NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting

The arteries in the neck that supply the brain can become narrowed by fatty deposits. Fragments of these fatty deposits can detach and block smaller arteries that supply blood to parts of the brain, causing a stroke or a 'mini stroke' (transient ischaemic attack; TIA). A stent can be used to open up the narrowed arteries but there is a risk that it may dislodge fatty deposits and cause a TIA or a stroke.

Transcervical extracorporeal reverse flow neuroprotection aims to reduce the risk of stroke by redirecting blood away from the brain into a filtering system outside the body. This removes any fragments that might detach while the stent is placed. The neuroprotection system is inserted through a small cut in the neck.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) 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 IP overview was prepared in October 2015 and updated in February 2016.

Procedure name

- Transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting

Specialist societies

- British Society of Interventional Radiology
- British Society of Neuroradiologists
- The Vascular Society

Description

Indications and current treatment

Narrowing of the carotid arteries by atherosclerosis may lead to transient ischaemic attack (TIA) or stroke. Treatment includes managing cardiovascular risk factors (stopping smoking, taking antithrombotic medication and statins). In some people, surgical revascularisation (carotid endarterectomy) or carotid artery angioplasty and stenting may be considered. Debris dislodged during carotid artery stenting can embolise to the cerebral circulation and cause a TIA or stroke.

The risk of an embolic stroke during carotid artery stenting may be reduced either by using filters to capture any embolic debris (distal neuroprotection) or by temporarily reversing the blood flow through the stenotic lesion and away from the brain by blocking the flow in the carotid artery (proximal neuroprotection).

Neuroprotection devices may be introduced via the femoral or carotid artery.

What the procedure involves

Transcervical extracorporeal reverse flow neuroprotection is an approach to providing proximal neuroprotection during carotid artery angioplasty and stenting. By directly accessing the carotid artery, it aims to avoid the risks of endovascular manipulation within the aortic arch that occur with a transfemoral approach, and make access possible if there is unfavourable aortic arch anatomy or iliac artery disease.

With the patient under local, regional or general anaesthesia, a small incision is made in the neck and a catheter introduced into the common carotid artery. A catheter is then placed in the femoral or jugular vein. The common carotid artery is temporarily blocked and retrograde flow is established through the stenosis in the internal carotid artery. The blood is passed through a filtering system outside the body to remove any dislodged debris. It is then returned through the femoral or jugular vein. Once blood flow is reversed, carotid artery angioplasty and stenting are done. After the stent has been successfully placed, normal blood flow to the brain is allowed to resume and the catheters are removed.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting. The following databases were searched, covering the period from their start to 23 February 2016: 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 carotid artery stenosis having carotid artery stenting.
Intervention/test	Transcervical extracorporeal reverse flow neuroprotection
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 IP overview

This IP overview is based on 794 patients from 4 comparative studies[1–3, 9] and 5 case series[4–8].

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 transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting

Study 1 Alvarez B (2008)

Details

Study type	**Comparative study**
Country	Spain
Recruitment period	Transcervical carotid stenting (TCS): 2005–07 (prospective cohort) Carotid endarterectomy (CEA): 2002–05 (retrospective cohort)
Study population and number	n=**81 (36 TCS versus 45 CEA)** octogenarian patients with more than 70% carotid stenosis
Age and sex	TCS: mean 83.5 years; 86% (31/36) male CEA: mean 81.7 years; 80% (36/45) male
Patient selection criteria	Consecutive patients of at least 80 years old, treated for more than 70% carotid stenosis, with high surgical risk according to the SAPPHIRE criteria. Exclusion criteria for TCS: internal carotid kinking distal to the stenosis, preocclusive lesions difficult to cross with the stent or presence of severe atheromatosis in the common carotid artery.
Technique	TCS with flow reversal: all procedures were done under local anaesthesia. A shunt was created between the carotid artery and the jugular vein. 2 types of stents were used: Acculink (Guidant) and Carotid Wallstent (Boston Scientific). Atropine was used in case of important bradycardia and intra-arterial nitroglycerin was used in case of spasm of the distal carotid artery. CEA: all procedures were done under general anaesthesia. All patients were prescribed acetylsalicylic acid (300 mg/d) and clopidogrel (75 mg/d) for at least 4 days before the procedure. In cases of non-compliance with this treatment, a 300 mg loading dose of clopidogrel was administered 24 hours before the procedure. Double antiplatelet therapy (aspirin and clopidogrel) was maintained for the first 30 days and, thereafter, clopidogrel 75 mg/day was prescribed indefinitely.
Follow-up	**30 days**
Conflict of interest/source of funding	None

Analysis
Follow-up issues: None.
Study design issues:
- TCS was done by the same vascular surgeon.
- CEA was done by several vascular surgeons with extensive experience in this intervention (>40 CEAs per year).

Study population issues:
- Mean age significantly higher in TCS group (p=0.004).
- Percentage of patients with coronary artery disease and pulmonary disease significantly higher in TCS group: 44% (16/36) versus 22% (10/45), p=0.03 and 31% (11/36) versus 7% (3/45), p=0.005 respectively.
- Among TCS patients, 31% (11/36) had intracranial lesions and 19% (7/36) presented a decreased or exhausted cerebral vascular reactivity.
- None of the patients presented high-intensity transient signals in the pre-operative examination.

Other issues: There are probably overlaps of patients between this study, the Alvarez (2012) and the Matas (2007) studies.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 81 (36 TCS versus 45 CEA)

Technical success
TCS: 100% (36/36)

An increase in mean cerebral artery flow velocity (measured by transcranial Doppler) was reported in 100% (36/36) of patients at completion of the procedure.

Stent patency (at 24 hours and at 30 days)
TCS: 97% (35/36)

High intensity transient signals during the procedure: 3% (1/36)</td><td>TCS – Complications during the procedure
<table><tr><th>Safety event</th><th>Patients</th><th>Detail</th></tr><tr><td>Transient intolerance to flow reversal</td><td>3% (1/36)</td><td>The common carotid clamping was only maintained during the key steps of the procedure.</td></tr><tr><td>Bradycardia and hypotension related to balloon inflation</td><td>6% (2/36)</td><td>This was controlled with atropine.</td></tr><tr><td>Severe spasm of the distal carotid</td><td>3% (1/36)</td><td>This was treated by intra-arterial administration of nitroglycerin.</td></tr></table>
Complications within 30 days in both groups
<table><tr><th></th><th>TCS (n=36)</th><th>CEA (n=45)</th><th>p</th></tr><tr><td>Transient ischaemic attack</td><td>0</td><td>0</td><td>NS</td></tr><tr><td>Minor stroke</td><td>0</td><td>0</td><td>NS</td></tr><tr><td>Major stroke</td><td>0</td><td>2% (1/45)</td><td>NS</td></tr><tr><td>Myocardial infarction</td><td>0</td><td>2% (1/45)</td><td>NS</td></tr><tr><td>Death</td><td>0</td><td>0</td><td>NS</td></tr><tr><td>Cranial nerve palsy</td><td>0</td><td>4% (2/45)</td><td>NS</td></tr><tr><td>Cervical haematoma</td><td>0</td><td>2% (1/45)</td><td>NS</td></tr><tr><td>Major dissection in the common carotid artery</td><td>3% (1/36)*</td><td>0</td><td>NS</td></tr></table>
* This was treated by a bypass from the common carotid artery to the distal internal carotid artery.</td></tr>
<tr><td colspan="2">Abbreviations used: CEA, carotid endarterectomy; NS, not significant; TCS, transcervical carotid stenting.</td></tr>
</table>

Study 2 Leal I (2012)

Details

Study type	**Prospective non-randomised comparative study**
Country	Spain
Recruitment period	2008–09
Study population and number	n=**64 (31 transcervical carotid artery stenting [CAS] versus 33 transfemoral CAS)** consecutive patients with significant carotid stenosis
Age and sex	Transcervical CAS: mean 68.1 years; 87% (27/31) male Transfemoral CAS: mean 67.2 years; 94% (31/33) male
Patient selection criteria	Patients in a high-risk category for carotid endarterectomy, with an extracranial internal carotid artery stenosis greater than 70% and a minimum distance of 5 cm from the carotid bifurcation to the clavicle, as determined by an ultrasound study. Exclusion criteria: allergy to heparin, aspirin, clopidogrel, or iodinated contrast agents; contraindication to MRI studies; intracranial bleeding; haemorrhagic stroke or any stroke with mass effect demonstrated on MRI or computed tomography at 4 weeks or less of the index procedure; dementia or neurological illness that might confound the neurological evaluation during the study; total internal carotid artery occlusion; or common carotid artery calcification with contraindication for puncture or sheath placement.
Technique	All patients were treated with aspirin and clopidogrel before the procedure. All procedures were done under local anaesthesia with clinical monitoring of neurological function. The stents used were either Wallstents (Boston Scientific) or Protégé Rx (ev3 Endovascular). Transcervical CAS with flow reversal: Systemic anticoagulation with intravenous heparin (100 U/kg body weight) was conducted before carotid occlusion and was not reversed with protamine at the completion of the procedure. A shunt was created between the carotid artery and the jugular vein. Transfemoral CAS with distal filter protection: Patients had heparin (100 IU/kg) to achieve an activated clotting time of between 200 and 250 seconds. A cerebral protection device, a self-expanding Filter Wire EZ (Boston Scientific), was deployed in the cervical portion of the internal carotid artery. Atropine sulfate (1 mg) was intravenously administered before balloon inflations to prevent carotid sinus stimulation. Both groups were prescribed a daily dose of acetylsalicylic acid (100 mg) and clopidogrel (75 mg) for 1 month after the procedure.
Follow-up	**Mean 23.25 months**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues:

- Diffusion-weighted MRIs were conducted within 24 hours before and 24–48 hours after the procedure.
- All patients were evaluated by a neurologist before and after the procedure using the Rankin stroke scale and including sensory, motor, and autonomic testing. Neurological deficits lasting more than 24 hours were defined as stroke, and those lasting less than 24 hours were defined as transient ischaemic attacks.
- All patients were evaluated 30 days after surgery with a clinical assessment and carotid ultrasound imaging. Additional follow-up visits were done at 6 and 12 months.

Study design issues:

- Single-centre study.
- The procedures were done in 2 separate periods. During the first part of the study, 31 patients underwent transcervical CAS. During the second part of the study, 33 patients underwent transfemoral CAS with distal filter protection.
- All procedures were done by vascular surgeons experienced in CAS.
- Stent selection was determined by lesion characteristics and surgeon preference.
- Pre-operative and post-operative diffusion-weighted MRIs were read by 2 independent neuroradiologists unaware of the patient's clinical status and blinded to the timing (pre-operative or post-operative) of the paired scans.

Study population issues: None.

Other issues: The authors state that 'the real clinical relevance of post-operative diffusion-weighted MRI lesions has yet to be clarified'.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 64 (31 transcervical CAS versus 33 transfemoral CAS)

Procedural outcomes
• Predilatation was performed in 3 patients in the transcervical group and in 2 in the transfemoral group (p=0.694), using 3- to 4-mm diameter × 2-cm-long balloons inflated to 10 atm.
• Mean surgical time (±SD)
  ○ Transcervical CAS: 46±5.05 minutes
  ○ Transfemoral CAS: 52±10.14 minutes
  ○ p=0.324
• Mean carotid flow reversal time: 22 minutes
Technical success (stent satisfactorily deployed with less than 30% residual stenosis in the target segment)
• Transcervical CAS: 100% (31/31)
• Transfemoral CAS: 100% (33/33)

Early stroke
• After stenting, there were no changes in the stroke scale in any patient in either group.
• No strokes or transient ischaemic attacks occurred.
Stroke in the long term
All patients remained stroke-free during follow-up.

New ischaemic cerebral lesions (identified on diffusion-weighted MRI) within 48 hours of the procedure
<table>
<tr><th></th><th>Transcervical CAS (n=31)</th><th>Transfemoral CAS (n=33)</th><th>p</th></tr>
<tr><td>Patients with new lesions</td><td>13% (4/31)</td><td>33% (11/33)</td><td>0.03</td></tr>
<tr><td>Number of new lesions</td><td>4*</td><td>13</td><td>0.02</td></tr>
<tr><td>Localisation of new lesions</td><td></td><td></td><td></td></tr>
<tr><td>Ipsilateral</td><td>4</td><td>11</td><td>0.03</td></tr>
<tr><td>Contralateral</td><td>0</td><td>2</td><td>0.16</td></tr>
</table>
* Flow interruptions occurred because the carotid sheath was dislodged during the procedure. All interruptions were due to movement and exit of the carotid sheath by accidental manipulation in the surgical field, needing to interrupt flow reversal, and in some cases, carotid artery clamping was needed to reintroduce the sheath.

Neurological evaluation
The Rankin stroke scale did not deteriorate in any patient. After the procedure, the Rankin scale slightly improved in both groups, but the difference did not reach significance. During follow-up, it remained unchanged in all patients.

Evaluation of predictors of embolisation
In the multivariate analysis, none of the tested variables (age, sex, operator, type of stent used, symptomatic status) reached significance to predict the presence of embolisation in the post-operative diffusion-weighted MRI studies.
Adjusting analysis by type of treatment, age, recent symptomatic status, and closed-cell versus open-cell stent type were independent predictors of embolisation in the transfemoral group but not in the transcervical group (p<0.001 for all variables).
</td><td>
• Intolerance to carotid flow reversal was not detected in any patient.
• There were no complications related to access site in either group.
• No major adverse events occurred at 30 days after the procedure.
• During follow-up (mean 23.25 months), no new neurological events, deaths or hospital admissions were reported.
</td></tr>
<tr><td colspan="2">Abbreviations used: CAS, carotid artery stenting; CI, confidence interval; MRI, magnetic resonance imaging; RR, relative risk; SD, standard deviation.</td></tr>
</table>

Study 3 Lin J (2005)

Details

Study type	**Prospective non-randomised comparative study**
Country	Germany
Recruitment period	2002–04
Study population and number	n=**55 (31 transcervical carotid artery stenting [CAS] versus 24 transfemoral CAS)** high-risk patients with carotid artery stenosis
Age and sex	Not reported
Patient selection criteria	High-risk patients with American Society of Anesthesiologists class 3 and 4, recurrent carotid stenosis, hostile neck after radiation or previous surgery, recent myocardial infarction within last 6 months and pre-operative coronary artery bypass grafting. Exclusion criteria: patients with acute or fresh thrombotic occlusion, excessive tortuous internal carotid artery and semi-circular calcification.
Technique	All patients were given aspirin (325 mg/day) and clopidogrel (75 mg/day) for at least 3 days before the procedure. Intravenous heparin (5000 units) was given before intraoperative arteriography. Transcervical CAS with flow reversal was done with cervical block or local anaesthesia. A shunt was created between the carotid artery and the jugular vein. Retrograde flow in the internal carotid artery was confirmed by injecting contrast and using fluoroscopy. The carotid Wallstent Monorail (Boston Scientific) was deployed over the bifurcation of the carotid lesion. Balloon dilation after stent placement was done at the discretion of the surgeon. Transfemoral CAS was done under local anaesthesia. The Rx AccuNet embolic protection system (Guidant corporation) or Filter Wire EZ (Boston Scientific) was used. The carotid Wallstent Monorail (Boston Scientific) was deployed over the bifurcation of the carotid lesion.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues:

- Completion angiography was done in all patients to assess technical results and check for cerebral embolisation.

Study design issues:

- The authors initially started treating patients by transfemoral CAS and then switched to transcervical CAS.

Study population issues:

- In the transcervical CAS group, there were 12 asymptomatic, 18 symptomatic and 1 recurrent stenosis.
- In the transfemoral CAS group, there were 9 asymptomatic, 13 symptomatic and 2 recurrent stenoses.

Other issues: None

Key efficacy and safety findings

Efficacy

Number of patients analysed: **55 (31 transcervical CAS versus 24 transfemoral CAS)**

Technical failure (defined as residual stenosis of greater than 30% after CAS and angioplasty)

- Transcervical CAS: 10% (3/31)
- Transfemoral CAS: 8% (2/24)

The patients with technical failure in the transcervical group were immediately treated by open conversion and carotid endarterectomy.

Restenosis

- In the transfemoral CAS group, 1 patient developed restenosis within 12 months after CAS and was treated by an open carotid stent resection and placement of an interposition polytetrafluoroethylene graft. The restenosis was caused by concentric intimal hyperplasia.

Mean surgical time (± SD)

- Transcervical CAS: 64±20.1 minutes
- Transfemoral CAS: 80±34 minutes
- p<0.001

Stroke

	Transcervical CAS (n=31)	**Transfemoral CAS (n=24)**
Transient ischaemic attack	6% (2/31)	4% (1/24)
Stroke	0	4% (1/24)

Safety

Complications

	Transcervical CAS (n=31)	**Transfemoral CAS (n=24)**
Asystolic cardiac arrest	0	4% (1/24)
Bradycardia	13% (4/31)	0
Groin haematoma	NA	8% (2/24)
Cervical haematoma	6% (2/31)*	NA

*****One of the patients was treated by drainage and had no neurological sequelae.

All patients in the transcervical CAS group tolerated flow reversal.

Abbreviations used: CAS, carotid artery stenting; NA, not applicable.

Study 4 Alvarez B (2012)

Details

Study type	**Prospective case series**
Country	Spain
Recruitment period	2006–11
Study population and number	n=**212** high-risk patients (219 cases) over 70 years old with more than 70% carotid artery stenosis
Age and sex	Mean 79.9 years; 77% (168/219) male
Patient selection criteria	Consecutive patients over 70 years old with more than 70% carotid stenosis, at high risk for carotid artery endarterectomy. Exclusion criteria: kinking of the distal internal carotid very close to the stenosis, atheromatosis of the common carotid with more than 30% stenosis, and presence of the string sign (pseudo-occlusion).
Technique	Transcervical carotid artery stenting [CAS] was done under local anaesthesia. A shunt was created between the carotid artery and the jugular vein. Systemic heparin was administered to maintain the activated clotting time between 250 and 300 seconds. In the case of significant bradycardia, atropine (0.5–1 mg) was injected, and in case of spasm of the distal carotid, intra-arterial nitroglycerin (100–200 µg) could be used. All patients were prescribed acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) for at least 4 days before the procedure. In cases of non-compliance with this treatment, a 300-mg loading dose of clopidogrel was administered 24 hours before treatment. Double antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was maintained for the first 30 days and, thereafter, clopidogrel (75 mg/day) indefinitely was prescribed. The following self-expanding stents were implanted: Carotid Wallstent (Boston Scientific), Acculink (Guidant) and ViVEXX Carotid Stent (C.R. Bard). Post-angioplasty dilation was carried out in all patients. All patients were treated with atropine before angioplasty.
Follow-up	**Mean 18.8 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Procedure-related complications were recorded within the first 24 hours.
- Clinical and Doppler ultrasound follow-up examinations were done at 24 hours, at 1, 3, 6, and 12 months, and yearly thereafter.

Study design issues:

- All procedures were done by the same vascular surgeon who had extensive experience in transcervical CAS (more than 50 procedures per year).
- The periprocedural neurological evaluation was performed by an independent neurologist in accordance with the National Institutes of Health Stroke Scale.

Study population issues:

- The main indications for CAS were elevated cardiac risk in 55% (120/219) patients, severe obstructive pulmonary disease in 23% (50/219), contralateral laryngeal nerve palsy and non-viable femoral access in 2% (5/219), recurrent stenosis after CEA in 3% (6/219), recurrent stenosis after CAS in 1% (3/219), prior cervical radiotherapy in 3% (6/219) and a distal internal carotid lesion in 2% (5/219).
- Carotid stenosis greater than 70% was symptomatic in 44% of cases (97/219) and asymptomatic in 56% (122/219). Within the asymptomatic group, there was an associated intracranial lesion in 18% of cases (22 /122), contralateral carotid occlusion in 7% (8/122), decreased or exhausted cerebral haemodynamic reserve in 5% (6/122), and high-intensity transient signals in the pre-operative transcranial Doppler examination in 2% (2/122).

Other issues:

- There are probably overlaps of patients between this study, the Alvarez (2008) and the Matas (2007) studies.
- The paper usually reports the outcomes per case but sometimes also reports per patient.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **212** (219 cases)

Mean procedural time: 40 minutes (range 2560 minutes)

Mean (±SD) flow reversal time: 15±5 minutes

Technical success (less than 30% residual stenosis on arteriography at completion of surgery): **96%** (211/219) of cases.

- In 4 cases, the procedure could not be done because it was impossible to cross the very extensive, preocclusive internal carotid lesion. **The patients were subsequently treated by CEA**.
- In 2 patients, a major dissection was seen in the common carotid artery after completing stent placement. Because the dissections were close to the introducer sheath, it did not seem advisable to attempt endovascular treatment, and instead, a **bypass** from the common carotid artery to the distal internal carotid was done.
- In another patient, pre-angioplasty of the lesion was not achieved because of a large calcification. **The patient was subsequently treated by CEA.** This patient, who was symptomatic and had severe bilateral stenosis and a high cardiological risk, died of a myocardial infarction 48 hours after the CEA.
- Stent thrombosis was seen on DUS imaging follow-up at 24 hours in 1 patient who showed no neurological symptoms and had considerable respiratory comorbidity with an elevated risk for CEA. It was decided not to intervene to recover stent patency.

Stent patency: 99.5% (211/212) of patients

Stroke and death within 30 days

Event	Patients (n=212)	Detail
Stroke*	2% (4/212)	There were 1 transient ischaemic attack and 3 major strokes.

*There were no events in asymptomatic patients. The patients who had stroke and the patient who died from myocardial infarction were over 80 years old.

Ipsilateral stroke-free survival at 1, 2 and 3 years: 99%±1% (SE)

1 ipsilateral stroke was reported after 30 days.

Cumulative incidence of restenosis over 70% (±SE)

- **1 year:** 3%±1%
- **2 years:** 8%±1%
- **3 years:** 8%±1%

Cumulative incidence of restenosis over 50% (±SE)

- **1 year:** 19%±3%
- **2 years:** 27%±4%
- **3 years:** 27%±4%

Presence of chronic obstructive pulmonary disease was associated with restenosis (p=0.04).

Overall survival (±SE)

- **1 year:** 94%±2%
- **2 years:** 90%±3%
- **3 years:** 90%±3%

Safety

Intra-procedural complications

Complication	Patients (n=212) or cases (n=219)	Detail
Significant distal internal carotid spasm	2% (4/212 patients)	This was successfully treated by intra-arterial nitroglycerin administration in 1 patient and it resolved spontaneously after guide wire withdrawal in 3 patients.
Intolerance to flow reversal	1% (3/219 cases)	This was treated by declamping the common carotid artery and rapidly completing the procedure.

Post-procedural complications (within 30 days)

Complication	Patients (n=212)	Detail
Death*	1/212	**Myocardial infarction** at 48 hours.
Cervical haematoma	1/212	This was treated by surgical drainage.
Transient laryngeal nerve palsy	1% (2/212)	This was secondary to impregnation of the nerve with local anaesthesia.

Abbreviations used: CAS, carotid artery stenting; CEA, carotid endarterectomy; DUS, duplex ultrasound; SD, standard deviation; SE,

standard error.

Study 5 Kwolek C J (2015)

Details

Study type	**Prospective case series**
Country	US (18 sites)
Recruitment period	2012–14
Study population and number	n=**141** patients considered to be at high risk for complications from carotid endarterectomy
Age and sex	Mean 72.9 years; 65% (91/141) male
Patient selection criteria	Patients at increased risk for carotid endarterectomy with an asymptomatic stenosis of 70% or more or symptomatic stenosis of 50% or more. Exclusion criteria: cardiac emboli; atrial fibrillation or myocardial infarction <72 hours; recently implanted heart valve; major surgery within 30 days before or after the procedure; evolving stroke; history of spontaneous intracranial haemorrhage <12 months; recent stroke <7 days; transient ischaemic attack or amaurosis fugax <48 hours; severe dementia; other neurological disorders; bleeding disorders; life expectancy <12 months; previous stent in target vessel; common or internal carotid artery occlusion or string sign; ipsilateral intracranial or extracranial stenosis; severe ostial lesion; previous intervention ipsilateral proximal common carotid artery; common carotid artery disease at entry site; less than 5 cm clavicle to bifurcation; common carotid artery <6 mm diameter; contralateral lateral recurrent; laryngeal, or vagus nerve injury.
Technique	Enroute (Silk Road Medical) transcarotid neuroprotection system in conjunction with any US Food and Drug Administration-approved carotid artery stent used in patients at high risk for complications from carotid endarterectomy. A shunt was created between the carotid artery and the femoral vein. The flow line incorporates a flow regulator that allows the clinician to modify the flow (high or low) and to permit temporary cessation of flow for angiography. The procedure was done under general anaesthesia until the surgeons were familiar with the system and the technique. Patients were prescribed aspirin (75–325 mg/day for 72 hours before the procedure or a loading dose of 650 mg 4 hours before the procedure) plus clopidogrel (75 mg/day for 72 hours before the procedure or 450 mg loading dose for 4 hours before the procedure. 40 mg atorvastatin for 7 days before the procedure or an 80-mg loading dose for 12 hours was also prescribed. Systemic anticoagulation was done during the procedure.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was sponsored by Silk Road Medical.

Analysis

Follow-up issues: None.

Study design issues:

- The protocol included a lead-in phase of up to 5 patients per investigator to allow users to gain experience with the device before pivotal enrolment. 5 lead-in cases were used in 15 of the 18 centres. The 3 other centres were allowed fewer lead-in cases because they had prior transcervical CAS experience.
- 208 patients were originally enrolled: 67 as lead-in cases and 141 patients in the pivotal cohort who were evaluated for outcome analysis.
- For the pivotal phase, use of local or general anaesthesia depended on patient and physician preference.
- Choice of stent and lesion before and after dilatation were left to the discretion of the operator.
- A minimum sample size of 140 patients was calculated based on the following assumptions: power of 80% and a 1-sided significance level of 2.5%.
- An independent clinical events committee adjudicated the major adverse events using prespecified definitions.

Study population issues:

- 74% (105/141) patients were asymptomatic and 26% (36/141) were symptomatic.
- Mean index lesion length was 16.5±6.7 mm and the mean degree of stenosis of the index lesion was 86%±9%.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 141

Procedural parameters
<table>
<tr><th>Variables</th><th>% (n/N) or mean±SD (min, max)</th></tr>
<tr><td>Anaesthetic modality</td><td></td></tr>
<tr><td>Local anaesthesia</td><td>53% (74/141)</td></tr>
<tr><td>General anaesthesia</td><td>47% (67/141)</td></tr>
<tr><td>Procedure time (min)</td><td>73.6±30.77 (68.2, 78.2)</td></tr>
<tr><td>Flow reversal time (time on high-flow, min)</td><td>12.9±8.6</td></tr>
<tr><td>Acute device success</td><td>99% (140/141)</td></tr>
<tr><td>Technical success</td><td>99% (140/141)</td></tr>
<tr><td>Procedural success</td><td>96% (135/141)</td></tr>
</table>
Stroke within 30 days: 1% (2/141)
2 ipsilateral strokes, 1 on the evening of the procedure and 1 at 48 hours. The latter was a major protocol violation because significant tandem lesions of the ipsilateral middle cerebral artery that were present before the intervention were not prospectively identified with the exclusion criteria.</td><td>Major adverse event rate*: 4% (5/141)**
*Defined as stroke, death or myocardial infarction
**95%CI, 1.16–8.08; p=0.0047 versus the threshold of 11% derived from the Carotid Revascularisation with ev3 Arterial Technology Evolution (CREATE) 30-day stroke/death/myocardial infarction rate.

Death within 30 days: 1% (2/141)
• 1 died from respiratory failure.
• 1 died from myocardial infarction 15 days after the procedure, after readmission with pneumonia and diabetic ketoacidosis.

Myocardial infarction within 30 days: 1% (1/141)

Local complications
• 1 cranial nerve injury affecting the 10th nerve causing hoarseness, which fully resolved at 6 months.
• Arterial dissection: 6% (8/141).
○ For 5 of them, no treatment was needed. They were at the site of the arterial sheath or between the sheath and the carotid bifurcation.
○ For the 3 that needed treatment, 1 patient was converted to carotid endarterectomy at the index procedure, 1 needed the placement of a second stent at the index procedure and 1 was repaired surgically during the index procedure.
○ 1 of the patients with a dissection had a minor ipsilateral stroke 8 hours after the procedure that was judged as unrelated to the dissection because the second stent has adequately managed the intimal flap.
• Haematoma
○ Limited surgical wound haematoma needing treatment: 4% (5/141).
○ Haematoma needing wound exploration and evacuation: 1/141
○ Localised haematoma at the femoral venous access site which resolved without treatment: 1/141

Intolerance to flow reversal: 0%
Intolerance to high flow: 1% (1/141)</td></tr>
<tr><td colspan="2">Abbreviations used: CAS, carotid artery stenting; CI, confidence interval; SD, standard deviation; US, United States.</td></tr>
</table>

Study 6 Criado E (2007)

Details

Study type	**Case series**
Country	Spain
Recruitment period	2003-05
Study population and number	n=**97** consecutive patients (103 carotid artery stenting [CAS] procedures) with carotid artery stenosis
Age and sex	Mean 72 years; 85% (82/97) male
Patient selection criteria	Patients at higher risk for general anaesthesia or for a major procedure and who preferred a less invasive approach.
Technique	Transcervical CAS with carotid artery flow reversal. Either local/regional or general anaesthesia were used. A shunt was created between the carotid artery and the jugular vein. All patients took clopidogrel before stent placement. Systemic heparinisation was done with intravenous heparin (100 IU/kg). Predilatation of the carotid stenosis was done at the discretion of the operator. Biliary Wallstent, Monorail stents (Boston Scientific) and Exponent stents (Medtronic) were used. Post-stent dilation was done in all cases. Intra-arterial papaverine solution (1 mg/ml) was selectively used to treat residual carotid spasm. Clopidogrel was continued at 75 mg/day orally for at least 1 month and aspirin was continued indefinitely.
Follow-up	**3 years**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Post-operative neurological examinations were done by vascular surgeons, residents, fellows, and recovery room nurses. A post-operative physical examination and a carotid duplex scan were repeated in all patients at 1, 6, and 12 months, and yearly thereafter.
- Follow-up was conducted at 1, 6, 12, 24, and 36 months after surgery and included bilateral carotid artery duplex ultrasound imaging.
- There was no post-operative MRI evaluation.
- 7 patients were lost to follow-up.

Study design issues:

- All procedures were done on the basis of pre-operative duplex ultrasound imaging, without pre-operative angiography.
- All procedures were done by vascular surgeons.
- 2 stents were deployed in 1 carotid artery.

Study population issues:

- 36% (37/103) of patients presented with ipsilateral stroke (<6 months old, 14%) or transient ischaemic attack (TIA; 22%).
- 42% (43/103) of patients had a history of stroke (22%) or TIA (20%) more than 6 months before the procedure.
- The estimated degree of stenosis was more than 50% for symptomatic patients and more than 70% for asymptomatic patients.

Other issues: None.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **97 (103 CAS procedures)**

Procedural parameters

Variables	% (n/N) or mean (range)
Anaesthetic modality Local/ regional anaesthesia General anaesthesia	 70% (72/103) 30% (31/103)
Procedure time (min)	69 (20-180)
Flow reversal time (min)	21 (7-60)

Technical success (technical failure was defined as inability to access or to cross the lesion or inability to complete the procedure for any reason): 97% (100/103)

Conversion to endarterectomy: 3% (3/103)

Causes of the conversions:

- 1 common carotid dissection with the entry sheath
- 1 was caused by the inability to cross a very tight and angulated ICA origin lesion with the guide wire
- 1 caused by severe patient agitation that needed conversion to general anaesthesia and the surgeon chose to proceed with an endarterectomy rather than to pursue the stenting procedure.

Residual stenosis in ICA (30%): 1% (1/103)

Neurological complications: 4% (4/97)

Neurological complications	Patients (n/N)	Further details
Ipsilateral motor TIA	1% (1/97)	
Contralateral TIA	1% (1/97)	
Minor stroke	2% (2/97)	1 of these was in a patient with a previous ipsilateral stroke who developed worsening hemiparesis, and another patient sustained dysarthria. Both patients returned to their baseline neurological status within a week.

Neurological outcomes during follow-up

All patients remained neurologically unchanged

Stent occlusion

1 stent was occluded at 1 month after intervention.

Stroke-free patient survival at 40 months: 91%

Primary stent patency at 40 months: 95%

Safety

Death

- There were no deaths during the procedure.
- 5% (5/97) of patients died during the follow-up period.
  - 3 of causes not related to stroke
  - The cause of death could not be determined in 2 patients

Major adverse event rate: 0%

Common carotid artery dissection: 5% (5/103)

- 4 occurred during the first 12 procedures, at access site
  - 1 needed surgical repair with a proximal common carotid interposition graft
  - 3 resolved after placement of the stent intended to treat the stenosis without additional stenting.
- 1 occurred during the remaining 91 procedures
  - It occurred at vessel entry, which prompted 1 of the conversions to endarterectomy.

Wound haematoma: 2% (2/97)

Both needed surgical drainage under local anaesthesia.

Intolerance to flow reversal: 4% (3/72) of patients who had the procedure done under local anaesthesia.

- In 1 patient, the procedure was completed with antegrade flow without protection.
- In the second patient, the situation was solved with intermittent rather than continuous carotid flow reversal, allowing antegrade cerebral flow in between carotid instrumentation manoeuvres.
- The third patient was converted to endarterectomy.

Bradycardia or hypotension or both needing pharmacologic intervention occurred in response to carotid balloon dilatation in 23% (24/103) of cases.

Abbreviations used: CAS, carotid artery stenting; ICA, internal carotid artery; TIA, transient ischaemic attack.

Study 7 Matas M (2007)

Details

Study type	**Prospective case series**
Country	Spain
Recruitment period	2005–06
Study population and number	n=**62** high-risk patients with more than 70% stenosis.
Age and sex	Mean 76.5 years; 84% (52/62) male
Patient selection criteria	Patients in whom carotid revascularisation was indicated and who were at high risk for carotid endarterectomy according to the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE).
Technique	Transcervical carotid stenting: All patients were prescribed acetylsalicylic acid (300 mg/day) and clopidogrel (75 mg/day) for at least 4 days before the procedure. In cases of non-compliance with this treatment, a 300-mg loading dose of clopidogrel was administered 24 hours before the procedure. All procedures were done under local anaesthesia. A shunt was created between the common carotid artery and the jugular vein to establish retrograde flow in the internal carotid artery. Atropine (0.5–1 mg) was injected in the case of important bradycardia, and intra-arterial nitroglycerin (100 to 200 µg) was used in case of spasm of the distal carotid. Double antiplatelet therapy (aspirin and clopidogrel) was maintained for the first 30 days; thereafter, clopidogrel (75 mg/day) was prescribed indefinitely.
Follow-up	**1–18 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- Clinical and Doppler ultrasound follow-up studies were done at 24 hours, 1, 3, 6, and 12 months, and yearly thereafter.

Study design issues: None.

Study population issues:

- 39% (24/62) of patients presented with symptomatic >70 % carotid stenosis, of whom 3 had amaurosis fugax, 11 had hemispheric transient ischaemic attack, and 10 had previous ipsilateral stroke.

Other issues: There are probably overlaps of patients between this study, the Alvarez (2008) and the Alvarez (2012) studies.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **62** **Mean procedure time (min):** 50 (30–60) **Mean flow reversal time (min):** 15.1 (5–36) The arteriographic control showed flow reversal in all cases. **Technical success**: 97% (60/62) • In 1 patient, the procedure could not be done because it was impossible to cross the very extensive, preocclusive internal carotid lesion. The patient's clinical condition was such that the risk of surgery was acceptable; hence, CEA was done. • In the other patient, a major dissection was seen in the common carotid artery after the stent placement was completed. Given its proximity to the introducer sheath, it did not seem advisable to attempt endovascular treatment, and a bypass from the common carotid artery to the distal internal carotid was performed instead. Neither of these 2 patients presented neurological symptoms at the end of these procedures. **Perioperative high intensity transient signals:** 6% (2/62) **Flow reversal in the anterior cerebral artery:** 80% (28/62) **Flow reversal in the middle of the cerebral artery:** 0% A significant improvement in the middle cerebral artery mean flow velocity and pulsatility index was observed at completion of the procedure. **Stent patency**: 98% (61/62) **Restenosis during follow-up:** 5% (3/62) • 2 cases of significant restenosis (50% to 70%) • 1 restenosis of >70% **Stroke during the procedure**: 3% (3/62) • 1 patient had a **TIA of the anterior cerebral artery** territory that resolved within 12 hours. • 1 patient had a **stroke with contralateral hemiplegia**. • None of the patients presented neurological events in the stented carotid vascular territory during follow-up.	**Complications during the procedure** • Significant **distal internal carotid spasm** was observed in 2 patients and was treated successfully with intra-arterial nitroglycerin. • **Transient bradycardia** in response to post-angioplasty dilation was observed in 15% (9/62) of patients. • 1 patient presented **persistent hypotension** during the first 12 hours and needed noradrenaline infusion. • 1 patient returned with hemiplegia and aphasia after an episode of intense headache 48 hours after hospital discharge. A CT scan showed an **extensive cerebral haematoma** that needed surgical drainage. **Major complication** (cervical haematoma): 2% (1/62) **Intolerance to flow reversal**: 2% (1/62) The patient lost consciousness a few minutes after the common carotid artery was clamped. The procedure was done extremely rapidly and the patient recovered without sequelae after declamping. **Complications during follow-up** • No deaths or cardiac complication occurred in the first 30 days. • None of the patients presented neurological events in the stented carotid vascular territory during follow-up.
Abbreviations used: CEA, carotid endarterectomy; CT, computerised tomography; TIA, transient ischaemic attack.	

Study 8 Faraglia V (2009)

Details

Study type	**Case series**
Country	Italy
Recruitment period	2004–07
Study population and number	n=**48** patients with an increased risk for transfemoral carotid artery stenting (CAS)
Age and sex	Mean 78.3 years; 73% (35/48) male
Patient selection criteria	Patients ≥80 years, severe aortic and epiaortic vessel tortuosity, widespread calcification involving the aortic arch or emergence of the epiaortic vessels, severe aorto-iliac occlusive disease, large abdominal aortic aneurysm (>5 cm) or aortobifemoral prosthesis. Exclusion criteria: circumferential and diffuse atheromatous disease of the common carotid artery or an anatomically low carotid bifurcation (<5 cm above the clavicle).
Technique	Transcervical carotid stenting under local anaesthesia. A shunt was created between the common carotid artery and the jugular vein to establish retrograde flow in the internal carotid artery. All patients were taking aspirin before the procedure and had an oral loading dose of clopidogrel (300 mg) at least 3 hours before the procedure. An intravenous bolus of heparin (80 IU/kg) was given before common carotid artery clamping. During the procedure, if an activated clotting time of less than 250 seconds was found, the patient had an additional dose of heparin. Intra-arterial nitroglycerin (200 µg) was injected when spasm occurred. Wallstent (Boston Scientific) or Precise (Cordis) carotid stents were used.
Follow-up	**6 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues:

- Patients had MRI scans 3 days before and after the procedure. They also had neurological examinations.
- Only 43 patients had diffusion-weighted MRIs to assess new ischaemic lesions.

Study design issues:

- CAS was done by a vascular surgeon with experience in endovascular techniques.
- Tolerance to carotid clamping was assessed before initiation of neuroprotection.
- 2 expert neuroradiologists, not involved in the CAS procedures, compared the MRIs pre- and post-procedure and assessed the presence of recent ischaemic lesions.

Study population issues:

- 98% (47/48) of patients had primary atherosclerotic lesions.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **48** **Technical success for CAS** (defined as no residual stenosis or persistent stenosis of less than 20% on completion angiography)**: 100%** **Mean procedure time (min):** 68 (50–75) **Mean clamping time (min):** 47 (38–52) In all patients, internal carotid artery flow reversal was confirmed even though the velocity of contrast medium drainage varied among patients. **Stent patency up to 6 months follow-up:** 100% **New ischaemic lesions** (diagnosed on diffusion-weighted MRI): 16 lesions in 14% (6/43) of patients with a mean of 2.7 lesions per patient (range 2–4). • All lesions were ipsilateral to the operated carotid artery. • In 4 out of 6 patients, the new lesions remained asymptomatic. **Restenosis within 6 months:** none. **Stroke** • **Minor stroke: 2% (1/48)** (in the first patient). It developed after the introducer sheath was inserted into the common carotid artery. Post-operative diffusion-weighted MRI showed an ischaemic area in the frontal lobe. On discharge the patient had mild hemiparesis on the right upper extremity. • **Transient ischaemic attack**: **2%** (**1/48)**. The patient had a hemiparesis of the left arm after the procedure. This resolved within hours. • None of the patients had neurological events during follow-up.	**Peri-procedural complications:** • **Distal internal carotid artery spasm**: **13% (6/48)**. They were treated by intra-arterial nitroglycerin. • **Severe hypotension: 10% (5/48)** • **Bradycardia** after the procedure: **20% (10/48)** In 1 patient, hypotension and bradycardia caused myocardial necrosis enzymes to increase and myocardial infarction was diagnosed. In the other patients, hypotension and bradycardia responded to medication and normalised on discharge. No deaths were reported. None of the patients were intolerant to flow reversal.
Abbreviations used: CAS, carotid artery stenting.	

Study 9 Plessers M (2016)

Details

Study type	**Comparative study**
Country	Belgium
Recruitment period	Not reported
Study population and number	n=**34 (16 transcervical carotid artery stenting with dynamic flow reversal [CASfr] versus 10 carotid endarterectomy [CEA] versus 8 transcervical carotid artery stenting with distal protection filters [CASdp])** patients with significant carotid stenosis
Age and sex	Mean 68 years; 71% (24/34) male
Patient selection criteria	Patients with significant internal carotid artery stenosis (≥80% for asymptomatic and ≥60% for symptomatic patients on duplex ultrasound) and no ostial common carotid artery or tandem lesions, for whom transcranial Doppler ultrasonography could be performed.
Technique	CAS was done under local anaesthesia with selective predilation, mandatory stenting, and selective postdilation. CAS patients were on dual antiplatelet therapy before and after treatment. In transfemoral CAS, the same distal filter embolic protection was always used (Emboshield; Abbott Vascular). In transcervical CAS, dynamic flow reversal was created between the common carotid artery (CCA) and the contralateral common femoral vein using the ENROUTE Neuroprotection System (Silkroad Medical). CEA was always done under general anaesthesia using selective shunting and Dacron patch plasty.
Follow-up	**1 month**
Conflict of interest/source of funding	One of the authors was consulting for Silkroad Medical. The study was supported by a predoctoral research grant from the Fund for Scientific Research Flanders (FWO, Belgium) and by an FWO research grant.

Analysis

Follow-up issues:

- Initially, 48 patients were enrolled in the study. Of these, 29% (14/48) of those could not be monitored with transcranial Doppler and were therefore excluded from the analysis.
- All patients were clinically evaluated by a neurologist the day before the procedure and after 1 month.

Study design issues:

- The operator's choice of CEA or CAS was based on anatomical characteristics and patient comorbidities.
- Patients were monitored continuously with transcranial Doppler during the procedure to detect intraoperative embolisation.

Study population issues:

- There was a significant difference in age between the 3 groups: mean age was 71 in the CASfr group, 66 in the CEA group and 62 in the CASdp group (p=0.048).

Other issues: Not reported.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **34 (16 CASfr versus 10 CEA versus 8 CASdp)** All procedures were **technically successful** (defined as less than 30% residual stenosis). **Embolisation during the procedure (detected by transcranial Doppler)** • CASdp showed higher embolisation rates than CEA or CASfr in the pre-protection phase (p<0.001). • In the protection phase, CASdp was also associated with more embolisation compared with CEA and CASfr (p<0.001). • In the post-protection phase, no differences between the 3 groups were observed. • CASfr and CEA did not show significant differences in intraoperative embolisation during any of the phases.	**CCA dissection**: 12.5% (2/16) One occurred on introduction of the arterial sheath. For the second one, the Rummel loop was used as a tourniquet to stop inflow, but despite careful manipulation, the heavily calcified CCA was dissected. An additional stent was placed via the transfemoral route in the CCA in each case.
Abbreviations used: CAE, carotid endarterectomy; CAS, carotid artery stenting; CASdp, CAS with distal protection filters; CASfr, transcervical CAS with dynamic flow reversal; CCA, common carotid artery.	

Efficacy

Early stroke (within 30 days of the procedure)

In a comparative study of 64 patients treated by transcervical carotid artery stenting with flow reversal (n=31) or transfemoral carotid artery stenting with distal filter protection (n=33), there were no reports of stroke after stenting in either group. [2]

In a comparative study of 55 patients treated by transcervical carotid artery stenting with flow reversal or transfemoral carotid artery stenting with distal filter protection, 6% (2/31) of patients had a transient ischaemic attack (TIA) and none had a stroke in the transcervical carotid artery stenting group. In the transfemoral carotid artery stenting group, 4% (1/24) of patients had a TIA and 4% (1/24) had a stroke (timing not reported).[3]

In a prospective case series of 212 patients treated by transcervical carotid artery stenting with flow reversal, stroke occurred in 2% (4/212) of patients within 30 days of the procedure; there was 1 TIA and 3 major strokes.[4]

In a case series of 141 patients treated by transcervical carotid artery stenting with extracorporeal reverse flow neuroprotection, ipsilateral stroke within 30 days after the procedure was reported in 1% (2/141) of patients; 1 stroke occurred on the evening of the procedure and the other at 48 hours. The latter was a major protocol violation and the patient should have been excluded from the study because of a significant tandem lesion of the ipsilateral middle cerebral artery that was present before the intervention but not prospectively identified.[5]

In a case series of 97 patients treated by transcervical carotid artery stenting, stroke was reported in 4% (4/97) of patients. There were 2 major strokes (1 ipsilateral motor TIA and 1 contralateral ischaemic attack) and 2 minor strokes. One of the patients with the minor stroke developed worsening hemiparesis and the other one sustained dysarthria; both patients returned to their baseline neurological status within a week. [6]

In a case series of 62 patients treated by transcervical carotid artery stenting, a TIA of the anterior cerebral artery territory that resolved within 12 hours was reported in 1 patient and a stroke with contralateral hemiplegia was reported in 1 patient (no further details provided). [7]

In a case series of 48 patients treated by transcervical carotid artery stenting, a minor stroke occurred in 1 patient and a TIA occurred in another patient during the procedure. The minor stroke developed after the introducer sheath was inserted into the common carotid artery. Postoperative diffusion-weighted MRI showed an ischaemic area in the frontal lobe. On discharge the patient had mild hemiparesis of the right upper extremity. For the TIA, the patient had a hemiparesis of the left arm after the procedure that resolved within hours.[8]

Stroke during long-term follow-up

In the comparative study of 64 patients treated by transcervical carotid artery stenting or transfemoral carotid artery stenting, there were no significant changes in the Rankin stroke scale after the procedure in either group. [2]

In the prospective case series of 212 patients, ipsilateral stroke-free survival rates of 99%±1% (standard error; SE) were reported at 1 year, 2 years and 3 years; an ipsilateral stroke was reported in 1 patient after 30 days.[4]

In the case series of 97 patients treated by transcervical carotid artery stenting, the stroke-free survival rate was 91% at 40 months. [6]

Neurological evaluation

In the comparative study of 64 patients treated by transcervical carotid artery stenting or transfemoral carotid artery stenting, there were no significant changes in the Rankin stroke scale after the procedure in either group. [2]

In the case series of 97 patients, all patients remained neurologically unchanged during the 3-year follow-up. [6]

New ischaemic cerebral lesions within 48 hours of the procedure (identified on diffusion-weighted MRI)

In the comparative study of 64 patients, asymptomatic new ischaemic cerebral lesions were diagnosed on diffusion-weighted MRI in 13% (4/31) of patients in the transcervical group compared against 33% (11/33) in the transfemoral group (p=0.03). [2]

In the case series of 48 patients, there were 16 new ischaemic lesions (diagnosed on diffusion-weighted MRI 3 days after the procedure) in 14% (6/43) of patients (mean of 2.7 lesions per patient, range 2–4). All lesions were ipsilateral to the operated carotid artery. In 4 out of 6 patients, the new lesions remained asymptomatic. [8]

Overall survival

The prospective case series of 212 patients reported a 1-year overall survival of 94%±2% (SE) and of 90%±3% at 2 and 3 years. [4]

Conversion to endarterectomy

In the case series of 97 patients, 3% (3/103) of procedures were converted to endarterectomy. The reasons for the conversions were common carotid dissection with the entry sheath, inability to cross the lesion in the internal carotid artery with the guide wire and severe agitation in 1 patient who needed

conversion to general anaesthesia. In the patient with severe agitation the surgeon chose to proceed with an endarterectomy rather than stenting. [6]

High intensity transient signals identified by transcranial Doppler

In a comparative study of 81 patients treated by transcervical carotid artery stenting with flow reversal (n=36) or carotid endarterectomy (n=45), there were high-intensity transient signals detected by transcranial Doppler sonography during the procedure in 3% (1/36) of patients treated by transcervical carotid artery stenting (not reported for the carotid endarterectomy group). [1]

In the prospective case series of 62 patients, there were perioperative high-intensity transient signals in 6% (2/62) of patients.[7]

Cerebral artery flow velocity

In the comparative study of 81 patients treated by transcervical carotid artery stenting or carotid endarterectomy, there was an increase in mean cerebral artery flow velocity (measured by transcranial Doppler) after completion of the procedure in 100% (36/36) of patients treated by transcervical carotid artery stenting. [1]

In the prospective case series of 62 patients treated by transcervical carotid artery stenting with flow reversal, there was a significant improvement in the middle cerebral artery mean flow velocity and pulsatility index on completion of the procedure.[7]

Safety

Death

Death from myocardial infarction 48 hours after the procedure was reported in 1 patient in a prospective case series of 212 patients treated by transcervical carotid artery stenting with flow reversal.[4]

Death was reported in 2 patients in a case series of 141 patients treated by transcervical carotid artery stenting with flow reversal. One patient died from respiratory failure within 30 days of the procedure and another patient died from myocardial infarction 15 days after the procedure after readmission with pneumonia and diabetic ketoacidosis. [5]

Death was reported in 5% (5/97) of patients within a 3-year follow-up in a case series of 97 patients treated by transcervical carotid artery stenting. Three deaths were reported as not related to stroke and the cause of death could not be determined in 2 patients. [6]

Intolerance to flow reversal

Transient intolerance to flow reversal was reported in 1 patient treated by transcervical carotid artery stenting in a comparative study of 81 patients treated by transcervical carotid artery stenting (n=36) or carotid endarterectomy (n=45). Clamping of the common carotid artery was maintained only during the key steps of the procedure. [1]

Intolerance to flow reversal was reported in 1% (3/219) of procedures in the case series of 212 patients; this was treated by declamping the common carotid artery and rapidly completing the procedure. [4]

No intolerance to flow reversal was reported in the case series of 141 patients but intolerance to high flow was reported in 1 patient. [5]

Intolerance to flow reversal was reported in 4% (3/72) of patients who had the procedure done under local anaesthesia in the case series of 97 patients. In 1 patient, the procedure was completed with antegrade flow without protection. In the second patient, intermittent rather than continuous carotid flow reversal was done, allowing antegrade cerebral flow in between carotid instrumentation manoeuvres. The third patient was converted to carotid endarterectomy.[6]

Intolerance to flow reversal was reported in 1 patient in a case series of 62 patients treated by transcervical carotid artery stenting. The patient lost consciousness a few minutes after the common carotid artery was clamped. The procedure was done extremely rapidly and the patient recovered without sequelae after declamping.[7]

Arterial dissection

Major dissection of the common carotid artery was reported in 1 patient treated by transcervical carotid artery stenting in the comparative study of 81 patients. This was treated by a bypass from the common carotid artery to the distal internal carotid artery.[1]

Arterial dissection was reported in 6% (8/141) of patients in the case series of 141 patients. For 5 dissections, no treatment was needed; they were at the site of the arterial sheath or between the sheath and the carotid bifurcation. For the 3 dissections that needed treatment, 1 procedure was converted to carotid endarterectomy at the original procedure, 1 needed the placement of a second stent during the original procedure and 1 was repaired surgically during the original procedure. One of the patients with a dissection had a minor ipsilateral stroke 8 hours after the procedure. This was judged to be unrelated to the dissection because the second stent had adequately managed the intimal flap.[5]

Common carotid artery dissection was reported in 5% (5/103) of the procedures in the case series of 97 patients. Four dissections occurred at the access site during the first 12 procedures; 1 was repaired surgically with a proximal common carotid interposition graft and 3 resolved after placement of the stent intended to treat the stenosis without additional stenting. The fifth one occurred at vessel

entry during the remaining 91 procedures; the procedure was converted to endarterectomy. [6]

Common carotid artery dissection was reported in 12.5% (2/16) of patients treated by transcervical carotid stenting with dynamic flow reversal in a comparative study of 34 patients treated by transcervical carotid stenting with dynamic flow reversal (n=16), carotid endarterectomy (n=10) or transfemoral carotid artery stenting with distal filter protection (n=8). An additional stent was placed via the transfemoral route in the common carotid artery in each case.[9]

Spasm of the distal carotid during the procedure

Severe spasm of the distal carotid artery was reported in 1 patient treated by transcervical carotid artery stenting in the comparative study of 81 patients. [1]

Severe distal internal carotid spasm was reported in 2% (4/212) of patients in the case series of 212 patients; this was treated with intra-arterial nitroglycerin in 1 patient and it resolved spontaneously after guide wire withdrawal in 3 patients. [4]

Severe distal internal carotid spasm was reported in 2 patients in the case series of 62 patients; this was treated with intra-arterial nitroglycerin.[7]

Distal internal carotid artery spasm was reported in 13% (6/48) of patients in a case series of 48 patients treated by carotid artery stenting with flow reversal. This was treated with intra-arterial nitroglycerin. [8]

Bradycardia or hypotension

Bradycardia and hypotension related to balloon inflation was reported in 6% (2/36) of patients treated by transcervical carotid artery stenting in the comparative study of 81 patients. This was successfully treated with atropine. [1]

Bradycardia was reported in 13% (4/31) of patients in the transcervical carotid artery stenting with flow reversal group and in none of the patients in the transfemoral carotid artery stenting group with distal filter neuroprotection (n=24) in a comparative study of 55 patients. [3]

Bradycardia or hypotension or both needing pharmacological intervention and related to carotid balloon dilatation was reported in 23% (24/103) of procedures in the case series of 97 patients.[6]

Transient bradycardia related to dilation after angioplasty was reported in 15% (9/62) of patients in the case series of 62 patients. In the same study, 1 patient presented with persistent hypotension during the first 12 hours after the procedure and needed an infusion of noradrenaline.[7]

Severe hypotension was reported in 10% (5/48) of patients and bradycardia in 20% (10/48) of patients after the procedure in the case series of 48 patients. In 1 patient, hypotension and bradycardia caused a myocardial infarction. In the other patients, hypotension and bradycardia responded to medication and normalised on discharge.[8]

Cerebral haemorrhage

Extensive cerebral haematoma was reported in 1 patient in the case series of 62 patients; this was identified on a CT scan after the patient returned with hemiplegia and aphasia after an episode of intense headache 48 hours after hospital discharge. It was treated by surgical drainage. [7]

Cranial nerve injury

Transient laryngeal nerve palsy was reported in 1% (2/212) of patients in the case series of 212 patients; this was secondary to impregnation of the nerve with local anaesthesia. [4]

Cranial nerve injury affecting the 10th nerve was reported in 1 patient in the case series of 141 patients; this caused hoarseness, which fully resolved at 6 months.[5]

Wound haematoma

Cervical haematoma was reported in 6% (2/31) of patients treated by transcervical carotid artery stenting in the comparative study of 55 patients; one of the 2 patients was treated by surgical drainage and had no neurological sequelae. [3]

Cervical haematoma was reported in 1 patient in the case series of 212 patients; this was treated by surgical drainage. [4]

Limited surgical wound haematoma for which no treatment was needed was reported in 4% (5/141) of patients in the case series of 141 patients. In the same study, 1 surgical wound haematoma that needed wound exploration and evacuation and 1 localised haematoma at the femoral venous access site that resolved without treatment were also reported. [5]

Wound haematoma was reported in 2% (2/97) of patients in the case series of 97 patients; both were treated by surgical drainage under local anaesthesia. [6]

Cervical haematoma was reported in 1 patient in the case series of 62 patients.[7]

Validity and generalisability of the studies

- There were no randomised controlled trials identified.

- There is up to 3-year follow-up data but long-term follow-up is not necessarily needed.
- Most of the studies[1–4, 6–8] included in table 2 are about transcervical carotid stenting where the shunt is done between the carotid artery and the jugular vein. Two studies[5, 9] use the Enroute transcarotid neuroprotection system, which establishes a shunt between the carotid artery and the femoral vein and which also allows regulation of the blood flow.
- There are probably overlaps of patients between 3 studies[1,4,7].
- Some studies use diffusion-weighted MRI [2, 8] to identify new lesions after the procedure and the clinical relevance of this method is not yet established.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

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

- Carotid artery stent placement for symptomatic extracranial carotid stenosis. NICE interventional procedure guidance 389 (2011). Available from http://www.nice.org.uk/guidance/ipg389
- Carotid artery stent placement for asymptomatic extracranial carotid stenosis. NICE interventional procedure guidance 388 (2011). Available from http://www.nice.org.uk/guidance/ipg388

NICE guidelines

- Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE guideline 68 (2008). Available from https://www.nice.org.uk/guidance/cg68

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 is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing studies

- NCT01685567 Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (ROADSTER). Location: United States and Spain. Recruiting. Estimated enrolment: 283 patients. Estimated completion date: June 2015.
- NCT01958294 The MICHI NEUROPROTECTION SYSTEM: Evaluation of Performance in Carotid Artery Stent Procedures (The LOTUS Study). Location: UK. Recruiting. Estimated enrolment: 40 patients. Estimated completion date: July 2014.
- NCT01877174 MICHI Neuroprotection System (NPS+f) Filter Debris Analysis Study (The F-1 Study). Location: Belgium, Germany, Spain. Completed – no published results as yet. Estimated enrolment: 24 patients. Estimated completion date: October 2013.

References

1. Alvarez B, Ribo M, Maeso J et al. (2008) Transcervical carotid stenting with flow reversal is safe in octogenarians: a preliminary safety study. Journal of Vascular Surgery 47:96-100.
2. Leal I, Orgaz A, Flores A et al. (2012) A diffusion-weighted magnetic resonance imaging-based study of transcervical carotid stenting with flow reversal versus transfemoral filter protection. Journal of Vascular Surgery 56:1585-1590.
3. Lin JC, Kolvenbach RR, and Pinter L. (2005) Protected carotid artery stenting and angioplasty via transfemoral versus transcervical approaches. Vascular & Endovascular Surgery 39:499-503.
4. Alvarez B, Matas M, Ribo M et al. (2012) Transcervical carotid stenting with flow reversal is a safe technique for high-risk patients older than 70 years. Journal of Vascular Surgery 55:978-984.
5. Kwolek CJ, Jaff MR, Leal JI et al. (2015) Results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal. J Vasc.Surg 62:1227-1234.
6. Criado E, Fontcuberta J, Orgaz A et al. (2007) Transcervical carotid stenting with carotid artery flow reversal: 3-year follow-up of 103 stents. Journal of Vascular Surgery 46:864-869.
7. Matas M, Alvarez B, Ribo M et al. (2007) Transcervical carotid stenting with flow reversal protection: experience in high-risk patients. Journal of Vascular Surgery 46:49-54.
8. Faraglia V, Palombo G, Stella N et al. (2009) Cerebral embolization during transcervical carotid stenting with flow reversal: a diffusion-weighted magnetic resonance study. Annals of Vascular Surgery 23:429-435.
9. Plessers M, Van HI, Hemelsoet D et al. (2016) Transcervical Carotid Stenting With Dynamic Flow Reversal Demonstrates Embolization Rates Comparable to Carotid Endarterectomy. Journal of Endovascular Therapy 1-6.

Appendix A: Additional papers on transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting

The following table outlines the studies that are considered potentially relevant to the IP 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.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Chang DW, Schubart PJ, Veith FJ et al. (2004) A new approach to carotid angioplasty and stenting with transcervical occlusion and protective shunting: Why it may be a better carotid artery intervention. Journal of Vascular Surgery 39:994-1002.	Case series n=21 FU=2 years	Transcervical occlusion and protective shunting (TOPS) solves problems of access, embolisation into the cerebral and peripheral circulation, and specialised cerebral protection devices, and enables secure closure of the access vessel in patients given anticoagulation therapy. TOPS may provide a safer, more effective, economical means for performing CAS.	Larger studies or studies with longer follow-up already included in Table 2.
Criado E, Doblas M, Fontcuberta J et al. (2004) Carotid angioplasty with internal carotid artery flow reversal is well tolerated in the awake patient. Journal of Vascular Surgery 40:92-97.	Case series n=10 FU=2 months	Transcervical carotid angioplasty and stenting with ICA flow reversal is well tolerated in the awake patient, even in the presence of symptomatic carotid artery disease. Cerebral oxygenation during ICA flow reversal is comparable to that during CCA occlusion. ICA angioplasty balloon inflation produces a decrease in cerebral SVO2 significantly greater than that occurring during ICA flow reversal.	Larger studies or studies with longer follow up already included in Table 2.
Criado E, Doblas M, Fontcuberta J et al. (2004) Transcervical carotid stenting with internal carotid artery flow reversal: feasibility and preliminary results. Journal of Vascular Surgery 40:476-483.	Case series n=50 FU=1 year	Transcervical CAS with carotid flow reversal is feasible and safe. It can be done with the patient under local anesthesia, averts the complications of the transfemoral approach, and eliminates the increased complexity and cost of cerebral protection devices. Transcervical CAS is feasible when the transfemoral route is impossible or contraindicated, and may be the procedure of choice in a subset of patients in whom carotid stenting is indicated.	Same study population as in the Criado (2007) study with a 3-year follow-up which is included in Table 2.
Leal I, Rodriguez R, Peinado J et al. (2010) A prospective evaluation of cerebral infarction following transcervical carotid stenting: Results of neuroprotection with carotid flow reversal technique. Interactive Cardiovascular and Thoracic Surgery 10:S56-	Case series n=31 FU=30 days	Transcervical carotid stenting with carotid flow reversal carries a low incidence of new ischaemic infarcts, significantly lower than that reported with transfemoral CAS. The transcervical approach with carotid flow reversal may improve the safety of CAS, and has the potential to produce results at least comparable to that of carotid endarterectomy.	Same study population as in the Leal (2012) comparative study which is included in Table 2.
Ortega G, Alvarez B, Quintana M et al. (2014) Asymptomatic carotid stenosis and cognitive improvement using transcervical stenting with protective flow reversal technique. European Journal of Vascular & Endovascular Surgery 47:585-592.	Case series n=25 FU=6 months	Revascularisation by transcervical CAS with flow reversal for cerebral protection results in improved neurocognitive performance in asymptomatic elderly patients with severe carotid artery stenosis.	Larger studies or studies with longer follow-up already included in Table 2.
Ortega G, Alvarez B, Quintana M et al. (2013) Cognitive improvement in patients with severe carotid artery stenosis after transcervical stenting with protective flow reversal. Cerebrovascular Diseases 35:124-130.	Case series n=46 FU=6 months	Transcervical CAS and stenting with flow reversal for cerebral protection is a safe technique that will improve, or at least not worsen, cognitive performance.	Larger studies or studies with longer follow-up already included in Table 2.
Pipinos II, Johanning JM, Pham CN et al. (2005) Transcervical approach with protective flow reversal for carotid angioplasty and stenting. Journal of Endovascular Therapy 12:446-453.	Case series n=17 FU=12 months	Transcervical approach is a viable alternative for CAS. The procedure can be performed safely, with good initial clinical outcomes. The approach allows carotid flow reversal and emboli protection without introducing	Larger studies or studies with longer follow-up already included in Table 2.

		neuroprotection devices. The method appears best suited for patients at high risk for endarterectomy and transfemoral access.	
Pinter L, Ribo M, Roberts T et al. (2011) First clinical use of a novel neurovascular access and neuroprotection system demonstrates complete absence of emboli by transcranial Doppler during carotid artery stenting. Journal of Cardiovascular Surgery 52:853-857.	Single case report FU=30 days	The lesion was successfully treated with transcervical carotid access and reverse flow embolic protection (MICHI system) and the successful placement of a carotid stent followed by balloon post-dilatation. 2 micro embolic signals were recorded over the 30-minute procedure. There were no neurological complications reported during the follow-up period.	Larger studies or studies with longer follow-up already included in Table 2.
Pinter L, Ribo M, Loh C et al. (2011) Safety and feasibility of a novel transcervical access neuroprotection system for carotid artery stenting in the PROOF Study. Journal of Vascular Surgery 54:1317-1323.	Case series n=44 FU=30 days	In this first-in-man experience, Flow Altered Short Transcervical-CAS using the MICHI Neuroprotection System was shown to be a safe and feasible method for carotid revascularisation. Diffusion weighted-MRI findings suggest controlled reverse flow provides cerebral embolic protection similar to that seen with CEA.	Larger studies or studies with longer follow-up already included in Table 2.
Ribo M, Molina CA, Alvarez B et al. (2006) Transcranial Doppler monitoring of transcervical carotid stenting with flow reversal protection: a novel carotid revascularization technique. Stroke 37:2846-2849.	Case series n=23 FU=None	Transcervical carotid stenting with protective internal carotid artery flow reversal can eliminate showers of micoremboli during stent deployment making it a promising carotid revascularisation technique in high-risk patients with carotid stenosis.	Larger studies or studies with longer follow-up already included in Table 2.

Appendix B: Related NICE guidance for transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting

Guidance	Recommendations
Interventional procedures	**Carotid artery stent placement for symptomatic extracranial carotid stenosis. NICE interventional procedure guidance 389 (2011)** 1.1 Current evidence on the safety and efficacy of carotid artery stent placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit or research. 1.2 During the consent process, clinicians should ensure that patients understand the risk of stroke and other complications associated with this procedure. Clinicians should also ensure that patients understand the reasons for advising carotid artery stent placement rather than endarterectomy in their particular case. 1.3 Patient selection should be carried out by a multidisciplinary team, which should include an interventional radiologist or a neuroradiologist, a vascular surgeon and a physician with a specialist interest in stroke. 1.4 This procedure should only be carried out by clinicians with specific training and expertise in the technique who regularly perform complex endovascular interventions. The Royal College of Radiologists has produced training standards. **Carotid artery stent placement for asymptomatic extracranial carotid stenosis. NICE interventional procedure guidance 388 (2011)** 1.1 Current evidence on the safety of carotid artery stent placement for asymptomatic extracranial carotid stenosis shows well-documented risks, in particular the risk of stroke. The evidence on efficacy is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake carotid artery stent placement for asymptomatic extracranial carotid stenosis should take the following actions. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy, the risk of

	stroke and other complications, and the reasons for advising stenting rather than endarterectomy or best medical treatment alone in their particular case. Patients should be provided with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. 1.3 Patient selection should be carried out by a multidisciplinary team, which should include an interventional radiologist or a neuroradiologist, a vascular surgeon and a physician with specialist interest in stroke. Cardiac surgeons and cardiologists should liaise with the multidisciplinary team in relation to patients being considered for this procedure as a prelude to cardiac surgery. 1.4 This procedure should only be carried out by clinicians with specific training and expertise in the technique who regularly perform complex endovascular interventions. The Royal College of Radiologists has produced training standards. 1.5 NICE encourages clinicians either to enter patients into the ACST-2 trial (Asymptomatic Carotid Artery Surgery Trial 2) or to submit data to the Endovascular Carotid Register, run by the British Society of Interventional Radiology and the Vascular Society of Great Britain and Ireland. NICE may review this procedure on publication of further evidence.
NICE guidelines	**Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE guideline 68 (2008)** 1.2.4 Urgent carotid endarterectomy and carotid stenting 1.2.4.1 People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of 50–99% according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria, or 70–99% according to the ECST (European Carotid Surgery Trialists' Collaborative Group) criteria, should: • be assessed and referred for carotid endarterectomy within 1 week of onset of stroke or TIA symptoms • undergo surgery within a maximum of 2 weeks of onset of stroke or TIA symptoms • receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice). 1.2.4.2 People with stable neurological symptoms from acute non-disabling stroke or TIA who have symptomatic carotid stenosis of less than 50% according to the NASCET criteria, or

	less than 70% according to the ECST criteria, should: • not undergo surgery • receive best medical treatment (control of blood pressure, antiplatelet agents, cholesterol lowering through diet and drugs, lifestyle advice). 1.2.4.3 Carotid imaging reports should clearly state which criteria (ECST or NASCET) were used when measuring the extent of carotid stenosis.

Appendix C: Literature search for transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	23/02/2016	Issue 2 of 12, February 2016
Cochrane Central Database of Controlled Trials - CENTRAL	23/02/2016	Issue 1 of 12, January 2016
HTA database (Cochrane)	23/02/2016	Issue 1 of 4, January 2016
MEDLINE (Ovid)	23/02/2016	1946 to February Week 2 2016
MEDLINE In-Process (Ovid)	23/02/2016	February 22, 2016
EMBASE (Ovid)	23/02/2016	1974 to 2016 Week 08
PubMed	23/02/2016	n/a
JournalTOCS [for update searches only]	23/02/2016	n/a

Trial sources searched on 14/09/2015

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 14/09/2015

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

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

1 exp Carotid Artery Diseases/

2 Atherosclerosis/

3 (carotid* adj4 (stenos* or insufficien* or incompeten* or regurgitat* or trauma* or disorder* or disease* or occlus* or atheroscleros* or artherogenes* or injur* or thrombos* or narrow* or block*)).tw.

4 or/1-3

5 carotid arteries/

6 (carotid* adj4 arter*).tw.

7 or/5-6

8 Angioplasty/

9 Catheterization/

10 Stents/

11 or/8-10

12 7 and 11

13 (carotid* adj4 (stent* or sheath* or catheter* or angioplast*)).tw.

14 ((transcervical or transcarotid or transfemoral) adj4 access*).tw.

15 CAS.tw.

16 or/12-15

17 FAST-CAS.tw.

18 ((enroute or michi or gore) adj4 system*).tw.

19 Embolic Protection Devices/

20 (neuroprotect* adj4 (extracorporeal* or system*)).tw.

21 ((flow* or circulat*) adj4 (retrograde* or revers* or alter*)).tw.

22 ((cerebral* or brain* or embolic*) adj4 protect*).tw.

23 Cerebrovascular Circulation/

24 (cerebro* adj4 circulat*).tw.

25 or/17-24

26 exp Stroke/

27 Ischemic Attack, Transient/

28 stroke*.tw.

29 (transient adj4 (ischemic or ischaemic) adj4 attack*).tw.

30 TIA.tw.

31 Intracranial Embolism/

32 (intracranial adj4 emboli*).tw.

33 or/26-32

34 4 and 16 and 25 and 33

35 Animals/ not Humans/

36 34 not 35