPACE trial started in 2001 and ended prematurely in 2006. Of the 1,200 patients who were recruited, 1,183 (63% of the intended sample size of 1,900) were included in the analysis. The trial used a non-inferiority design with an inferiority margin of 2.5%. The primary outcome was the incidence of ipsilateral stroke or death at 30 days. With regard to this outcome, the study failed to prove non-inferiority of stenting: the incidence of the primary end-point was 6.34% in the surgical arm and 6.84% in the stenting arm (the one-sided p-value for non-inferiority was 0.09), revealing a trend towards more strokes in the stenting group, especially in elderly patients.

The SPACE study was heavily criticised for being underpowered and for using protection devices in only one-quarter of the stenting patients. Also, the 30-day incidence of death or total stroke exceeded the incidences reported in prior studies.[9]

At two-year follow-up,[14] there was no difference in the incidence of recurrent stroke between patients who underwent carotid endarterectomy and those who received carotid angioplasty with stenting for severe symptomatic carotid artery stenosis, because few clinical events occurred during the post-procedural phase (between day 31 and two years after treatment). Instead, the main difference between the groups was the higher peri-procedural event rate in the stenting group during the first five days after the procedure; event rates after day five were almost identical. Another finding from the two-year follow-up was that patients under 68 years of age who were treated with carotid stenting had a significantly lower risk of recurrent stroke than patients treated with carotid endarterectomy.

ICSS

The International carotid stenting study (ICSS, or CAVATAS II) was a multicentre, international randomised trial. Patients with symptomatic severe carotid stenosis were randomly assigned in a 1:1 ratio to stenting or endarterectomy. The primary outcome was the three-year incidence of major stroke. Severe carotid stenosis was defined as >50% as per the NASCET criterion. Interventionalists were required to have previously performed at least 50 stenting procedures, of which at least 10 had to be in the carotid artery. Physicians who did not meet these criteria had to be proctored until they fulfilled these requirements.

The trial enrolled 1,713 patients from 50 academic centres in Europe, Australia, New Zealand and Canada. The interim safety analysis[15] showed that the rate of stroke, death or procedural MI 120 days after randomisation was significantly higher in the stenting patients than in the endarterectomy patients (8.5 versus 5.2%; p=0.006). All-cause mortality was higher in the stenting group than in the endarterectomy group (2.3 versus 0.8%; p=0.017). The stenting group performed worse regardless of whether intention-to-treat analysis or per-protocol analysis was used. In the surgical arm, a higher incidence of cranial nerve palsies and severe haematomas was observed. A blinded subanalysis of brain magnetic resonance imaging findings showed a significantly higher incidence of ischaemic lesions in the stenting group (50%) than in the surgical group (17%, adjusted odds ratio 5.21, 95% CI 2.78–9.79; p<0.0001).[16] The authors stated that most of the excess non-disabling strokes in the stenting group occurred on the first day after the procedure and were due to instrumentation of the

carotid artery. Several different stents and protection devices were used in this trial and neuroprotection devices were not used in about 28% of the stenting procedures.

The authors of ICSS performed a meta-analysis of the 30-day event rates in the ICSS, EVA 3S and SPACE trials and concluded that endarterectomy had much more favourable outcomes than stenting (odds ratio for stroke, death or MI within 30 days after the procedure 1.73, 95% CI 1.29–2.32). The ICSS has been criticised for many of the same reasons as previous trials. For example, the interventionalists in this trial were much less experienced than the surgeons. However, as in the EVA 3S trial, in a subgroup analysis the authors showed that inexperience was not a factor in the underperformance of stenting in the ICSS trial, although this remains a matter of debate.

Critical Analysis of EVA 3S, SPACE and ICSS

In addition to the previously mentioned points, several other major limitations of these three trials were identified in a thorough and thoughtful analysis by Fiehler and colleagues.[17] First, the non-inferiority comparison design poses several challenges and the results are often misinterpreted. Second, the early discontinuation of the EVA 3S and SPACE trials makes the results not fully interpretable. Third, the inclusion and exclusion criteria of each trial were significantly heterogeneous. Fourth, MI and cranial nerve palsies were not considered as end-points in the EVA 3S and SPACE trials, but whether this is grounds for criticism remains a matter of debate. Fifth, the analyses in these trials showed no effect of operator or centre experience, a finding that is somewhat counterintuitive. Sixth, the trials did not compare the methods and detailed techniques used in stenting or endarterectomy, which would have a substantial effect on the outcomes.[17]

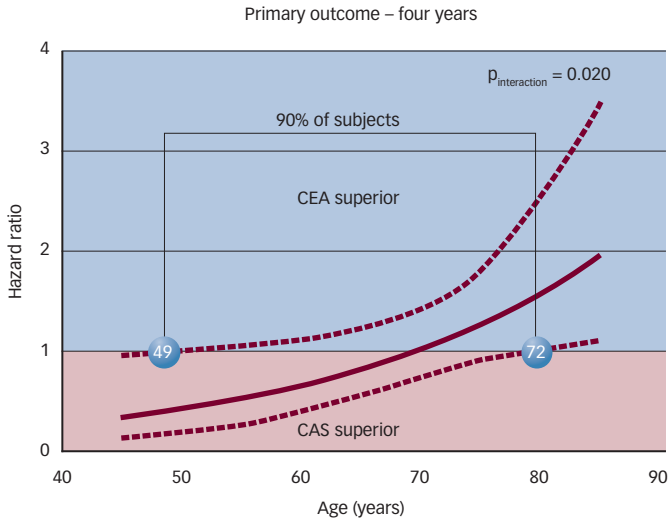
Another limitation of these trials was the variability in the use of dual antiplatelet therapy, which was not mandated in the EVA 3S and ICSS trials (unlike the SPACE trial). About 15% of patients in EVA 3S did not receive dual antiplatelet therapy.

CREST

The Carotid revascularisation endarterectomy versus stenting trial (CREST)[18] was a randomised, controlled trial in which patients with severe carotid stenosis (symptomatic or asymptomatic) underwent stenting or endarterectomy. Symptomatic patients were eligible if they had 50% stenosis on angiography or 70% on ultrasonography, computed tomography or magnetic resonance angiography; asymptomatic patients were eligible if they had 60% stenosis on angiography, 70% on ultrasonography or a combination of 50–69% on ultrasonography and more than 80% on computed tomography or magnetic resonance angiography. The primary composite end-point was stroke, MI or death from any cause during the peri-procedural period or any ipsilateral stroke within four years after randomisation. The statistical analysis of the trial used a superiority design.

The trial enrolled 2,502 patients from 108 centres in the US and Canada. It was partly sponsored by Abbott Vascular. The protocol specified the use of the Rx Acculink stent (Abbott Vascular, Redwood City, CA, USA) and recommended the use of the Rx Accunet embolic-protection device (Abbott Vascular). The study specified dual antiplatelet therapy with aspirin and clopidogrel 48 hours before the procedure (98% of patients) and for up to four weeks after the procedure (about 99% of patients). Embolic protection was used in 96% of the patients.[18]

Figure 1: Age and Its Relationship to the Hazard Ratio for Endarterectomy versus Stenting in the CREST Trial



CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy. Courtesy of Abbott Vascular, Redwood City, CA, US.

There was no significant difference in the estimated four-year rates of the primary end-point between the stenting group (7.2%) and the endarterectomy group (6.8%, hazard ratio with stenting 1.11, 95% CI 0.81–1.51; p=0.51). Peri-procedural rates of the individual components of the end-point differed between the stenting group and the endarterectomy group: for death (0.7 versus 0.3%; p=0.18), for stroke (4.1 versus 2.3%; p=0.01) and for MI (1.1 versus 2.3%; p=0.03). There has been debate over the use of MI as an end-point in this trial and whether it should be given the same weight as stroke.

An interesting finding was the effect of age on the primary end-points: younger patients did better with stenting, whereas more elderly patients did better with endarterectomy, presumably because the elderly patients had more vascular tortuosity and calcification. This finding was seen in the SPACE trial as well, with the age cut-off being 68 years in SPACE and 70 years in CREST; however, this relationship not a simple linear one (see *Figure 1*).

Another interesting finding of CREST was that among asymptomatic patients the rate of stroke or death in the carotid artery stenting group was 2.5%, which was similar to the rate seen in the Asymptomatic carotid atherosclerosis study (ACAS)[19] and lower than that reported in the Asymptomatic carotid surgery trial (ACST).[20] Additionally, the rate of stroke and death in CREST's carotid endarterectomy group (1.4%) was lower than that in ACAS and ACST.

In CREST, high-risk patients were excluded, but unlike other previously mentioned trials (EVA 3S, SPACE and ICSS), CREST included asymptomatic patients. It also used broader composite end-points, had greater power to detect differences in these end-points, had longer follow-up and eventually had lower event rates; for example, the incidence of stroke or death in symptomatic carotid stenosis was 6.0% in CREST compared with 9.6% in EVA 3S. This difference underlines the importance of training and credentialling interventionalists,[21] because operators in CREST were required to complete a rigorous lead-in phase to consolidate their skills. This difference comes from other factors as well, including CREST's better design and structure, more frequent use of antiplatelet therapy,

Table 1: Operator Qualifications and Study Protocols for Randomised Controlled Trials of Carotid Endarterectomy versus Carotid Angioplasty and Stenting

Trial	Operator Qualifications		Protocol Comments		
	CEA	CAS	Use of Protection Devices	Coagulation Regimen Before Procedure	Coagulation Regimen After Procedure
EVA3S (2006)	≥25 CEAs in past year	≥12 CAS or ≥5 CAS + ≥30 PTA of other supra-aortic vessels (treatment of enrolled patients under a tutor's supervision)	Recommended (actually used in 92%)	Recommended: aspirin and clopidogrel/ticlopidine for 3 days (actually used in 82.9%)	Recommended: 30 days (actually used in 85.4%)
SPACE (2006)	≥25 consecutive CEAs with documented mortality and morbidity rates	≥25 carotid PTAs/CAS, (from 2002 onward) certification after 10 CAS, remaining CAS performed under guidance "of an experienced colleague"	Optional (actually used in 26%)	Mandatory: 100mg aspirin and 75mg clopidogrel daily for ≥3 days	Mandatory: 100mg aspirin and 75mg clopidogrel daily for 30 days
ICSS (2010)	≥50 CEAs (annual rate ≥10), accreditation, mortality and morbidity rate ≤6%	≥50 PTAs, including ≥10 CAS, complete CAS training sessions, accreditation, mortality and morbidity rate ≤6%	Recommended (actually used in 72%)	Recommended: aspirin and clopidogrel	
CREST (2010)	Certification followed by validation, >12 CEAs/year, stroke and death rates <3% among asymptomatic patients and <5% among symptomatic patients	Certification followed by satisfactory evaluation of clinician's endovascular experience (>15 procedures), participation in hands-on training, participation in a lead-in phase of training	Mandated (actually used in 96%)	Aspirin 325mg and clopidogrel 75mg twice daily for ≥48 hours; 650mg aspirin and 450mg clopidogrel given ≥4 hours before procedure	1 or 2 doses of 325mg aspirin daily for 30 days and either 75mg clopidogrel daily or 250mg ticlopidine twice daily, for 4 weeks

CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; PTA = percutaneous transluminal angioplasty. Modified with permission of Fiehler et al., 2010.[17]

Table 2: Study Design and Protocol

Trial	Inclusion Criteria (Incl. % Stenosis)	Centres	Design	Planned n	Actual n	Power/Alpha (Type 1 Error Probability)	Primary End-point Stenting/Surgery
EVA3S (2006)	≥60% NASCET symptomatic	30 in France	Randomised, non-inferiority	872	527	80%/0.05 (one-sided)	Death or stroke at 30 days 9.6%/3.9%
SPACE (2006)	≥50% NASCET or ≥70% ECST symptomatic	35 in Germany, Austria, and Switzerland	Randomised, non-inferiority	1,900	1,187	80%/0.05 (one-sided)	Death or stroke at 30 days 6.84%/6.34% (p=0.09 for non-inferiority)
ICSS (2010)	>50% NASCET symptomatic	50 in 12 European countries plus Canada, Australia, and New Zealand	Randomised	1,500	1,713	80% to detect 4.7% difference in 30-day outcome rate	Death, stroke or MI at 120 days 8.5%/5.2% (p=0.006)
CREST (2010)	≥50%* NASCET or ≥60%* ECST symptomatic	108 in the US and Canada	Randomised, superiority	2,500	2,502	90% to detect a hazard ratio <0.54 or >1.49 with CAS compared with CEA	Death, stroke or MI at 4 years 7.2%/6.8% (p=0.51)

*CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; MI = myocardial infarction. *As assessed angiographically. Different percentages of stenosis were required when stenosis was measured by ultrasonography, magnetic resonance angiography or computed tomography. Modified with permission from Fiehler et al., 2010.*[17]

mandatory use of neuroprotection and predominant use of one kind of stent and protection device. *Tables 1* and *2* summarise several aspects of the most recent trials discussed above.

Further analysis of the CREST trial showed significantly lower four-year survival in patients who had periprocedural MI than in patients who had periprocedural stroke (75 versus 95%, p=0.0015). Additionally, the 30-day event rate in the stenting group was much lower in the later portion of the study period than in the earlier portion, which reflects the operator learning curve and the technological improvements that took place during the study period.

In light of the results of the CREST trial, a US Food and Drug Administration (FDA) panel recently voted seven to three in favour of broadening the approval of carotid stenting to include standard-risk patients with carotid stenosis. The FDA's final decision is still pending at the time of writing.

Future Trials

The Transatlantic asymptomatic carotid intervention trial (TACIT) is a multicentre, randomised, controlled trial that is to be conducted in the US and Europe. It will recruit about 3,700 patients with asymptomatic severe carotid stenosis of 60% or more. The trial is intended to test the hypothesis that optimal medical therapy plus revascularisation by either endarterectomy or stenting will reduce the five-year incidence of stroke or peri-procedural death compared with optimal medical therapy alone.[22] This study will also look at cost-effectiveness as well as the long-term ultrasonographic changes associated with each treatment. This trial faces major funding issues and its fate is still not clear.

The Asymptomatic carotid surgery trial (ACST-2)[23] is a large international randomised, controlled trial with an intended sample size of 5,000 patients with severe asymptomatic carotid stenosis. The trial is sponsored by the University of Oxford and several other UK organisations. There are other registries and trials in progress, as well.

Current Status and Future Trends

Reimbursement from the Centers for Medicare and Medicaid Services (CMS) in the US is limited to qualified institutions and physicians using approved stents and protection devices for high-risk patients with symptomatic stenosis greater than 70%. Apart from this, the great majority of carotid stenting in the US is being performed in carotid registries such as CHOICE and SAPPHIRE World Wide. These registries mainly include asymptomatic patients, who constitute the majority of patients with severe carotid disease. The insurance coverage for carotid stenting to treat asymptomatic severe carotid stenosis has lagged behind the increasing evidence of the safety and efficacy of carotid stenting produced by recent trials and registries in the US and abroad. The future of carotid stenting holds great promise. There is continuous improvement in carotid stenting and neuroprotection techniques that will mitigate the current limitations of carotid stenting. The Achilles' heel of carotid stenting has been distal embolisation right after stenting and after dilatation of the lesion; this is a particular problem in high-risk patients (see *Table 3*). Proximal protection devices have been developed to decrease the risk of distal embolisation and trials of these devices have produced encouraging results, especially in elderly patients.[24] The Embolic Protection with Reverse Flow Study of the GORE Flow Reversal System in Carotid Stenting of Subjects at High Risk for Carotid Endarterectomy (EMPiRE) trial was a non-randomised study that tested this device in 245 patients at 28 sites. The 30-day stroke, death and MI rate was quite low, at 3.7% for all patients, 3.8% for symptomatic patients and 2.6% for octogenarians.[25] This remarkably low incidence of adverse events in octogenarians has been the lowest reported, as these patients generally have a higher risk of stroke than younger patients because elderly patients have more arterial tortuosity and calcification, as well as decreased cerebrovascular reserve. This study was sponsored by WL Gore and Associates (Flagstaff, AZ, US).

Table 3: Predictors of Poor Outcomes After Carotid Stenting

Patient age ≥80 years
Presence of symptoms
Aortic arch anatomy: type III
Plaque morphology: fatty or fibrofatty, ulcerations, thrombotic lesions, long lesions, calcification, ostial lesions
Contralateral internal carotid artery occlusion
Poor cerebral functional reserve and severe intracranial disease
Operator experience
Type of cerebral protection device used
Suboptimal anticoagulation or platelet inhibition
Long procedure time

The results of the ARMOUR trial[26] were recently published. This pilot study included 252 patients with severe carotid stenosis who were treated with the Mo.Ma proximal protection device (Invatec Inc., Roncadelle, Italy). At 30 days, 0.9% of patients died and 0.9% had major strokes. Surprisingly, there were no major strokes in the symptomatic group.

Catheter thrombectomy has been shown in our experience to be safe and possibly, helpful in decreasing distal embolisation.[27,28] Other potential improvements include developing a way to decrease the distal embolisation of particles of sizes <100 microns. Additionally, the data available to date suggest that further studies are needed to look into certain subgroups that could benefit more from stenting than from endarterectomy. In addition to clinical criteria, the use of criteria regarding the composition of the carotid lesions could lead to better schemes for allocating specific therapies. ■

1. Bates ER, Babb JD, Casey DE, Jr, et al., ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting), *J Am Coll Cardiol*, 2007;49:126–70.
2. Naylor AR, Bolia A, Abbott RJ, et al., Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial, *J Vasc Surg*, 1998;28:326–34.
3. 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.
4. Yadav JS, Wholey MH, Kuntz RE, et al., Protected carotid-artery stenting versus endarterectomy in high-risk patients, *N Engl J Med*, 2004;351:1493–501.
5. Gurm HS, Yadav JS, Fayad P, et al., Long-term results of carotid stenting versus endarterectomy in high-risk patients, *N Engl J Med*, 2008;358:1572–9.
6. Friedman HS, Carotid-artery stenting versus endarterectomy, *N Engl J Med*, 2005;352:624–7, author reply 627.
7. SAPPHIRE World Wide Investigators, The SAPPHIRE worldwide registry: 30-day outcomes of 4,007 patients undergoing carotid artery stenting with distal embolic protection. Available at: www.slideshare.net/ncvhonline/the-sapphire-worldwide-registry-30day-outcomes-of-4007-patients-undergoing-carotid-artery-stenting-with-distal-embolic-protection-1712440 (accessed 22 July 2010).
8. Mas JL, Chatellier G, Beyssen B, et al., Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis, *N Engl J Med*, 2006;355:1660–71.
9. Naylor AR, SPACE: not the final frontier, *Lancet*, 2006;368:1215–6.
10. Furlan AJ, Carotid-artery stenting—case open or closed?, *N Engl J Med*, 2006;355:1726–9.
11. Bertog S, Franke J, Hornung M, et al., An update on carotid stent trials and perspectives, *Interv Cardiol*, 2009;4:92–7.
12. 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*, 2008;7:885–92.
13. Ringleb PA, Allenberg J, Bruckmann 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*, 2006;368:1239–47.
14. 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*, 2008;7:893–902.
15. 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*, 2010;375:985–97.
16. Bonati LH, Jongen LM, Haller S, et al., New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS), *Lancet Neurol*, 2010;9:353–62.
17. Fiehler J, Bakke SJ, Clifton A, et al., Plea of the defence-critical comments on the interpretation of EVA3S, SPACE and ICSS, *Neuroradiology*, 2010;52:601–10.
18. Brott TG, Hobson RW, II, Howard G, et al., Stenting versus endarterectomy for treatment of carotid-artery stenosis, *N Engl J Med*, 2010;363:11–23.
19. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, *JAMA*, 1995;273:1421–8.
20. Halliday A, Mansfield A, Marro J, et al., Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial, *Lancet*, 2004;363:1491–502.
21. Davis SM, Donnan GA, Carotid-artery stenting in stroke prevention, *N Engl J Med*, 2010;363:80–2.
22. Transatlantic Asymptomatic Carotid Intervention Trial (TACIT): Phase III clinical trial protocol summary. Available at: www.sirfoundation.org/misc/Protocol_Summary_for_Web.pdf (assessed 11 July 2010).
23. Asymptomatic Carotid Surgery Trial 2 (ACST-2). Available at: www.acst.org.uk/index.html (accessed 11 July 2010).
24. Micari A, Stabile E, Cremonesi A, et al., Carotid artery stenting in octogenarians using a proximal endovascular occlusion cerebral protection device: a multicenter registry, *Catheter Cardiovasc Interv*, 2010;76:9–15.
25. Schwartz Communications Inc., for W. L. Gore & Associates, GORE flow reversal system cleared by FDA: breakthrough system provides neuroprotection during carotid artery stenting by reversing blood flow at the treatment site and continuously directing emboli away from the brain. Available at: www.gore.com/en_xx/news/flowreversalsystem.html (accessed 22 July 2010).
26. Ansel GM, Hopkins LN, Jaff MR, et al., Safety and effectiveness of the INVATEC MO.MA proximal cerebral protection device during carotid artery stenting: results from the ARMOUR pivotal trial, *Catheter Cardiovasc Interv*, 2010;76(1):1–8.
27. Hernandez E, Goel N, Dougherty KG, et al., Benefits of catheter thrombectomy during carotid stenting: a preliminary study, *Tex Heart Inst J*, 2009;36:404–8.
28. Shabaneh B, Dougherty K, Hernandez E, et al., Catheter aspiration thrombectomy during carotid stenting is safe and potentially efficacious: a pilot retrospective study, *J Cardiovasc Surg (Torino)*, 2010;51:865–72.