NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of carotid artery stent placement for symptomatic extracranial carotid stenosis

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Treating symptomatic narrowed carotid arteries using stents

The main arteries in the neck (the carotid arteries) can become narrowed by fatty deposits. Blood clots can form on these fatty deposits and fragments can detach and lodge in thinner arteries that supply blood to parts of the brain, causing a transient ischaemic attack (TIA, sometimes called a 'mini stroke') or a stroke.

In this procedure a metal mesh called a stent is used to widen the narrowed carotid artery. This procedure does not involve making a cut in the neck. Instead a fine wire is inserted into an artery in the leg and passed up into the carotid artery, and the stent is then moved into place along the wire. Some stenting also includes protective devices, to help to prevent any fragments loosened by the stent insertion from reaching smaller arteries and causing a stroke.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2010.

Procedure name

- Carotid artery stent placement for symptomatic extracranial carotid stenosis

Specialty societies

- The Vascular Society
- British Society of Interventional Radiology
- British Society of Neuroradiologists
- Association of Stroke Physicians.

Description

Indications and current treatment

Stenosis of the extracranial carotid arteries due to atherosclerosis occurs most commonly in the area of the carotid bifurcation in the neck. Thrombus may form on the stenotic area or plaque may rupture, producing emboli which pass to the small arteries in the brain causing transient ischaemic attacks (TIAs) or stroke; or to the eye, causing transient loss of vision (amaurosis fugax) or permanent blindness in one eye. When a patient has had any symptoms like these in the presence of a carotid stenosis, their risk of further more serious symptoms is increased. Risk of stroke is the main concern.

Medical treatment is essential and includes antithrombotic medication (commonly aspirin), a statin, and advice on smoking cessation. Control of risk factors like hypertension and diabetes is also fundamental. In addition, expeditious treatment of the carotid stenosis which has caused the symptoms is often indicated. Patient selection is by stroke physicians or neurologists, working in collaboration with vascular surgeons and radiologists.

Carotid endarterectomy has been the standard treatment for patients with symptomatic stenosis. Carotid stenting is a less invasive percutaneous procedure than carotid endarterectomy for the treatment of carotid stenosis. It avoids the need for an incision in the neck and the potential morbidity from surgical dissection, but there has been concern about the risk of stroke due to embolic material becoming dislodged during the procedure.

What the procedure involves

Carotid stenting is usually carried out with the patient under local anaesthesia, and involves passing a guidewire into the carotid artery, commonly with a cerebral protection device at its tip, which is designed to prevent any debris from passing into the cerebral circulation during the procedure. The carotid stenosis is then usually predilated using a balloon catheter. A metal mesh (stent) is inserted, which keeps the artery open to maintain blood flow and prevent restenosis and further embolism.

Once the stent has been implanted, the protection device is removed via the delivery catheter.

Carotid stenting is a less invasive percutaneous procedure than endarterectomy that aims to avoid wound complications associated with carotid endarterectomy.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to carotid artery stent placement for symptomatic extracranial carotid stenosis. Searches were conducted of the following databases, covering the period from their commencement to 28 August 2010 and updated to 6 January 2011: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with symptomatic extracranial carotid stenosis.
Intervention/test	Carotid artery stent placement.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 575,556 patients from 2 meta-analyses[1,2], 4 randomised controlled trials (RCTs)[3,4,5,6], 2 nonrandomised controlled studies[7,8], 5 case series[9,10,11,12,13], and 4 case reports[14,15,16,17].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on carotid artery stent placement for symptomatic extracranial carotid stenosis

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Meier P (2010)[1] **Meta-analysis** International studies Recruitment period: studies published 1998 to 2009 Study population: **mixed** patients with carotid stenosis with or without symptoms. Age: not reported, Sex: not reported. **n = 4796 (2402 stent, 2394 endarterectomy)** Naylor (1998) Alberts (2001) WALLSTENT CAVATAS (2001) Brookes (2001) Brookes (2004) Yadav (2008) SAPPHIRE Mas (2008) EVA -3S Ringleb (2007) SPACE Hoffmann (2008) BACASS Steinbauer (2008) ICSS (2009) Patient selection criteria: not reported Technique: Carotid artery stenting (not otherwise described) vs endarterectomy Follow-up: **maximum**	Number of patients analysed: **Varies from outcome to outcome** **Composite endpoints** Intermediate term stroke or death. There was no statistically significant difference in the rate of stroke or death between the two groups; HR 1.11, 95% CI 0.91 to 1.35 (p = 0.315) (length of follow-up and absolute figures not reported). It is not clear from the study report whether all of these events were strictly between 30 days and longer term follow-up.	**Complications** **Composite endpoints** *30-day stroke or death* Pooled risk of stroke or death was significantly lower in the endarterectomy groups (5.4% [131/2350]) than in the stenting groups (7.3% [193/2359]); OR 0.67, 95% CI 0.47 to 0.95 (p = 0.025). No significant heterogeneity (p = 0.071). *30-day disabling stroke or death* There was no statistically significant difference in the rate of disabling stroke or death between the endarterectomy groups (2.9%) and the stenting groups (3.8%); OR 0.74, 95% CI 0.53 to 1.08 (p = 0.600) (absolute figures not reported). **Stroke** 30-day stroke Pooled risk of stroke was significantly lower in the endarterectomy groups (4.2% [106/2238]) than in the stenting groups (5.7% [163/2252]); OR 0.65, 95% CI 0.43 to 1.00 (p = 0.049). **Mortality** 30-day death There was no statistically significant difference in the rate of periprocedural mortality in the endarterectomy groups (1.4% [17/1381]) compared with the stenting groups (1.2% [15/1399]); OR 1.14, 95% CI 0.56 to 2.31 (p = 0.697). **MI** 30-day MI Pooled risk of MI was significantly higher in the endarterectomy groups (2.6% [17/692]) than in the stenting groups (0.9% [6/693]); OR 2.69, 95% CI 1.06 to 6.79 (p = 0.036). No significant heterogeneity (p = 0.700).	**Follow-up issues**: Studies assessed for quality based on intention- to-treat analysis. **Study design issues**: Thorough search strategy. Duplicate study selection. Assessment of study quality without a formal score given. Pooling by random effects model. **Study population issues**: Some heterogeneity of studies – sensitivity analysis undertaken. Authors state that asymptomatic patients were under represented in this analysis (proportion not stated) and generalisation for this population would be speculative. **Other issues**: Publication bias assessed using visual funnel plot. Individual studies defined periprocedural stroke differently. Authors state that there may be a learning curve

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
4 years Conflict of interest/source of funding: one author is a consultant to manufacturer.			with carotid artery stenting with improvement in equipment design, patient selections and training.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Bonati LH (2010)[2] CSTC **Meta-analysis** International studies Recruitment period: not reported Study population: patients with moderate or severe **symptomatic** carotid stenosis considered at standard surgical risk. Age: 69 years (mean). Sex: 72% male. Severe stenosis (> 70%) = 81%. **n = 3433 (1725 stent, 1708 endarterectomy)** Mas (2008) EVA -3S Ringleb (2007) SPACE ICSS (2009) Patient selection criteria: Patients with ≥ 50% reduction in lumen diameter. Technique: Stenting (not otherwise described) vs open endarterectomy. Follow-up: **120 days (median)** Conflict of interest/source of funding: None	Number of patients analysed: **(1725 stent, 1708 endarterectomy)** **Composite endpoints** *Short-term stroke or death (follow-up not reported – possibly 120 days)* **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 8.9% (153/1725) | 5.8% (99/1708) | 1.53 (1.20 to 1.95) | 0.0006 No significant heterogeneity (p = 0.27) The pooled risk ratio was significantly different among patients < 70 years old (1.00 [95% CI 0.68 to 1.47]) and patients > 70 years old (2.04 [1.48 to 2.82]) (p = 0.0053 for interaction value). *Short-term disabling stroke or death (follow-up not reported – possibly 120 days)* **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 4.8% (82/1725) | 3.7% (64/1708) | 1.27 (0.92 to 1.74) | 0.15 No significant heterogeneity (p = 0.94) **Mortality** **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 1.9% (32/1725) | 1.3% (22/1708) | 1.44 (0.84 to 2.47) | 0.18 No significant heterogeneity (p = 0.07) **Stroke** **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 8.2% (141/1725) | 4.9% (84/1708) | 1.66 (1.28 to 2.15) | 0.0001 No significant heterogeneity (p = 0.23)	Number of patients analysed: **(1679 stent, 1645 endarterectomy – per protocol analysis)** **Composite endpoints** *30-day stroke or death* **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 7.7% (130/1679) | 4.4% (73/1645) | 1.74 (1.32 to 2.30) | 0.0001 No significant heterogeneity (p = 0.10) *Short-term disabling stroke or death* **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 3.9% (65/1679) | 2.6% (43/1645) | 1.48 (1.01 to 2.15) | 0.04 No significant heterogeneity (p = 0.93) **Mortality** **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 1.1% (19/1679) | 0.6% (10/1645) | 1.86 (0.87 to 4.00) | 0.10 No significant heterogeneity (p = 0.41) **Stroke** **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 7.4% (125/1679) | 4.3% (70/1645) | 1.74 (1.31 to 2.32) | 0.0001 No significant heterogeneity (p = 0.10) **MI** **Stent** | **CEA** | **Relative risk (95% CI)** | **p** 0.2% (4/1679) | 0.4% (7/1645) | Not reported | Not reported **Severe wound infection** **Stent** | **CEA** | **Relative risk (95% CI)** | **p**	**Follow-up issues**: Intention-to-treat analysis for short-term (120 days) outcome. Per protocol analysis used for 30-day outcome analysis. **Study design issues**: Pre-planned meta-analysis from three trials. Outcome assessment blinded to study group. Pooling with fixed effect model. Across all study sites a median of 52 patients (interquartile range 29 to 108) were recruited. **Study population issues**: No statistically significant difference in clinical or demographic characteristics between the groups. 15% (251/1679) of patients in the stenting group were undertaken with a supervisor. **Other issues**: This meta-analysis includes studies with only symptomatic patients. The risk of the composite endpoint of stroke or death was similar across all age groups in the

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.						
Study details	**Key efficacy findings**	**Key safety findings**				**Comments**
		0.1% (1/1679)	0.2% (4/1645)	Not reported	Not reported	endarterectomy group.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Brott TG (2010)[3] CREST **Randomised controlled study** USA and Canada Recruitment period: not reported Study population: **mixed** patient with symptomatic or asymptomatic extracranial carotid stenosis. Age: 69 years. Sex: 65%, asymptomatic 47% **n = 2522 (1271 stent, 1251 endarterectomy)** Patient selection criteria: (symptomatic) Stenosis ≥ 50% on angiography, or ≥ 70% on US, CT or MRI. (asymptomatic) ≥ 60% on angiography, ≥70% on US, or ≥ 80% on CT or MRI. No previous severe stroke, no chronic AF, or paroxysmal AF within 6 months or that required anticoagulation, MI within 30 days, or unstable angina. Technique: Carotid artery stenting with RX stent and embolic protection where feasible vs endarterectomy **Follow-up: 2.5 years (median)** Conflict of interest/source of funding: supported by national grant and manufacturer. At least	Number of patients analysed: **2502 (1262 stent, 1240 endarterectomy)** Follow-up including periprocedural period **Mortality** **Stent** 11.3% — **CEA** 12.6% — **Hazard ratio** 1.12 (95% CI 0.83 to 1.51) — **p** 0.45 **Stroke** **Stent** 10.2% — **CEA** 7.9% — **Hazard ratio** 1.40 (95% CI 1.40 to 1.89) — **p** 0.03 **Composite endpoint** Any stroke, MI or death within the perioperative period, or ipsilateral stroke to 4-year follow-up. **Stent** 5.2% (66/1262) — **CEA** 4.5% (56/1240) — **Hazard ratio** 1.18 (95% CI 0.82 to 1.68) — **p** 0.38 Stroke or death following perioperative period – symptomatic **Stent** 8.0% — **CEA** 6.4% — **HR** 1.37 (95% CI 0.90 to 2.09) — **p** 0.14 (Absolute figures not reported) **Quality of life** at 1-year follow-up Effect of outcome on SF-36 score (physical component) (change in score from baseline group means) Major stroke –15.8 points Minor stroke –4.5 points MI –3.0 points	**Complications** **Stroke** *Periprocedural* **Stent** 4.1% (52/1262) — **CEA** 2.3% (29/1240) — **Hazard ratio** 1.79 (95% CI 1.14 to 2.82) — **p** 0.01 **Mortality** *Periprocedural* **Stent** 0.7% (9/1262) — **CEA** 0.3% (4/1240) — **Hazard ratio** 2.25 (95% CI 0.69 to 7.30) — **p** 0.18 **MI** *Periprocedural* **Stent** 1.1% (14/1262) — **CEA** 2.3% (28/1240) — **Hazard ratio** 0.50 (95% CI 0.26 to 0.94) — **p** 0.03	**Follow-up issues**: Intention-to-treat analysis. 2.6% loss to follow-up in the stenting group and 3.8% in the endarterectomy group. **Study design issues**: 117 study centres. Centralised web-based randomisation stratified for centre and symptomatic status. Sample size calculated on 90% power to detect a hazard ratio of less than 0.54 or more than 1.49. Clinicians documented to have performed more than 12 stenting procedures a year with acceptable complication rates. Outcome assessment blinded to treatment groups. **Study population issues**: Patients were considered symptomatic if they had history of TIA, amaurosis fugax, or prior minor non-disabling stroke. Trial initially open to symptomatic patients only but expanded to asymptomatic to improve recruitment. **Other issues**: Embolic protection

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
one author is a consultant to manufacturer.			device used in 96.1% of stenting procedures.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Brown M (2010) ICSS[6] **Randomised controlled study** International Recruitment period: 2001 to 2008 Study population: patient with **symptomatic** extracranial carotid stenosis. Age: 70 years. Sex: 71% male. 90% of patients with 70 to 99% stenosis. **n = 1713 (855 stent, 858 endarterectomy)** Patient selection criteria: Stenosis >50%, with symptoms within last year. Patients without major stroke, previous carotid intervention, or planned CABG procedure. Technique: Stenting with a range of devices vs endarterectomy **Follow-up: 4 months (median)** Conflict of interest/source of funding: supported by manufacturer, charity, and public funding.	Number of patients analysed: **n = 1713 (853 stent, 857 endarterectomy) for intention to treat analysis** **Survival** Group mean all cause death 120-day follow-up **Stent** 2.2% (19/853) **CEA** 0.8% (7/857) **Hazard ratio 95% CI** 2.76 (1.16 to 6.56) **p=** 0.017 **Composite endpoint** Stroke, death 120-day follow-up, or periprocedural MI **Stent** 8.4% (72/853) **CEA** 5.1% (44/857) **Hazard ratio 95% CI** 1.69 (1.16 to 2.45) **p=** 0.006 Any stroke or death 120-day follow-up **Stent** 8.4% (72/853) **CEA** 4.7% (40/857) **Hazard ratio 95% CI** 1.86 (1.26 to 2.74) **p=** 0.001 Disabling stroke or death 120-day follow-up **Stent** 4.0% (34/853) **CEA** 3.2% (27/857) **Hazard ratio 95% CI** 1.28 (0.77 to 2.11) **p=** 0.34	**Complications** **n = 1649 (828 stent, 821 endarterectomy) per protocol analysis** **Stroke** Any periprocedural stroke to 30 days **Stent** 7.0% (58/828) **CEA** 3.3% (27/821) **Risk ratio 95% CI** 2.13 (1.36 to 3.33) **p=** 0.001 **Mortality** Procedural death to 30 days **Stent** 1.3% (11/828) **CEA** 0.5% (4/821) **Risk ratio 95% CI** 2.73 (0.87 to 8.53) **p=** 0.072 **Composite** Stroke, death, or MI to 30 days **Stent** 7.4% (61/828) **CEA** 4.0% (33/821) **Risk ratio 95% CI** 1.83 (1.21 to 2.77) **p=** 0.003	**Follow-up issues**: 3 patients withdrew consent after randomisation but before treatment. **Study design issues**: 50 participating centres. Patients randomised by computer sequence and stratified for age, sex, side of carotid treatment, and presence of contralateral occlusion. Intention to treat analysis, and per protocol analysis for 30-day follow-up. Open label trial, but follow-up by independent clinicians and outcome assessment blinded to allocation. **Study population issues**: Patients in the stenting group were treated more quickly after randomisation ($p < 0.0001$) and sooner after last event ($p = 0.013$). **Other issues**: Cerebral protection used whenever safe to do so but not mandatory. 2 centres withdrawn during study due to concerns about stenting results.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Mas J-M (2006)[4] EVA-3S **Randomised controlled trial** France Recruitment period: 2000 to 2005 Study population: **Symptomatic** patients age: 70 years (mean), Sex: 75% male **n = 520 (261 stent, 259 endarterectomy)** Patient selection criteria: Patients with hemispheric or retinal transient ischaemic attack or non-disabling stroke within 120 days of enrolment. Ipsilateral carotid stenosis of > 60% on angiography or duplex scanning and MRI. Patients without disabling stroke, non-atherosclerotic disease, severe tandem lesion, previous revascularisation, bleeding disorder, hypertension, diabetes, unstable angina, or contraindication to blood thinning medication. Technique: Carotid stenting with cerebral protection devices (from 2003 onwards) vs endarterectomy. Follow-up: **not reported**	Number of patients analysed: **520 (261 stent, 259 endarterectomy)** **Stroke** Any stroke between 31 days and 6 months follow-up **Stent** 11.7% (31/261) **CEA** 6.1% (16/259) **p** 0.02 P value calculated by log-rank test	**Complications** **Composite endpoint** Any stroke or death within 30 days follow-up **Stent** 9.6% (25/261) **CEA** 3.9% (10/259) **Relative risk** 2.5 (95% CI 1.2 to 5.1) **p** 0.01 The relative risk did not differ significantly between centres that enrolled fewer or more patients, or between experienced clinicians and trainees. Disabling stroke or death within 30 days follow-up **Stent** 3.4% (9/261) **CEA** 1.5% (4/259) **Relative risk** 2.2 (95% CI 0.7 to 7.2) **p** 0.26 Any stroke or death within 30 days or ipsilateral stroke between 31 days and 6 months follow-up. P value calculated by log-rank test **Stent** 10.2% **CEA** 4.2% **p** 0.008 Disabling stroke or death within 30 days or any stroke between 31 days and 6 months follow-up. P value calculated by log-rank test **Stent** 10.9% **CEA** 4.6% **p** 0.007 **Stroke** Non-fatal stroke within 30 days follow-up **Stent** 8.8% (23/261) **CEA** 2.7% (7/259) **Relative risk** 3.3 (95% CI 1.4 to 7.5) **p** 0.004 **Mortality** within 30 days follow-up **Stent** 0.8% (2/261) **CEA** 1.2% (3/259) **Relative risk** 0.7 (95% CI 0.1 to 3.9) **p** 0.68 **MI** within 30 days follow-up **Stent** 0.4% (1/261) **CEA** 0.8% (2/259) **Relative risk** 0.5 (95% CI 0.04 to 5.4) **p** 0.62	**Follow-up issues**: Intention-to-treat analysis. Safety committee stopped the trial in September 2005 on grounds of safety and futility. Given the observed 30-day risk it was deemed unlikely that the trial would reach its objectives. **Study design issues**: 30 study centres. Surgeons required to have performed 25 endarterectomies in the previous year, and interventional radiologists 12 carotid stenting procedures or 35 in the supra-aortic trunk including 5 in the carotid artery. Computer block randomisation stratified for centre and degree of stenosis. **Study population issues**: Study populations similar at baseline except that more patients in the endarterectomy group had a history of stroke (p = 0.02). **Other issues**: Study included in both meta-analyses above. Use of cerebral

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Conflict of interest/source of funding: publicly funded. Two authors received lecture fees from manufacturer.		**Other** Major local complications within 30 days follow-up **Stent** 3.1% (8/261) **CEA** 1.2% (3/259) **Relative risk** 2.6 (95% CI 0.7 to 9.9) **p** 0.22	protection devices became mandatory in the stenting group during the study.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Eckstein H-H (2008)[5] SPACE **Randomised controlled trial** International Recruitment period: 2001 to 2006 Study population: Patients with **symptomatic** severe carotid stenosis. Age: 68 years (mean), Sex: 72% male **n = 1214 (613 stent, 601 endarterectomy)** Patient selection criteria: > 70% stenosis, in previous 6 months. Technique: carotid stenting (not otherwise described) vs endarterectomy. **Follow-up: 2 years (median)** Conflict of interest/source of funding: supported by public grant and manufacturers.	Number of patients analysed: **1196 intention to treat analysis (607 stent, 589 endarterectomy)** **Procedural characteristics** Procedural failure (including inability to treat with the allocated technique) **Stent** / **CEA** / **Relative risk** 3.5% (21/607) / 2.5% (15/589) / 1.36 (95% CI 0.72 to 2.58) p = Not statistically significant **Medication requirement** % patients requiring antithrombotic agents at 2-year follow-up **Drug** / **Stent n = 512** / **CEA n = 494** Aspirin / 69.0% / 78.5% (388/494) Clopidogrel / 16.4% (84/512) / 10.7% (53/494) Aspirin plus dipyridamole / 0.6% (3/512) / 1.6% (8/494) Aspirin plus clopidogrel / 8.2% (42/512) / 2.0% (10/494) Phenprocoumon / 5.3% (27/512) / 5.3% (26/494) None / 0.6% (3/512) / 1.8% (9/494) p < 0.0001 for difference between groups **Stroke** Ipsilateral stroke between 31 days and 2 years follow-up **Stent** / **CEA** / **Hazard ratio** 2.2% / 1.9% / 1.17 (95% CI 0.51 to 2.70) p = not statistically significant **Restenosis** Restenosis of > 70% on US occurred more frequently in the stenting group (10.7%) than in the endarterectomy group (4.6%) (p = 0.0009) at 2 years follow-up (absolute figures not reported).	**Complications** No significant difference between groups for any outcome **Composite endpoint** Any stroke or death within 30-day follow-up. **Stent** / **CEA** / **Relative risk** 6.9% (25/607) / 6.5% (38/589) / 1.07 (95% CI 0.70 to 1.63) Disabling stroke or death **Stent** / **CEA** / **Relative risk** 4.9% (30/607) / 3.7% (22/589) / 1.32 (95% CI 0.78 to 2.25) **Mortality** within 30-day follow-up **Stent** / **CEA** / **Relative risk** 1.0% (6/607) / 0.8% (5/589) / 1.16 (95% CI 0.38 to 3.56) **Stroke** within 30-day follow-up **Stent** / **CEA** / **Relative risk** 7.2% (44/607) / 6.3% (37/589) / 1.15 (95% CI 0.76 to 1.76)	**Follow-up issues**: Intention to treat and per protocol analysis, prospective follow-up. 89% of patients in each group had clinical follow up data at 2 years. **Study design issues**: Multicentre study Randomisation by data study without stratification for centre. Non-inferiority study design with a 2.5% margin. Surgeons and radiologists required to have completed 25 successful procedures including bifurcating arteries. **Study population issues**: There were no statistically significant differences between the groups in terms of demographic or clinical variables at baseline. **Other issues**: Same patients as reported in the two meta-analyses above – but longer follow-up is reported here.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Giles K A (2010)[7] **Nonrandomised controlled study** USA Recruitment period: 2004 to 2007 Study population: **Mixed** patients with symptomatic (9.8%) or asymptomatic (90.2%) stenosis **n = 538,958 (56,564 stent, 482,394 endarterectomy)** Age: 70 years (mean) Sex: 60% male. Patient selection criteria: patients <18 years, without primary diagnosis of MI Technique: carotid artery stenting vs endarterectomy (no details reported) **Follow-up: not reported** Conflict of interest/source of funding: supported by manufacturer	Number of patients analysed: **n = 538,958 (56,564 stent, 482,394 endarterectomy)** **Survival** Rate of mortality by group **Stenting** | **Endarterectomy** | **p =** 1.5% (846/56,564) | 0.5% (2432/482,394) | <0.001 **Stroke** Rate of all stroke by group **Stenting** | **Endarterectomy** | **p =** 1.9% (1093//56,564) | 1.0% (4727/482,394) | <0.001 **Composite endpoints** Rate of all stroke or death by group **Stenting** | **Endarterectomy** | **p =** 3.2% (1780/56,564) | 1.4% (6670/482,394) | <0.001 Multivariate analysis reported that the following variables were independent predictors of an outcome of stroke or death **Factor** | **OR (95% CI)** | **p =** Stenting procedure | 2.4 (2.1 to 2.8) | <0.001 Symptomatic at baseline | 6.8 (6.1 to 7.6) | <0.001 High risk at baseline | 1.6 (1.4 to 1.8) | <0.001 Year treated | 0.9 (0.8 to 0.97) | <0.01	**Complications** Rate of 'global complications (not otherwise described)' per group **Stenting** | **Endarterectomy** | **p =** 13.6% | 9.6% | <0.001 (Absolute figures not reported).	**Follow-up issues**: Retrospective database analysis Not clear if outcomes relate to periprocedural period or longer follow-up. **Study design issues**: Multicentre study No outcomes reported separately for patients with symptomatic or asymptomatic stenosis. Study included patients undergoing revascularisation for CABG, valve procedures, or percutaneous coronary artery intervention. No details reported regarding outcome assessment protocol. **Study population issues**: Patients undergoing stenting had symptomatic stenosis, were significantly younger, and were more often male ($p < 0.010$) for all. **Other issues**: Subgroup analysis of 'high risk' patients not extracted here.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Giacovelli J K (2010)[8] **Nonrandomised controlled study** USA Recruitment period: 2005 to 2007. Study population: **Mixed** patients with symptomatic (%) or asymptomatic (%) stenosis **n = 9838 (4919 stent, 4919 endarterectomy** Age: 72 years (mean) Sex: 57% male. Patient selection criteria: patients not undergoing repair for endocranial vessels, or carotid dissection, and not having concomitant major intervention (CABG, or valve replacement) Technique: carotid artery stenting vs endarterectomy (no details reported) **Follow-up: not reported** Conflict of interest/source of funding: none	Number of patients analysed: **overall n = 9838 (4919 stent, 4919 endarterectomy). n = 1086 (543 stent, 534 endarterectomy) for symptomatic patients** **Survival** Rate of mortality by group for symptomatic patients **Stenting** / **Endarterectomy** / **p=** 3.68% / 1.29% / 0.012 (absolute figures not reported) **Stroke** Rate of stroke by group for symptomatic patients **Stenting** / **Endarterectomy** / **p=** 5.71% / 4.05% / 0.216 (absolute figures not reported) **Composite endpoints** **Rate of stroke or mortality by group for symptomatic patients** **Stenting** / **Endarterectomy** / **p=** 8.29% / 4.60% / 0.014 (absolute figures not reported)	**Complications** Rate of postoperative complications by treatment group for symptomatic patients Rate of mortality by group for symptomatic patients **Outcome** / **Stent** / **Endarterectomy** / **p=** Cardiac / 5.52% / 6.08% / 0.696 Nonvascular neurologic / 2.21% / 0.37% / 0.008 Bleeding / 3.31% / 4.48% / 0.612 Venous thromboembolism / 0.37% / 0.00% / 0.157 Cranial neuropathy / 0.18% / 0.00% / 0.317 (absolute figures not reported)	**Follow-up issues**: Retrospective database analysis Not clear if outcomes relate to periprocedural period or longer follow-up. **Study design issues**: Multicentre study Patients matched for propensity analysis. Patients without codes relating to symptomatic stenosis on admission were assumed to be asymptotic. No details reported regarding outcome assessment protocol. **Study population issues**: Patients matched for comorbidities. Patients undergoing stenting were significantly younger, and were more often male ($p < 0.010$) for both. After matching there were no significant differences between groups for clinical or demographic characteristics. **Other issues**: None.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Wholey M H (2003)[9] **Case series** International Recruitment period: 1997 to 2002. Study population: **Mixed** patients with symptomatic or asymptomatic stenosis (range 26% to 100% symptomatic) **n = 11,243** Age: not reported Sex: not reported Patient selection criteria: not reported Technique: carotid artery stenting with cerebral protection device (n = 4221), or without (n = 6753) **Follow-up: not reported** Conflict of interest/source of funding: one author has a financial interest in the subject	Number of patients analysed: **11,243 (12,392 arteries)** **Procedural characteristics** Procedural success (<30% residual stenosis) was reported in 98.9% (12,254 /12,392) of arteries. **Neurological events** New ipsilateral neurological events occurred in 4.5% (49/1095) of patients at 48-month follow-up **Restenosis** Restenosis of >50% on US occurred in 5.6% (61/1095) of patients at 48-month follow-up.	**Complications** **Mortality** Non procedural related deaths occurred in 0.8% (95/12,392) of arteries treated at up to 30-day follow-up Rate of complications up to 30-day follow-up **Outcome** / **Rate** Death: 0.6% (79/12,392) Major stroke: 1.2% (149/12,392) Minor stroke: 2.1% (265/12,392) TIA: 3.1% (381/12,392) Based on the number of patients treated, 30-day stroke and death rate was 5.2% (absolute figures not reported) 30-day stroke or procedure-related death occurred more frequently among symptomatic patients (4.9% [315/6392]) than in asymptomatic patients (2.9% [135/4581]) ($p < 0.0001$). 30-day stroke or procedure-related death occurred more frequently among patients treated without cerebral protection (5.3% [357/6753]) than in patients treated with a cerebral protection device (2.2% [94/4221]) ($p < 0.0001$).	**Follow-up issues**: Coverage of registry not reported. Observational retrospective study. **Study design issues**: Patient selection criteria not reported. Potentially a highly selected population. 53 participating centres. Outcome denominator used was either number of vessels or number of patients. Severely impaired or totally restricted cerebral flow for 1 to 15 minutes from use of cerebral protection device was sometimes recorded as a TIA. **Study population issues**: The proportion of patients who were symptomatic varies between centres with a range of 26% to 100%. **Other issues**: Numerators for some outcomes calculated from the percentages provided in the study report.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
Goode S D (2010)[10] BSIR registry **Case series** UK Recruitment period: 1998 to 2009 Study population: Mixed patients with carotid artery disease. Data for patients with **symptomatic** disease are reported. 37% TIA, 23% amaurosis fugax, 20% recovered stroke. <1% bilateral, 35% had 81 to 90% stenosis. **n = 1154 (953 symptomatic, 291 asymptomatic)** Age: 71 to 75 years range (median), Sex: 68% male Patient selection criteria: 56% unsuitable for CEA, 15% unfit for CEA, 9% CEA restenosis. Technique: Carotid artery stenting using a range of stents. 84% with cerebral protection device. **Follow-up: Maximum follow-up recorded is to 7 years. Patients usually assessed at 6 weeks, 6 months, 1 year, 2 years, and 4 years.** Conflict of interest/source of funding: None	Number of patients analysed: **1154 (953 symptomatic, 291 asymptomatic)** **Mortality** at 5-year follow-up The mortality rate was 18.5% (actuarial analysis, n = 173 available for evaluation). **Composite endpoint** *Mortality or disabling stroke at 5-year follow-up* The mortality or disabling stroke rate was 20.8% (actuarial analysis, n = 167 available for evaluation). **Stroke** *Stroke at 5-year follow-up* The stroke rate was 6.5% (actuarial analysis, n = 156 available for evaluation). *Stroke or TIA at 5-year follow-up* The stroke or TIA rate was 13.6% (actuarial analysis, n = 144 available for evaluation).	**Complications** All outcomes within 30-day follow-up **Outcome** — **Rate** TIA — 3.9% (32/829) Non-disabling stroke — 3.1% (26/829) Disabling stroke — 1.0% (8/829) Retinal — 0.8% (7/829) Death — 1.7% (14/829) Groin complication — 2.3% (19/829) MI — 0.7% (6/829) Other — 2.8% (23/829) None — 84.9% (704/829) Other outcomes included: angina (requiring listing for CABG), transient visual disturbance during the procedure, grand mal seizure for 4 minutes, severe headache, hypotension (requiring prolonged admission) and hyperperfusion. There were no significant differences in rates of complications to 30 days between symptomatic and asymptomatic patients. **Composite endpoint** Rate of complications up to 30-day follow-up **Outcome** — **Rate** Death or disabling stroke — 2.4% (20/829) Death or disabling stroke or MI — 2.4% (20/829) Death or any stroke or MI — 5.5% (46/829) There was no significant difference in the rate of disabling stroke or death based on age (68 years cut off), gender, or use of cerebral protection device	**Follow-up issues**: Coverage of registry was compared to Hospital Episode Statistics (HES) data. In 2006/07 152 cases were included in the registry and 160 in HES. In 2008/09 the coverage of the registry was lower, which may be due to patients being added retrospectively once follow-up is documented causing a lag. **Study design issues**: Voluntary national registry; 33 sites. Data entry moved to web-based system in recent years. **Study population issues**: Some patients were receiving a staged procedure with carotid stenting before CABG – these patients are likely to have a worse risk factor. Most patients had atherosclerosis but a minority had other indications such as trauma or pseudo aneurysm. **Other issues**: Some indication that outcome for disabling stroke and death were worse in centres that had submitted very few cases.

Abbreviations used: AF, atrial fibrillation; CABG, coronary artery bypass grafting; CEA, carotid artery endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; MI, myocardial infarction; MRI, magnetic resonance imaging; OR odds ratio; RR, relative risk; TIA, transient ischaemic attack; US, ultrasonography.

Study details	Key efficacy findings	Key safety findings	Comments
	Complications		
Chaer R A (2005)[11] Case series **n = 43 mixed**	An occlusion balloon was used in 43/165 patients treated with stenting for high-grade stenosis. Symptomatic cerebral hypoperfusion occurred during temporary occlusion in 10/43 patients. Causing a mean decrease in Glasgow coma score from 15 to 10 points, this returned to normal after balloon deflation.		All stenting procedures were completed as planned.
Park S-H (2008)[14] Case report **n = 1 symptomatic**	Contralateral cerebral infarction with generalised seizure at 30 minutes following stent placement for right carotid stenosis. MRI revealed left hemispheric cerebral infarction, thought to be due to ipsilateral embolic infarction or contrast toxicity. The patients remained in a nearly vegetative state.		
Rosenkranz M (2003)[12] Case series **n = 28 symptomatic**	Ispilateral Horner syndrome occurred in 11/28 patients treated with stenting; 10 patients had evidence of a carotid wall haematoma. All symptoms resolved within 7-day follow-up.		
Friedman J A (2004)[15] Case report **n = 1 symptomatic**	Stenting chosen over endarterectomy due to patient age, comorbidity and preference. At 45 minutes the patient developed acute hemiplegia in the left arm and face, and paresis in the left leg. CT scan showed a right thalamic haemorrhage which was fatal.		
Surdell D (2007)[16] Case report **n = 1 symptomatic**	Carotid stent placement in the right internal artery. US follow-up at 6 months showed 70% in-stent restenosis with stent fracture. This was successfully treated with a second oversized stent.		
Tsutsumi M (2007)[13] Case series **n = 118 symptomatic**	Stenting using a balloon embolic protection device in 118 procedures. Spasm was reported in 26.3% (31/118) of procedures. This resolved in all patients and no ischaemic events relating to spasm occurred.		Operator experience not reported.
Jeyabalan G (2009)[17] Case report **n = 1 symptomatic**	Two-stage stenting procedure. At 1-month follow-up stent was patent but the patient complained of voice fatigue/hoarseness and dysphagia to liquids. Laryngoscopy showed left vocal cord paralysis which persisted to 4-month follow-up. Symptoms improved with voice therapy.		

Efficacy

For the purpose of this overview efficacy outcomes have been chosen as those reported at >30-day follow-up (unless specified otherwise).

Mortality

A meta-analysis of 3433 symptomatic patients reported no statistically significant difference in mortality rate between patients treated by stenting (1.9% [32/1725]) and endarterectomy (1.3% [22/1708]); relative risk (RR) 1.44, 95% CI 0.84 to 2.47 (p = 0.18) at 120-day follow-up[2].

An RCT of 2522 patients reported no statistically significant difference in mortality between patients treated by stenting (11.3%) and those treated by endarterectomy (12.6%); hazard ratio (HR) 1.12, 95% CI 0.83 to 1.51 (p = 0.45) at 2.5-year follow-up[3].

A UK national register of 953 symptomatic patients treated by stenting reported a 5-year mortality rate of 18.5%[10].

Stroke

An RCT of 1214 symptomatic patients reported no statistically significant difference in the rate of ipsilateral stroke between 31-day and 2-year follow-up between patients treated by stenting (2.2%) and by endarterectomy (1.9%); HR 1.17, 95% CI 0.51 to 2.70 (p = not significant)[5].

The UK national register of 953 symptomatic patients treated by stenting reported a 5-year incidence of stroke of 6.5%[10].

Composite endpoints

The meta-analysis of 3433 symptomatic patients reported that the pooled rate of short-term stroke or death was significantly higher following stenting (8.9%) than following endarterectomy (5.8% [94/170); RR 1.53, 95% CI 1.20 to 1.95 (p = 0.0006) at 120-day follow-up[2].

The RCT of 2522 patients reported that among symptomatic patients there was no statistically significant difference in the rate of stroke or death following stenting (8.0%) and endarterectomy (6.4%); HR 1.37, 95% CI 0.90 to 2.00 (p = 0.14) at 2.5-year follow-up (absolute figures not reported)[3].

An RCT of 1713 symptomatic patients reported that there was no statistically significant difference in the rate of disabling stroke or death between the stenting group (5% [43/853]) and the endarterectomy group (3% [27/857]); HR 1.28, 95% CI 0.77 to 2.11 at 120-day follow-up[6].

A nonrandomised controlled study of 9838 patients (1086 symptomatic) reported that there was a statistically significant difference in the rate of stroke or death

following carotid stenting (8%) and endarterectomy (5%) in symptomatic patients (p = 0.01) (absolute figures and length of follow-up not reported[8]).

The UK national register of 953 symptomatic patients treated by stenting reported a 5-year mortality or disabling stroke rate of 20.8%[10].

Safety

Mortality

The meta-analysis of 3433 symptomatic patients reported no statistically significant difference in mortality at 30-day follow-up between patients treated by stenting (1.1% [19/1679]) and those treated by endarterectomy (0.6% [10/1645]); RR 1.86, 95% CI 0.87 to 4.00 (p = 0.10)[2].

In the UK national register of 953 symptomatic patients treated by stenting, mortality in the 30 days following the procedure was 1.7%.

Stroke and/or TIA

The meta-analysis of 3433 symptomatic patients reported that the rate of stroke at 30-day follow-up was significantly higher following stenting (7.4% [125/1679]) than following endarterectomy (4.3% [70/1645]); RR 1.74, 95% CI 1.31 to 2.32 (p = 0.0001)[2]. This excess stroke was attributable largely to patients older than 70 years.

The UK national register of 953 symptomatic patients treated by stenting reported disabling stroke in 1.0% (8/829) of patients, non-disabling stroke in 3.1% (26/829) and TIA in 3.9% (32/829) at 30-day follow-up[10].

Myocardial infarction

An RCT of 2252 patients reported that there was a significantly lower incidence of perioperative myocardial infarction following carotid stenting (1% [14/1262]) than following endarterectomy (2% [28/1240]); HR 0.50, 95% CI 0.26 to 0.94 (p = 0.03)[3].

An RCT of 520 symptomatic patients reported that there was no statistically significant difference in the rate of myocardial infarction (MI) at 30-day follow-up between patients treated by stent placement (less than 1% [1/261]) and those undergoing endarterectomy (1% [2/259]); RR 0.5, 95% CI 0.04 to 5.4 (p = 0.62)[4].

The UK national register of 953 symptomatic patients treated by stenting reported a rate of MI of 0.7% within 30 days of the procedure[10].

Composite endpoints

The RCT of 1214 symptomatic patients reported no statistically significant difference in the rate of any stroke or death between patients treated by stenting (6.9%) and those treated by endarterectomy (6.5%); RR 1.07, 95% CI 0.70 to 1.63 at 30-day follow-up[5]. Similarly, there was no significant difference in the 30-day rate of disabling stroke or death (4.9% [30/607] vs 3.7% [22/589]); RR 1.32, 95% CI 0.78 to 2.25.

Other

The UK national registry of 1154 patients reported 1 or more occurrences of the following complications in symptomatic patients at up to 30-day follow-up: angina requiring listing for coronary artery bypass grafting, transient visual disturbance, grand mal seizure, severe headache, hypotension requiring prolonged admission, and hyperperfusion[10].

Validity and generalisability of the studies

- RCTs are particularly useful in the assessment of this procedure owing to the potential for selection bias in non-randomised designs.
- Definitions used for stroke vary between studies making comparison of studies and interpretation of meta-analyses difficult.
- Operator experience with the stenting procedure is not always described and may have influenced outcomes.
- Efficacy and safety outcomes are often difficult to disaggregate because of the way outcomes were reported. This is particularly a problem with efficacy outcomes at longer follow-up because it is often not clear whether outcomes analysis has included events that occurred in the early postoperative period, or whether these are genuinely additional events in the long term.
- Many patients (74%) in the endovascular treatment arm of the CAVATAS study did not receive a stent as part of their treatment. This study contributed 504 patients (out of a total of 4769) to the meta-analysis from Meier (2010). There was some duplication of patients included in the two meta-analyses presented in table 2. However, the Bonati (2010) meta-analysis was included as it reported specifically on symptomatic patients.
- The stenting procedure varied within and between studies. Most (but not all) patients were treated using a cerebral protection device.

Existing assessments of this procedure

Canadian Agency for Drugs and Technologies in Health. 'Carotid artery stenting versus carotid endarterectomy: a review of the clinical and cost-effectiveness' (September 2009)

'According to the current literature, CAS is associated with an increased risk of stroke, MI, recurrent carotid stenosis, and re-stenosis and patient adverse events and higher average costs compared with CEA. Two large RCTs are on-going, and their results have not been published. It is a challenge to draw solid conclusions on the clinical effectiveness of CAS compared with CEA for carotid artery stenting based on the available evidence and limited experience with the CAS procedure'.

Blue Cross Blue Shield Association. Technology evaluation centre assessment programme Vol 22, No 1. Angioplasty and stenting of the cervical carotid artery with embolic protection of the cerebral circulation (June 2007)

'Available evidence permits conclusions regarding periprocedural complication rates (particularly death or stroke) following CAS among symptomatic or asymptomatic patients treated under current U.S. Food and Drug Administration (FDA) labeling. Periprocedural death/stroke rates exceed those established as clinically acceptable and associated with a net clinical benefit following CEA. There is limited evidence and a clinical rationale to suggest CAS may be beneficial in the subgroup of patients with unfavorable anatomy. But because outcomes have been reported only for a small number of patients, the accompanying uncertainty is substantial. Thus, evidence is insufficient to define possible benefit in this subgroup with unfavorable anatomy.

Available evidence supports concluding that CAS with embolic protection device (EPD) does not improve the net health outcome.

Available evidence supports concluding that CAS with EPD is not as beneficial as: 1) best medical therapy for symptomatic or asymptomatic patients with medical comorbidities or unfavorable anatomy; or 2) CEA for symptomatic patients without medical comorbidities or unfavorable anatomy. Whether CAS with EPD is as beneficial as CEA or medical therapy for asymptomatic patients without medical comorbidities or unfavorable anatomy cannot be determined because available evidence is insufficient to permit conclusions. CAS with EPD has not been demonstrated to improve health outcomes in the investigational setting.

Based on the above, use of carotid artery angioplasty and stenting with embolic protection of the cerebral circulation for patients with carotid artery stenosis does not meet the technology evaluation centre criteria.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Extracranial to intracranial bypass for intracranial atherosclerosis. NICE interventional procedures guidance 348 (2010). Available from www.nice.org.uk/guidance/IPG348
- Endovascular stent insertion for intracranial atherosclerotic disease. NICE interventional procedures guidance 223 (2007). Available from www.nice.org.uk/guidance/IPG223

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr T Cleveland and Dr A Nicholson (British Society of Interventional Radiology), Dr A Molyneux (British Society of Neuroradiologists), Mr S Ashley (Association of British Neurologists).

- All the Specialist Advisors classified the procedure as 'established and no longer new'.
- The main comparator for the procedure is carotid endarterectomy at the carotid bifurcation.
- In many clinical situations the two procedures are useful for different groups of patients, and are complementary.
- Patient selection is important. Age, sex, pathology, anatomical site of occlusive disease, the state of the opposite carotid system and the intracerebral circulation, and the time interval between symptoms and treatment are all important in the decision whether to treat or not and whether to treat with open surgery or stenting.

- Adverse events known from reports or experience include access site complications, peripheral emboli, carotid artery rupture, femoral catheter access site damage, reactions to contrast material, stroke, MI, TIA and death.
- Additional theoretical adverse events might include, radiation-induced neoplasia.
- The key efficacy outcomes for this procedure include long-term stroke prevention.
- There are real concerns regarding the incidence of complications during the learning curve of carotid stenting.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient opinion for this procedure.

Issues for consideration by IPAC

- Some larger RCTs and meta-analyses have included mixed cohorts of symptomatic and asymptomatic patients. The largest and most recent of these have been included in the overview for this indication and the overview for asymptomatic patients.
- Carotid revascularisation is undertaken to prevent future events, so the rate of periprocedural complications is particularly important.
- Much of the data available come from studies that have included a mixture of patients with symptomatic and asymptomatic carotid stenosis. It is difficult to draw conclusions regarding treatment of symptomatic patients specifically from such data.
- The criteria used to define symptomatic patients vary from study to study.
- Few comparative data are available comparing stenting with medical therapy alone.

References

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2 Bonati LH, Dobson J, Algra A et al. (2010) Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. Lancet 376: 1062–73.

3 Brott TG, Hobson RW, Howard G et al. (2010) Stenting versus endarterectomy for treatment of carotid-artery stenosis. New England Journal of Medicine 363 (1): 11–23

4 Mas JL, Chatellier G, Beyssen B et al. (2006) Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. New England Journal of Medicine 355: 1660–71.

5 Eckstein HH, Ringleb P, Allenberg JR et al. (2008) Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. Lancet Neurology 7: 893–902.

6 ICSS (2010) 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 375; 9719: 985–97.

7 Giles KA, Hamdan AD, Pomposelli FB et al. (2010) Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. Journal of Vascular Surgery 52 (6): 1497–504.

8 Giacovelli JK, Egorova N, Dayal R et al. (2010) Outcomes of carotid stenting compared with endarterectomy are equivalent in asymptomatic patients and inferior in symptomatic patients. Journal of Vascular Surgery 52 (4): 906–13.

9 Wholey MH, Al-Mubarek N, Wholey MH (2003) Updated review of the global carotid artery stent registry. Catheterization & Cardiovascular Interventions 60: 259–66.

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11 Chaer RA, Trocciola S, DeRubertis B et al. (2006) Cerebral ischemia associated with PercuSurge balloon occlusion balloon during carotid stenting:

Incidence and possible mechanisms. Journal of Vascular Surgery 43: 946–52.

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16 Surdell D, Shaibani A, Bendok B et al. (2007) Fracture of a nitinol carotid artery stent that caused restenosis. Journal of Vascular & Interventional Radiology 18: 1297–9.

17 Jeyabalan G, Golla S, Makaroun M et al. (2009) Recurrent laryngeal nerve injury following uncomplicated carotid angioplasty and stenting. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists 16: 345–8.

Appendix A: Additional papers on carotid artery stent placement for symptomatic extracranial carotid stenosis

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies. Only RCTs not included within the meta-analyses included in table 2, other large named trials, and studies reporting on safety outcomes are listed here.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bush RL, Bhama JK, Lin PH et al. (2003) Transient ischemic attack due to early carotid stent thrombosis: successful rescue with rheolytic thrombectomy and systemic abciximab. Journal of Endovascular Therapy 10 (5): 870–4	n = 1 FU = 6 months	Access to a mechanical thrombectomy device was essential for rapid thrombus extraction, and adjunctive abciximab aided in residual clot dissolution. As a result of this combined method of clot removal, a disastrous outcome was averted	Larger studies included in table 2
Cremonesi A, Gieowarsingh S, Spagnolo B et al. (2009) Safety, efficacy and long-term durability of endovascular therapy for carotid artery disease: the tailored-Carotid Artery Stenting Experience of a single high-volume centre (tailored-CASE Registry). Eurointervention 5 (5): 589–98	n = 1523 FU = not reported	Results from this large cohort show that carotid stenting in a real-world setting is safe and efficacious, and durable in the long-term prevention of stroke	Larger studies included in table 2
Gray WA, Chaturvedi S, Verta P (2009) Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. Circulation: Cardiovascular Interventions 2 (3): 159–66	n = 6320 FU = 30 days	Outcomes for carotid artery stenting in non-octogenarian, high-surgical-risk patients have improved since the pivotal Food and Drug Administration approval trials, and have achieved American Heart Association standards in both symptomatic and asymptomatic lesions	Larger studies included in table 2
Gray WA, Hopkins LN, Yadav S et al. (2006) Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. Journal of Vascular Surgery 44 (2): 258–68	n = 581 FU = 1 year	The ARCHeR results demonstrate that extracranial carotid artery stenting with embolic filter protection is not inferior to historical results of endarterectomy and suggest that carotid artery stenting is a safe, durable, and effective alternative in high-surgical-risk patients	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Gray WA, Yadav JS, Verta P et al. (2007) The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. Catheterization and Cardiovascular Interventions 70 (7): 1025–33	n = 3500 FU = 30 days	Carotid stenting is performed safely in patients with severe stenosis at high surgical risk, with best outcomes in younger asymptomatic patients. However, there are certain patient and procedural characteristics that are associated with poorer outcomes	Larger studies included in table 2
Higashida RT, Popma JJ, Apruzzese P et al. (2010) Evaluation of the Medtronic Exponent self-expanding carotid stent system with the Medtronic Guardwire temporary occlusion and aspiration system in the treatment of carotid stenosis: combined from the MAVErIC (Medtronic AVE Self-expanding CaRotid Stent System with distal protection In the treatment of Carotid stenosis) I and MAVErIC II trials. Stroke 41 (2): e102–9	n = 489 FU = 1 year	Treatment of carotid artery disease with carotid artery stenting with a self-expanding stent and distal embolic protection results in a low 30-day adverse event rate, including the occurrence of stroke in patients at high risk for carotid endarterectomy	Larger studies included in table 2
Iyer SS, White CJ, Hopkins LN et al. (2008) Carotid artery revascularization in high-surgical-risk patients using the Carotid WALLSTENT and FilterWire EX/EZ: 1-year outcomes in the BEACH Pivotal Group. Journal of the American College of Cardiology 51 (4): 427–34	n = 480 FU = 1 year	The BEACH trial results demonstrate that CAS with the WALLSTENT plus FilterWire embolic protection is non-inferior (equivalent or better than) to CEA at 1 year in high-surgical-risk patients	Larger studies included in table 2
Katzen BT, Criado FJ, Ramee SR et al. (2007) Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. Catheterization and Cardiovascular Interventions 70 (2): 316–23.	n = 1493 FU = 30 days	Using a comprehensive training program, carotid artery stenting by operators with differing experience in a variety of practice settings yielded safety and efficacy outcomes similar to those reported in the SAPPHIRE trial	Larger studies included in table 2
Massop D, Dave R, Metzger C, et al. (2009) Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPPHIRE Worldwide Registry first 2001 patients. Catheterization and Cardiovascular Interventions 73 (2) 129–36	n = 2001 FU = 30 days	The SAPPHIRE Worldwide Registry supports the use of CAS as an alternative to CEA in patients who are at high risk for surgery due to anatomic risk factors	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Matsumura J S, Gray W, Chaturvedi S et al. (2010) CAPTURE 2 risk-adjusted stroke outcome benchmarks for carotid artery stenting with distal embolic protection. Journal of Vascular Surgery 52 (3): 576–83.	n = 5297 FU = 30 days	CAS outcomes in patients at high surgical risk have comparable periprocedural outcomes to published randomised trials of endarterectomy for patients at standard surgical risk	Larger studies are included in table 2
Mehta RH, Zahn R, Hochadel M et al. (2007) Comparison of in-hospital outcomes of patients with versus without previous carotid endarterectomy undergoing carotid stenting (from the German ALKK CAS Registry). American Journal of Cardiology 99 (9): 1288–93	n = 3070 FU = to discharge	Data for a large number of patients who underwent CAS in a recent contemporary community-based practice showed low risk of periprocedural events in patients with recurrent stenosis after previous CEA	Larger studies included in table 2
Naylor AR, Bolia A, Abbott RJ et al. (1998) Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. Journal of Vascular Surgery 28 (2): 326–34	n = 17 FU = not reported	After referral, the Data Monitoring Committee invoked the stopping rule and the trial was suspended	Larger studies included in table 2
Park S-H, Lee CY (2008) Contralateral cerebral infarction after stent placement in carotid artery: An unexpected complication. Journal of Korean Neurosurgical Society 44 (3): 159–62	n = 1 FU = 4 hours	Difficult carotid artery catheterisation, with aggressive manoeuvring during stenting, likely injured the tortuous, atherosclerotic aortic arch, and led to infarction of the contralateral cerebral hemisphere by thromboemboli formed on the wall of the atherosclerotic aorta	Larger studies included in table 2
Perona F, Castellazzi G, Valvassori L et al. (2008) Safety of unprotected carotid artery stent placement in symptomatic and asymptomatic patients: a retrospective analysis of 30-day combined adverse outcomes. Radiology 250 (1): 178–83	n = 397 FU = 30 days	Stent placement without embolic protection device was performed with a high technical success rate. For asymptomatic patients, the combined 30-day adverse outcomes rate was within the limits recommended by the American Heart Association for carotid endarterectomy and compared favourably with results reported for CAS with embolic protection device. When a TIA is excluded, the 30-day combined death and stroke rate among patients with prior symptoms also compared favourably with published results	Intervention without embolic protection. Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Pieniazek P, Musialek P, Kablak-Ziembicka A et al. (2008) Carotid artery stenting with patient- and lesion-tailored selection of the neuroprotection system and stent type: early and 5-year results from a prospective academic registry of 535 consecutive procedures (TARGET-CAS). Journal of Endovascular Therapy 15 (3): 249–62	n = 499 FU = 23 months	Tailored CAS is associated with a low complication rate and high long-term efficacy. CAS operators should have a practical knowledge of different neuroprotection devices, including at least one proximal type	Larger studies included in table 2
Rhee-Moore SJ, DeRubertis BG, Lam RC et al. (2008) Periprocedural complication rates are equivalent between symptomatic and asymptomatic patients undergoing carotid angioplasty and stenting. Annals of Vascular Surgery 22 (2): 233–7	n = 193 FU = 41 weeks	CAS with cerebral protection can be performed safely in both symptomatic and asymptomatic patients. The presence of preoperative neurological symptoms does not significantly increase the risk of adverse events in the perioperative period in this study	Larger studies included in table 2
Safian RD, Bacharach JM, Ansel GM et al. (2004) Carotid stenting with a new system for distal embolic protection and stenting in high-risk patients: the carotid revascularization with ev3 arterial technology evolution (CREATE) feasibility trial. Catheterization and Cardiovascular Interventions 63 (1): 1–6	n =30 FU = 30 days	This study supports the feasibility of percutaneous carotid artery revascularisation with the Protege self-expanding stent and Spider distal embolic protection system, which will be evaluated in a large multicentre pivotal trial	Larger studies included in table 2
Shin SH, Stout CL, Richardson AI et al. (2009) Carotid angioplasty and stenting in anatomically high-risk patients: Safe and durable except for radiation-induced stenosis. Journal of Vascular Surgery 50 (4): 762–7	n = 230 FU = 10.5 to 21.5 months	CAS is as technically feasible, safe, and durable in anatomically high-risk patients as in medically high-risk patients, with similar rates of periprocedural stroke and death and late restenosis	Larger studies included in table 2
Sganzerla P, Bocciarelli M, Savasta C et al. (2004) The treatment of carotid artery bifurcation stenoses with systematic stenting: experience of first 100 consecutive cardiological procedures. Journal of Invasive Cardiology 16 (10): 592–5	n = 94 FU = 30 days	Systematic CAS is a feasible treatment of the carotid artery bifurcation stenosis with high procedural success and low perioperative and short term complications	Larger studies included in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Sugita J, Cremonesi A, Van, Elst F et al. (2006) European cartid PROCAR Trial: prospective multicenter trial to evaluate the safety and performance of the ev3 Protege stent in the treatment of carotid artery stenosis – 1- and 6-month follow-up. Journal of Interventional Cardiology 19 (3): 215–21	n = 77 FU = 6 months	The PROCAR trial shows that the Protege stent with adjuvant use of a filter embolic protection device satisfies safety and performance criteria for the treatment of carotid artery stenosis.	Larger studies included in table 2
White CJ, Iyer SS, Hopkins LN et al. (2006) Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. Catheterization and Cardiovascular Interventions 67 (4): 503–12	n = 747 FU = 30 days	The similarity in periprocedural event rates for the Pivotal and Roll-in groups suggests a flat learning curve for experienced operators using this carotid stent system	Larger studies included in table 2
Witt K, Borsch K, Daniels C et al. (2007) Neuropsychological consequences of endarterectomy and endovascular angioplasty with stent placement for treatment of symptomatic carotid stenosis: a prospective randomised study. Journal of Neurology 254 (11): 1524–32	n = 45 FU = 30 days	These results provide some reassurance that CAS is not associated with greater cognitive deterioration than CEA is	Larger studies included in table 2
Zahn R, Roth E, Ischinger T et al. (2005) Carotid artery stenting in clinical practice results from the Carotid Artery Stenting (CAS)-registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK). Zeitschrift fur Kardiologie 94 (3): 163–72	n = 1888 FU = to discharge	The multi-centre ALKK CAS Registry data confirm the feasibility and short-term safety of CAS even in daily clinical practice. There was a rapid penetration of the use of embolic protection devices, an increase in treatment of asymptomatic carotid stenoses and a decrease in acute complication rates from 1996 to 2004	Larger studies included in table 2

Appendix B: Related NICE guidance for carotid artery stent placement for symptomatic extracranial carotid stenosis

Guidance	Recommendations
Interventional procedures	**Endovascular stent insertion for intracranial atherosclerotic disease. NICE interventional procedures guidance 233 (2007)** 1.1 The evidence on the efficacy of endovascular stent insertion for intracranial atherosclerotic disease is currently inadequate and the procedure poses potentially serious safety concerns. Therefore, this procedure should only be used in the context of clinical research including collecting data which should be submitted to a national register when available. Research should clearly define patient selection and be designed to provide outcome data based on follow-up of at least 2 years **Extracranial to intracranial bypass for intracranial atherosclerosis. NICE interventional procedures guidance 348 (2010)** 1.1 Current evidence on the efficacy and safety of extracranial to intracranial (EC–IC) bypass for intracranial atherosclerosis is inconsistent and remains limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research 1.2 Clinicians wishing to undertake EC–IC bypass for intracranial atherosclerosis should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy in relation to symptom reduction and stroke prevention, and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended • Audit and review clinical outcomes of all patients having EC–IC bypass for intracranial atherosclerosis (see section 3.1). 1.3 Patient selection for EC–IC bypass for intracranial atherosclerosis should be carried out by a multidisciplinary team with experience of managing patients with cerebral hypoperfusion syndromes who are undergoing this procedure. The team should include a neuroradiologist, neurologist/stroke physician and vascular neurosurgeon. The procedure should be done only by surgeons with specific training 1.4 NICE encourages further research into EC–IC bypass for intracranial atherosclerosis. Research studies should clearly define patient selection criteria and report symptomatic and quality of life outcomes. NICE is aware of current clinical trials involving this procedure and may review the procedure on publication of further evidence

Appendix C: Literature search for carotid artery stent placement for symptomatic extracranial carotid stenosis

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	20/08/2010	August, 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	20/08/2010	n/a
HTA database (CRD website)	20/08/2010	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	20/08/2010	August, 2010
MEDLINE (Ovid)	20/08/2010	1950 to August Week 2 2010
MEDLINE In-Process (Ovid)	20/08/2010	August 19, 2010
EMBASE (Ovid)	20/08/2010	1980 to 2010 Week 32
CINAHL (NLH Search 2.0/EBSCOhost)	20/08/2010	n/a
Zetoc	20/08/2010	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Carotid Arteries/su
2	*Stents/
3	Angioplasty/
4	Catheterization/
5	or/3-4
6	2 and 5
7	1 and 6
8	(Carotid* adj3 Arter* adj3 Stent* adj3 (Place* or Surg* or Procedure* or Tech*)).tw.
9	(Carotid* adj3 Arter* adj3 (Angioplast* or Endovascular* or Catheterization* or Catheterisation* or Cannula*)).tw.
10	(CAS adj3 (Place* or Surg* or Procedure* or Tech*)).tw.
11	Acculink.tw.

12	(Precise adj3 stent*).tw.
13	(Exponent adj3 stent*).tw.
14	Xact.tw.
15	NexStent.tw.
16	Protege.tw.
17	or/7-16
18	Carotid Artery Diseases/
19	Carotid Stenosis/
20	(Carotid* adj3 Arter* adj3 (Diseas* or Stenos* or Obstruct* or Disorder* or Narrow* or Plaque* or Ulcer* or Block*)).tw.
21	(Carotid* adj3 Atherosclero*).tw.
22	or/18-21
23	17 and 22
24	Animals/ not Humans/
25	23 not 24