NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of extracranial to intracranial bypass for intracranial atherosclerosis

In cerebrovascular disease, blood vessels in the head or neck become narrowed or blocked, limiting the blood supply to the brain. Extracranial to intracranial bypass surgery may improve blood flow to the brain by joining a blood vessel from outside the skull to one inside the skull, bypassing the blocked vessel and helping to prevent stroke.

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 April 2017.

Procedure name

- Extracranial to intracranial bypass for intracranial atherosclerosis

Specialist societies

- Society of British Neurological Surgeons
- Royal College of Surgeons of England.

Description

Indications and current treatment

Intracranial atherosclerosis is usually a progressive condition which narrows and hardens the blood vessels supplying the brain, limiting its blood supply. This can cause transient ischaemic attacks or permanent neurological damage (stroke).

Conservative management of atherosclerosis includes smoking cessation, antiplatelet, lipid-lowering and antihypertensive medication. Endovascular techniques (angioplasty or stenting) may be used to dilate an arterial narrowing.

What the procedure involves

The aim of extracranial to intracranial (EC–IC) bypass for intracranial atherosclerosis is to increase blood flow in intracranial arteries to relieve symptoms of cerebral hypoperfusion or reduce the risk of stroke. With the patient under general anaesthesia, the extracranial donor artery (usually the superficial temporal artery) is joined (anastomosed) to a superficial cerebral artery (usually a subpial middle cerebral artery branch) using a mini-craniotomy. Typically, an end-to-side anastomosis is used. A graft (for example a radial artery or a saphenous vein graft) may be needed when more distant vessels are anastomosed to allow higher flow.

Careful pre-operative planning involving using ultrasound, angiography, computed tomography (CT), single-photon emission CT scanning or brain reserve testing is needed.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to extracranial to intracranial bypass for intracranial atherosclerosis. The following databases were searched, covering the period from their start to 15 of November 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 intracranial atherosclerosis.
Intervention/test	Extracranial to intracranial bypass for intracranial atherosclerosis.
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 about 4,295 patients from 2 systematic reviews, 3 randomised controlled trials and 4 case series.

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 extracranial to intracranial bypass for intracranial atherosclerosis

Study 1 Fluri F (2010)

Details

Study type	**Systematic Review** (2 RCTs and 19 non-randomised studies) International
Country	Switzerland
Recruitment period	papers published up to June 2009
Study population and number	**n=2,591**, patients with symptomatic carotid artery occlusion
Age and sex	Not reported.
Patient selection criteria	Occlusion showed angiographically with less than 50% stenosis of the contralateral internal carotid artery. Patients with transient ischaemic monocular blindness were not eligible unless hemispheric symptoms were also present. All studies included patients with non-atherosclerotic conditions (for example carotid dissection, fibromuscular dysplasia, Moyamoya disease and arteritis)
Technique	EC-IC bypass plus best medical treatment versus best medical treatment only. The systematic review is divided in 2 parts: Part 1 (analysing RCTs only) and Part 2 (analysing all studies except for the RCTs). Death or dependency outcome used a modified Rankin Scale (independence= 0 to 2, dependence=3 to 5). If a Glasgow outcome scale (1= good outcome, 5= death) was used, good recovery and moderate disability were used as surrogates for independence and severe disability and persistent vegetative state as dependence.
Follow-up	**56 months and 25 months for 2 RCTS (not reported for 19 non-randomised studies).**
Conflict of interest/source of funding	The authors received an in-house grant from the Department of Neurology, University Hospital Basel, to do the review.

Analysis

Follow-up issues: Unclear how many patients were lost to follow-up in each of the studies included.

Study design issues: Cochrane review. Comprehensive literature search. Two review authors independently selected the studies for inclusion. Loss to follow-up or dropouts were assessed in each study. Authors used an intention-to-treat analysis. There were 118 patients who did not meet the inclusion criteria and were excluded from the analysis published in 1985 (EC/IC Bypass Study 1985), that were also included in the systematic review. Authors report that the overall quality of included studies was poor.

Study population issues: Most studies included patients irrespective of their cerebral haemodynamics.

Included studies:
2 RCTs: EC/IC bypass study 1985, JET 2006
19 Non-randomised studies: Auer 1980, Benvenuti 1984, De Weerd 1989, Hartmann 1987, Heilbrun 1982, Ishikawa 1992, Jeffree 2009, Jordan 1984, Karnick 1992, Kobayashi 1991, Ma 2007, Powers 1989, Satiani 1985, Tanahashi 1985, Thomas 1984, Yasui 1991, Yonas 1996, Yoshimoto 1995, Yoshinaga 1996.

Other issues: Percentage of patients with non-atherosclerotic diseases included in the original trials was not stated by the authors. This study was included in table 2 in the previous version of the guidance.

Key efficacy and safety findings

Efficacy	Safety
n=2,591 Overall conclusion: EC/IC bypass surgery with best medical treatment was not superior or inferior to best medical treatment alone. **PART 1 - RCTs (n = 1,691)** Any stroke: OR: 0.99 (95% CI: 0.79 to 1.23, p = 0.91) (2 RCTs, n=1,691) Ischaemic stroke: OR: 0.69 (95% CI 0.44 to 1.08, p=0.11) (2 RCTs, n=1,573) **PART 2 - non-randomised studies (n=900)** Any Stroke: OR 0.80 (95% CI: 0.54 to 1.18, p = 0.25) (18 studies, n=881) Ischaemic stroke: OR: 0.72 (95% CI 0.44 to 1.18, p=0.19) (13 studies, n=640) Intracranial haemorrhage: OR: 1.14 (95% CI: 0.44 to 2.93, p = 0.79) (4 studies, n=361) TIA or amaurosis: OR: 0.34 (95% CI: 0.16 to 0.69, p = 0.003) (11 studies, 524 studies) [favours surgical group] Failure to normalise cerebral haemodynamics: OR: 6.63 (95% CI 1.85 to 23.78) (3 studies, n=56)	**PART 1 - RCTs (n = 1,691)** **Follow-up of 56 months and 25 months** All-cause mortality: OR: 0.81 (95% CI: 0.62 to 1.05, p = 0.11) (2 RCTS, n=1,691) Death or dependency: OR: 0.94 (95% CI: 0.74 to 1.21, p = 0.64) (1 RCT, n=1,377) Vascular death[1]: OR: 0.96 (95% CI: 0.71 to 1.29, p = 0.77) (1 RCT) Stroke, vascular event or vascular death: OR: 0.68 (95% CI: 0.51 to 0.91, p = 0.009) [favours surgical group] (2 RCTs, n=1,573) Myocardial infarction: OR: 0.78 (95% CI: 0.46 to 1.32, p = 0.35) (2 RCTs, n=1522) **PART 2 - non-randomised studies (n=900)** All-cause mortality: OR: 1.00 (95% CI: 0.62 to 1.62, p = 0.99) (11 studies, n=900) Death or dependency: OR 0.80 (95% CI: 0.50 to 1.29, p = 0.37) (8 studies, n=346) Vascular death: OR: 0.95 (95% CI: 0.5 to -1.63, p = 0.86) (19 studies, n=900) Stroke, serious vascular events or vascular death: OR: 0.69 (95% CI: 0.45 to 1.04, p = 0.079) (13 studies, n=673) Myocardial infarction: OR: 2.67 (95% CI: 0.41 to 17.60, p = 0.31) (2 studies, n=79) [1]Death from stroke or its complications, coronary artery disease or its complications, sudden death, pulmonary embolism, peripheral vascular disease, haemorrhage.
Abbreviations used: EC-IC, extracranial- intracranial; JET, Japanese EC-IC bypass trial; OR, odds ratio; nRCS, non-randomised comparative studies; RCT, randomised controlled trial, TIA, transient ischaemic attack.	

Study 2 Garrett MC (2009)

Details

Study type	**Systematic review** (23 case series)
Country	USA
Recruitment period	1985 to 2007
Study population and number	**n=506**, patients with symptomatic haemodynamic failure secondary to atherocclusive disease
Age and sex	Not reported
Patient selection criteria	The included studies reported outcomes of patients with compromised cerebral haemodynamics (defined on dynamic testing, for example with xenon-enhanced CT, looking at degree of vascular dilation response after acetazolamide infusion or CO_2 inhalation; or using PET scanning to calculate oxygen extraction fraction) treated by EC-IC bypass.
Technique	The literature review used Medline together with manual search for relevant articles. Articles were divided is 3 categories: natural history of patients with stage I haemodynamic failure (16 studies, 2,320 patients), natural history of patients with stage II haemodynamic failure (3 studies, 163 patients) and outcomes of patients with haemodynamic failure treated by EC-IC bypass.
Follow-up	**14 days to 67 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Unclear how many patients were lost to follow-up in each of the included studies.

Study design issues: Only MEDLINE searched and only English language articles included. Lack of information on the quality, inclusion criteria and completeness of follow-up in the studies included in the review.

The author has identified publication bias towards reporting positive surgical outcomes. The author reported that most studies were underpowered and included poor or no control groups; patients were never randomised and study heterogeneity was considerable (designs, methodologies, management and patient populations).

Study population issues: Age and sex have not been reported because data are only available for 4 and 5 studies respectively.

The nature of the studies is not clear, in particular whether the studies were comparative. Some comparative analysis is presented in the paper, but the comparators and the methods used to produce these estimates are not described, therefore these data were not extracted and are not presented in the table

Other issues: One study (Ma 2007, n=11) was also included in the systematic review by Fluri 2010. This study was included in table 2 in the previous version of the guidance.

Key efficacy and safety findings

Efficacy

n=506

Stroke (reported by 6 of the 23 studies)

Study	Follow-up (months)[1]	Overall stroke rate	Annual stroke rate
Ma (2007)	12	17% (1/6)	17%
Schick (1996)	67 (mean)	21% (10/47)	4%
Przybylski (1998)	18	0%	0%
Schmiedek (1994)	34	4 % (1/28)	2%
Sasoh (2003)	18	0%	0.0%
Takagi (1997)	17 to 5	0%	0.0%
Total	-	9%[2] (12/130)	-

Risk of cerebral infarction (12 months after surgery)

Haemodynamic category	Annual stroke rates		Logistic regression[3]	
	Medically treated	Surgically treated	OR	95% CI
Mild stage I failure[4]	5%	5%	1.00	-
Severe stage I failure	19%	1%	2.18	1.17 to 4.08, p=0.015
Stage II failure[5]	13%	0%	1.80	0.89 to 3.63, p=0.10
Surgery (stage I and II)			0.38	0.16 to 0.92, p=0.03

[1]Unclear if mean, median or protocol length unless otherwise stated

[2]Calculated by IP analyst

[3]The author created a logistic regression model using the mild stage I failure group as control.

[4]Stage I failure – loss of autoregulatory vasodilation

[5]Stage II failure - autoregulatory failure characterised by decreases of cerebral blood flow and increases of oxygen extraction fraction

Safety

No adverse events reported.

Abbreviations used: CI, confidence interval; CT, computerised tomography; EC-IC, extracranial-intracranial; OR, odds ratio.

Study 3 The EC-IC Bypass Study Group (1985)

Details

Study type	**RCT (prospective multicentre)**
Country	International
Recruitment period	1977 to 1982
Study population and number	**n = 1,377** (663 EC-IC bypass vs. 714 medical), patients with symptomatic atherosclerotic disease of the internal carotid artery (ICA)
Age and sex	Bypass group: 56 years (mean), 81.0% (537/663) male Medical group: 56 years (mean), 81.9% (585/714) male
Patient selection criteria	Patients were eligible if within 3 months of entry they had either 1 or more transient ischaemic attack or 1 or more minor completed strokes in the carotid distribution. Arteries appropriate to the patient's symptoms had to have 1 or more of the following atherosclerotic lesions: - stenosis or occlusion of the trunk or major branches before the bifurcation or trifurcation of the middle cerebral artery - stenosis of the ICA at or above the C-2 vertebral body (i.e. place inaccessible to endarterectomy), or occlusion of the internal carotid artery. Patients were excluded if they couldn't meet the following criteria: (i) capability of self-care for most activities of daily living (may need some assistance); (ii) retention of some useful residual function in the affected arm or leg; (iii) comprehension intact with no evidence of Wernicke's receptive aphasia; (iv) no, or only mild, motor (expressive, Broca's) aphasia; (v) ability to handle their own oropharyngeal secretions. **Other exclusion criteria**: inability to provide informed consent; evidence that the original stroke was due to cerebral haemorrhage; within 8 weeks of an acute cerebral ischemic event; exhibition of non-atherosclerotic conditions causing or likely to cause cerebral dysfunction (fibromuscular dysplasia, arteritis, blood dyscrasia, a cardiac source of cerebral emboli, chronic atrial fibrillation, complete heart block, significant valvular heart disease, cardiomyopathy, or non-atherosclerotic dissection); the presence of any morbid condition(s) likely to lead to death within 5 years (cancer, renal failure (BUN >50 mg%), cardiomegaly (cardiothoracic ratio of >0.50 (>0.55 in Japanese patients) or any hepatic or pulmonary disease constituting an unacceptable anaesthetic risk); the occurrence of ischemic symptoms isolated to the vertebrobasilar circulation; previous participation in the study (regardless of the occurrence of new ischemic events or success or failure of previous therapy); myocardial infarction within the preceding 6 months; a fasting blood sugar of 300 mg% or more on the most recent assessment despite appropriate therapy; diastolic blood pressure > 110 mm Hg (using disappearance of sounds for diastolic pressure) despite appropriate medical therapy. Once uncontrolled diabetes or hypertension were corrected, otherwise eligible patients could be entered.
Technique	EC-IC bypass (STA or OA to cortical branch of MCA) plus best medical care vs best medical care. All patients had aspirin (325 mg 4 times per day) throughout the trial unless contraindicated or not tolerated.
Follow-up	**Mean 56 months (range 28 to 90)**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: No patients were lost to follow-up and none were withdrawn. An additional 118 patients were entered into the study but did not meet selection criteria (unclear if they were randomised) and were excluded from this paper. Also, 115 eligible patients refused to enter the trial, 52 other eligible patients did not enter because their physician insisted that they had bypass and 11 other eligible patients did not enter the trial (no reason given).

Study design issues: Decision to exclude ineligible patients was taken by people blinded to treatment assignment and outcome after randomisation.

Randomisation method was satisfactory. Imaging for all patients (unclear what diagnostic test is used) were reviewed by the principle neuroradiologists at the Central Office for the trial. All EC-IC bypass patients had postoperative angiography and these films were reviewed at Central Office.

An intention-to-treat analysis was used – stroke outcomes for 'crossover' patients were recorded in the original treatment limb in the primary analysis. 1.3% (9/714) of medical patients crossed into the bypass arm and had the procedure on the same side as the lesion for which they were randomised. In addition, 0.8% (6/714) of medical patients crossed over to the bypass arm and were operated on the opposite side to the lesion they were randomised for. 1.7% (11/663) of patients randomised to bypass did not undergo the procedure. The procedure was done on average 9 days after randomisation.

No significance test results were reported for comparison of death or stroke between groups.

Study population issues: Characteristics for both groups appear similar; however, no significance tests were reported.

There were 74% of patients with some abnormalities on neurological examination at entry; however, 93% had either minimal or no functional impairment (no n values given).

Other issues: This RCT was included in the systematic review by Fluri (2010)[1]. The exclusion criteria were published in a separate publication. This study was included in table 2 in the previous version of the guidance.

Key efficacy and safety findings

Efficacy

n = 1,377 (663 EC-IC bypass vs 714 medical),

Perioperative ischaemic events (within 30 days of procedure for bypass group and within 39 days of randomisation for medical group)

	Bypass group (n=663)	Medical group (n=714)	Total (n = 1377)
All cerebral and retinal ischaemic events	12% (81/663)	3% (24/714)	8%[a] (105/1377)
Major stroke[b] (before procedure)	2% (10/663)[c]	1% (9/714)	3[a] (39/1377) (reported in abstract as 3%; no n value given)
Major stroke[b] (within 30 days of procedure)	3% (20/663)[d]		

Stroke (56-month follow-up)

Authors reported that surgery contributed to a 14% (90% CI 3 to 34) increase in the relative risk of fatal and nonfatal stroke (Mantel-Haenszel chi-square =1.72) at a mean follow-up of 56 months, p value not reported.

Graft patency

EC-IC bypass group:

- Postoperative bypass patency rate (angiograms conducted at median of 32 days after procedure): 96% (576/600)
- 14% of stenotic lesions of MCA had progressed to occlusion (no patient numbers available).

Functional impairment (all patients)

	Bypass group (n=663)	Medical group (n=714)
None	57% (378/663)	56% (400/714)
Minor[a]	19% (126/663)	19% (136/714)
Major[b]	7% (46/663)	5% (36/714)

Frequencies were calculated by the IP analyst as author reported percentages only.

[a] Defined as difficulty in functioning

[b] Defined as 'inability to function without assistance'

Remaining patients all died.

Safety

Postoperative mortality (within 30 days of procedure for bypass group and within 39 days of randomisation for medical group)

	Bypass group (n=663)	Medical group (n=714)	Total (n=1377)
Mortality	1% (7/663)	0.1% (1/714)	0.6% (8/1377)[a] (reported in abstract as 0.6%; no n value given)
Myocardial infarction	NR	0.1% (1/714)[e]	-

Mortality (56 -month follow-up)

	Bypass group (n=663)	Medical group (n=714)	Total (n=1377)
All-cause mortality	17%[a] (112/663)	20%[a] (140/714)	18%[a] (252/1377)
Cerebrovascular death	5% (31/663)	5% (34/714)	5%[a] (65/1377)
Myocardial infarction death	4% (25/663)	5% (32/714)	4%[a] (57/1377)
Sudden death	2% (10/663)	3% (19/714)	2%[a] (29/1377)
Other cardiovascular death	3% (21/663)	2% (15/714)	3%[a] (36/1377)
Other death	4% (25/663)	6% (40/714)	5%[a] (65/1377)

Frequencies were calculated by the IP analyst as author reported percentages only.

[a]Percentage calculated by IP analyst based on data presented by the author.

Abbreviations used: CI, confidence interval; EC-IC, extracranial to intracranial; ICA, internal carotid artery ; MCA, middle cerebral artery; OA, occipital artery ;STA, superficial temporal artery ; TIA, transient ischemic attack.

Studies 4 & 5 Grubb RL (2013) and Powers (2011) (COSS)

Details

Study type	**RCT**
Country	USA
Recruitment period	2002 to 2010
Study population and number	**n=195** (97 surgical group, 98 to the medical group) patients with complete internal carotid artery (ICA) occlusion and an elevated oxygen extraction fraction in the cerebral hemisphere distal to the carotid occlusion
Age and sex	
Patient selection criteria	Participants with angiographic confirmed complete occlusion of the ICA causing either a TIA or ischemic stroke within 120 days and hemodynamic cerebral ischemia showed by an increased OEF measured by PET were randomised to either surgical or medical treatment. Full eligibility criteria was reported elsewhere.
Technique	The surgical patients had an STA-MCA cortical branch anastomosis. If the STA was not suitable for anastomosis to the MCA, the occipital artery could be used in place of the STA. All surgical patients were placed on 81 mg or 325 mg of aspirin daily before the bypass procedure.
Follow-up	**Median surgical group - 723 days (IQR 288 to 730)** **Median medical group - 722 days (IQR 271 to 730)**
Conflict of interest/source of funding	This research was supported by United states Public Health Service grants from the National Institutes of Neurological Disorders and Stroke.

Analysis

Follow-up issues: The first follow-up visit was 30 to 35 days after randomisation. Surgical participants had a repeat PET scan 30 to 60 days postoperatively. Subsequent follow-up visits were at 3-month intervals until 24 months or the end of the trial. At 2-year follow-up was complete in 99% of patients.

One patient died in the peri-operative period and graft patency data was not recorded in 2 other patients at the 30 day follow-up visit.

Study design issues: This was a parallel group, prospective, 1:1 randomised (via website), open-label, blinded-adjudication treatment trial. An intention-to-treat analysis was used.

Surgeons were certified for the study by: (1) attending an initial training workshop in St. Louis where videotape instruction and surgical practice of microvascular anastomosis was done on frozen cadaver heads and live rat carotid arteries, or (2) showing at least 80% bypass graft patency and less than or equal to 10% stroke and death at one month in at least 10 consecutive STA-MCA bypass surgeries.

The authors reported that for a 5% 2-sided test to have 90% power to detect this difference, 354 participants (177 per group) were needed (nQuery Advisor Version 4, Statistical Solutions, Saugus, MA). To account for death from nonstroke causes, the sample size was increased by 5% to 372.

Study population issues: There were 4 patients randomised to the surgical group that didn't have surgery. There were no strokes between randomisation and surgery. Thirty different surgeons did 92 STA-MCA bypasses and 1 OA-MCA bypass.

Other issues: A previous publication of the trial (Powers 2011) reported it had been stopped for futility in June 2010, but this was because of an error in the interim analysis program. A posterior interim analysis was done (December 2010) using the correct data showing that the pre-specified futility boundary of 35% hadn't been crossed. The trial remained closed nonetheless.

Study methodology was reported in a separate paper (Powers 2011) and electronically: (http://www.ctsdmc.org/projects/coss/inclusionsExclusions.html).

Key efficacy and safety findings

Efficacy

n=195 (97 surgical group, 98 to the medical group)

Bypass patency – 98% (86/90) at mean 605 days (range 28 to 1596) post-operatively[1]

OEF ratio

Baseline – 1.258

30 to 60 day post-operatively – 1.109 (improved)

	Surgical group (n=97)	Medical group n=98)	Difference
Stroke (30-day peri-operative)	14% (14/97)[2]	-	-
Stroke (within 30 days of randomisation)	2% (2/97)	2% (2/98)	-
Ipsilateral ischemic stroke (30 days postoperatively)	14% (14/97)	2% (2/98)	12% (95% CI, 5% to 20%)
Ipsilateral ischaemic stroke (2-year)	21% (95% CI 13 to 29)	23% (95% CI 14 to 32)	2% (95% CI −10 to 14), p=0.81
Graft failure	2% (2/97)		
TIA[3]	4% (4/97)	-	

[1]Patients with available patency data.

[2]Of the 14 stokes 12 occurred within the first 2 days after surgery and 2 occurred at 5 and 15 days after surgery.

[3]At day 30 post-operatively.

Safety

Adverse events (30 days postoperatively)	Surgical group (n=97	Medical group n=98)
Death[4]	1% (1/97)	
Epidural/subdural haematoma	2% (2/97)	-
Seizures	2% (2/97)	-
Myocardial infarction	1% (1/97)	-
Respiratory disorder	1% (1/97)	-
Hypotension	1% (1/97)	-
Wound infection	1% (1/97)	-
DVT*	1% (1/97	-
Atrial flutter*	1% (1/97	-
Cardiac tamponade*	1% (1/97	-
Pulmonary embolus*	1% (1/97	-

[4]Patient had 2 ipsilateral strokes on the day of surgery, a vertebrobasilar artery distribution stroke on postoperative day 1 and died on postoperative day 4.

*Occurred in the same patient.

Abbreviations used: COSS, carotid occlusion surgery study; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; OEF, oxygen extraction fraction; PET, positron emission tomography; TIA, transient ischemic attack.

Study 6 Marshal RS (2014) (RECON trial)

Details

Study type	**RCT**
Country	USA
Recruitment period	2004 to 2012
Study population and number	**n=41 randomised** (19 surgical, 22 medical), patients with symptomatic internal carotid artery (ICA) occlusion and increased oxygen extraction fraction (OEF) on PET.
Age and sex	**Surgical group**: mean 57 (±10 SD), 11 males and 2 females **Medical group**: mean 57 (±8 SD), 12 males and 4 females
Patient selection criteria	**Inclusion criteria:** 1) age 18 to 85, 2) complete ICA occlusion (confirmed by catheter angiography before randomisation), 3) hemispheric transient ischaemic attack (TIA) or minor stroke in the territory of the carotid occlusion within 120 days before enrolment, 4) Barthel Index ≥12/20 at the time of enrolment (after the qualifying event), 5) education level >4 years, 5) no previous diagnosis of dementia. Only patients with asymmetrically increased OEF by PET, with an OEF ratio >1.13 on the side of occlusion (stage II hemodynamic failure) were included. Non-atherosclerotic causes of carotid occlusion were excluded.
Technique	At baseline and at 2 years, patients had a 1-hour neurocognitive battery consisting of 14 standardised neuropsychological tests, administered by a neuropsychologist or trained technician blinded to the patient's treatment arm. The battery was designed to assess left hemisphere function, right hemisphere function, and global function. Patients also completed the Centre for Epidemiological Studies depression (CES-D) scale (range 0 to 60, a score of 16 points or more indicates depression).
Follow-up	**2 years**
Conflict of interest/source of funding	The authors were supported by the National Institute of Neurological Disorders and Stroke.

Analysis

Follow-up issues: All patients were administered all 14 neurocognitive tests.

Eighty-nine patients were enrolled; 41 had increased OEF and were randomised. Two died (medical arm), 2 were lost to follow-up (surgical arm), and 2 refused 2-year testing (medical arm). Of the 35 remaining, 6 had ipsilateral stroke or death (4 surgical and 2 medical), leaving 13 surgical and 16 medical patients.

Study design issues: The 1:1 randomisation was done as part of the parent clinical trial (COSS) using permuted blocks with stratification for clinical site using the SAS uniform random number generator. Cognitive assessments were done by testers blinded to the treatment arm.

A power calculation based on definitions of small, moderate, and large effect size determined that a sample population greater than 30 randomised patients was needed to identify a large effect size of 0.8 SD for the primary outcome.

Study population issues: Average neurocognitive composite z score at baseline across all patients was 1.2 SD below the age- and education-adjusted mean (range 23.7 to 20.3); there was no difference in cognitive scores between groups at baseline.

Other issues: The RECON study was an ancillary study of the COSS. Studies samples overlap.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>n=13 surgical and 16 medical patients

<table>
<tr><th></th><th>Surgical group</th><th>Medical group</th><th>p</th></tr>
<tr><td>OEF PET ratio (baseline)</td><td>1.2 (0.15)</td><td>1.2 (0.06)</td><td>0.5</td></tr>
<tr><td>OEF PET ratio (30-day postoperatively)</td><td>1.14
p=0.013</td><td>-</td><td>-</td></tr>
<tr><td>CES-D baseline</td><td>18
(SD 9)</td><td>18
(SD 12)</td><td>0.84</td></tr>
</table>

<u>Neurocognitive function</u>
Controlling for age, education, depression and baseline composite neurocognitive z score, no difference was found in the change of composite z score between groups over the 2-year follow-up: point estimate 0.02, (95% CI 20.50 to 0.54), p=0.93.

<u>Univariate analysis of independent variables for patients with no ipsilateral stroke</u> (n=26)
<table>
<tr><th>Variable</th><th>Estimate</th><th>SE</th><th>95% CI</th><th>p</th></tr>
<tr><td>Treatment (medical =0, surgical=1)</td><td>0.087</td><td>0.20</td><td>-0.32 to 0.50</td><td>0.67</td></tr>
<tr><td>CES-D 2-year</td><td>-0.0072</td><td>0.013</td><td>-0.034 to 0.020</td><td>0.59</td></tr>
<tr><td>Change in CES-D</td><td>-0.0064</td><td>0.011</td><td>-0.03 to 0.017</td><td>0.58</td></tr>
</table>

[a]PET ratio of OEF ipsilateral-to-contralateral. Significant after multivariable analysis.</td><td>No safety events reported.</td></tr>
<tr><td colspan="2">Abbreviations used: : COSS, carotid artery surgery study; ICA, internal carotid artery; MCA, middle cerebral artery; OEF, oxygen extraction fraction; PET, positron emission tomography; RECON, randomised evaluation of carotid occlusion and neurocognition; SAS, statistical analysis system; SD, standard deviation; SE, standard error; TIA, transient ischemic attack.</td></tr>
</table>

Studies 7 & 8 Taylor AW (2014) and Amin-Hanjani S (2005)

Details

Study type	**Case series (retrospective)**
Country	USA
Recruitment period	Taylor (2014): 2004 to 2010 Amin-Hanjani (2005): 1992 to 2001
Study population and number	Taylor (2014): **n=876** (249 EC-IC and 627 ICS) Amin-Hanjani (2005): **n = 415** (patients with occlusive cerebrovascular disease)
Age and sex	Taylor (2014) **EC-IC group**: mean 53.3 years (±14.2), 48% male I**CS group**: mean 62.2 years (±14.2), 54 % male Amin-Hanjani (2005): mean 60 years, 57% (237/415) male
Patient selection criteria	Taylor (2014) The National Inpatient Sample (NIS) was searched for patients with the relevant ICD-9 intracranial atherosclerotic disease who had EC-IC bypass or ICS during the years 2004 to 2010. Amin-Hanjani (2005) Patients on the NIS hospital discharge database with relevant ICD-9-CM procedure codes and diagnosis of unruptured IC aneurysm, subarachnoid haemorrhage and ischaemic cerebrovascular disease from 1992 to 2001 who had an EC-IC bypass.
Technique	Retrospective database analysis. Patient characteristics, demographics, perioperative complications, outcomes, and discharge data were collected. Taylor (2014) Comorbidity score was calculated based on the Elixhauser comorbidity scoring system.
Follow-up	**Hospital discharge**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: None reported.

Study design issues: Population based case series.

The publication by Amin-Hanjani (2005) included patients with intracranial aneurysms. The results are split by patient type so only the cerebrovascular patients are reported here.

Study population issues: The NIS database represents about 20% of all inpatient admissions to non-federal hospitals in the USA.

Taylor (2014)

Patients treated by ICS were significantly older than those treated by EC-IC bypass (62.2± 14.2 years versus 53.3± 14.2 years; $P < 0.001$), had a significantly higher mean number of comorbidities (2.4± 1.6 comorbidities versus 2.1± 1.5 comorbidities; $P = 0.027$), were more frequently symptomatic at presentation (61.2% versus 50.6%; $P = 0.004$) and were more often admitted non-electively (67.5% versus 44.2%; $P < 0.001$).

Amin-Hanjani (2005)

It was not possible to distinguish the type of bypass patients were treated with. Patency of graft bypass and postoperative neurological state not reported. A small number of bypasses were

done in patients that were initially diagnosed with a tumour. These were very few and too diversified to report in detail, and were included in the analysed population.

Other issues:

Amin-Hanjani (2005)

Authors report in the discussion section that Medicare stopped reimbursing EC-IC bypass for treatment or prevention of stroke (41.0% [170/415] of the study sample were Medicare patients). This paper was included in table 2 in the previous version of the guidance.

Key efficacy and safety findings

Efficacy

Taylor (2014)

n=876 (249 EC-IC and 627 ICS)

	EC-IC (n=249)	ICS (n=627)	p
Asymptomatic Patients			
Admission*	**n=123**	**n=243**	
Nonelective	25% (31/123)	37% (89/243)	0.037
Elective	75% (92/123)	63% (154/243)	
Post-procedure stroke	2% (2/123)	4% (10/243)	0.341
Discharge*	**n=121**	**n=237**	
Home	84% (102/121)	91% (216/237)	0.08
Transfer	16% (19/121)	9% (21/237)	
Symptomatic patients			
Admission*	**n=126**	**n=384**	
Nonelective	63% (79/126)	87% (334/384)	<0.001
Elective	37% (47/126)	13% (50/384)	
Post-procedure stroke	25% (32/126)	10% (40/384)	<0.001
Discharge*	**n=121**	**n=338**	
Home	34% (41/121)	47% (158/338)	0.02
Transfer	66% (80/121)	53% (180/338)	

Multivariate analysis
Symptomatic patients treated by ICS were 2.6 times more likely to experience post-procedure stroke (p=0.011) than asymptomatic patients.
Symptomatic patients treated by EC-IC were 18.1 times more likely to experience post-procedure stroke than asymptomatic patients (p<0.001).

Amin-Hanjani (2005)

n= 415 with occlusive cerebrovascular disease (patients with subarachnoid haemorrhage and aneurysms have been excluded)

Condition	Discharge home	Discharge to STF	Discharge to LTF	Total[a]
Occlusive cerebrovascular disease without stroke	86% (295/343)	9% (32/343)	3% (11/343)	99% (338/343)
Occlusive cerebrovascular disease with stroke	59% (41/69)	25% (17/69)	9% (6/69)	93% (64/69)
All occlusive cerebrovascular	82% (336/412)	12% (49/412)	4% (17/412)	98% (402/412)

*Frequencies calculated by the IP analyst given the percentages and mortality data

[a]Remaining 10 patients died in hospital

Safety

Taylor (2014)

Mortality

Asymptomatic patients EC-IC 1.6% (2/123) versus ICS 2.5% (6/243), p=0.887

Symptomatic patients EC-IC 4% (5/126) versus ICS 12% (46/384), p=0.015

Overall mortality
EC-IC 3% (7/249) versus ICS (8% (52/627), p<0.001)

Multivariate analysis
Symptomatic patients treated by ICS were 6.1 times more likely to die (p=0.011) than asymptomatic patients.

Multivariate analysis identified symptomatic presentation as the strongest predictor of death in patients treated by EC-IC bypass, but this did not reach statistical significance (p=0.241).

Amin-Hanjani (2005)

Death occurred in 1% (5/343) of the patients with occlusive cerebrovascular disease without stroke and 7% (5/69) in the stroke group. Total mortality was 2% (10/412).

Haemorrhage, haematoma complicating the procedure, hydrocephalus, ventriculostomy, mechanical ventilation, deep vein thrombosis, pulmonary embolism and placement of an inferior vena cava filter were described as complications for EC-IC bypass but no rates in the population were reported.

Abbreviations used: EC-IC, extracranial to intracranial; ICS, intracranial stenting; ICD-9-CM, international classification of diseases and related healthcare problems; LTF, long term facility; STF, short term facility.

Study 9 Kataoka M (2015) (JET-2)

Details

Study type	**Case series** (prospective multicentre)
Country	Japan
Recruitment period	2002 to 2007
Study population and number	**n=132** (18 Group A, 31 Group B, 26 Group C, 56 Group D), patients with haemodynamic ischemia due to asymptomatic major cerebral arterial occlusive diseases (n=103, medical arm of the JET study)
Age and sex	- Group A: mean 64.1 (±6.7), 78% males - Group B: mean 62.4 (±8.4), 90% males - Group C: mean 58.2 (±11.5), 85% males - Group D mean 60.9 (±9.3), 80% males
Patient selection criteria	Inclusion criteria: age under 73 years at the time of registration, independent on daily life (modified Rankin disability scale score of 0 to 2); lack of large infarction spread widely over the territory of a main arterial trunk and lack of contrast enhancement in the infarcted area in CT/MRI; occlusion or severe stenosis in the main trunk of the middle cerebral artery or the internal carotid artery (except for candidates for carotid endarterectomy) on angiography; 80% of normal value < CBF < 90% of normal value or 10% < CVR < 30% on PET/SPECT. Exclusion criteria**:** not independent in daily life (modified Rankin disability scale score of 3–5), major cerebral arterial occlusive lesions due to diseases other than atherosclerosis, malignant tumours or organ failure of the heart, liver, kidney, or lung; myocardial infarction within the past 6 months; uncontrolled diabetes mellitus showing a serum fasting blood glucose level > 300 mg/dL, or requires insulin; hypertension with a diastolic blood pressure of > 110 mmHg; artery to artery embolism; cardioembolism.
Technique	Patients were categorised based on rest CBF and CVR into 4 subgroups: - Group A: 80%<CBF<90% and CVR<10% - Group B: CBF<80% and 10%<CVR<20% - Group C: 80%<CBF<90% and 10%<CVR<20% - Group D CBF<90% and 20%<CVR<30% Primary endpoints: (1) completed stroke causing significant morbidity (modified Rankin disability scale score of 3–5), (2) vascular death, (3) significant morbidity and mortality from other causes, and (4) requirement of EC-IC bypass as determined by a registered neurologist. Secondary end points: (1) ipsilateral completed stroke causing significant morbidity (modified Rankin disability scale score of 3–5) and (2) death associated with ipsilateral completed stroke. The rate of patients reaching the end points and length of time without end points were compared between the medical arm of the JET study and the JET-2 study.
Follow-up	**2 years**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: Patients were followed-up for 2 years under best medical treatment. Two patients of group B and 2 patients of group D were dropped out from the follow-up.

Study design issues: The medical arm of the JET study (multicentre, prospective randomised trial of extracranial-intracranial (EC-IC) bypass for treating adult patients with moyamoya disease who suffered episodes of intracranial bleeding) was used as comparison arm. There were different methods of CBF across centres of the study.

Study population issues: The medical arm of JET study consists of patients enrolled according to the same inclusion and exclusion criteria except for the values of CBF and CVR, and randomised to the medically treated group. The inclusion criteria for hemodynamic compromise of the JET study was CBF < 80% and CVR < 10%.

Other issues: None.

Key efficacy and safety findings

Efficacy

n=128

Endpoint rate (JET-2 subgroups)

	Group A (n=18)	Group B (n=30)	Group C (n=26)	Group D (n=54)	p
Primary endpoint	3 (16.7%)	2 (6.7%)	3 (11.5%)	1 (1.9%)	0.13
stroke	1	1			
Death			2	1	
EC-IC bypass	1	1	1		
Secondary endpoint	(5.6%)	1 (3.3%)	0	0	0.29

Endpoint rate (JET versus JET-2)

	JET-2 (n=128)	**Medical arm of JET (n=103)**	**p**
Primary endpoint	7% (9/128)	17% (17/103)	0.02
Any stroke	2	9	-
EC-IC bypass	3	4	-
MI*	-	2	-
Death*	4	2	-
Secondary endpoint	4% (5/128)	10% (11/103)	0.04
Ipsilateral stroke	2	7	-
EC-IC bypass	3	4	-

The rates of the primary end point and the secondary end point did not differ among the 4 groups, p=0.13 for the primary endpoint, p=0.29 for the secondary endpoint, χ^2 test.

The log-rank test revealed that the JET group was at significantly higher risk than the JET-2 group for both the primary (p=0.02) and secondary (p=0.04) endpoints.

The author reported that the rate of stroke recurrence in medically treated patients increased if rest CBF was less than 80% of a normal value and CVR was less than 10%. EC-IC bypass surgery is unlikely to benefit patients with rest CBF > 80% or CVR > 10%.

Safety

Safety events frequencies reported in the efficacy column to avoid duplication.

Abbreviations used: CBF, cerebral blood flow; CVR, cerebral vascular reactivity; CT, computerised tomography; EC-IC, extracranial to intracranial; JET, Japanese EC-IC bypass trial; MI, myocardial infarction; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Study 10 Srodon PD (2005)

Details

Study type	**Case series**
Country	UK
Recruitment period	1976 to 1983
Study population and number	**n=204 patients** (229 EC-IC bypass procedures)
Age and sex	Mean 57 years, 79% (160/204) males
Patient selection criteria	Preoperative angiogram results: 58.3% (119/204) had ICA occlusion (94 carotid territory symptoms and 25 no carotid territory symptoms); 17.6% (36/204) had ICA stenosis; 19.1% (39/204) were non-specific.
Technique	A computerised database of consecutive transcranial bypass procedures (St. Bartholomew's Hospital, London) was used to record patient's characteristics and angiogram firings. The National Statistics Office, health authorities, general practitioners, current hospital computer records and patients' notes were used to determine the final outcome for the patients in 2003.
Follow-up	**Up to 20 years**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Consecutive patients who had transcranial bypass followed up to 1999 or 2003, using statistics and health records (of primary care physician, health authority and hospital records). There were 46 patients lost to follow-up at the end of the 27-year follow-up period, their outcome is unknown.

Study design issues: Retrospective single centre study. The database did not include objective tests of the degree of cognitive impairment or memory loss pre and post-operatively.

Study population issues: Preoperative symptoms: 37.3% (76/204) stroke; 42.6% (87/204) TIA; 2.5% (5/204) vertigo; 7.4% (15/204) memory loss; 3.4% (7/204) had no recorded symptoms.

Other issues: This study was included in table 2 in the previous version of the guidance.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 204
<u>Survival</u>
Final number of patients alive at 27 years: 8.8% (18/204)[a]

<table>
<tr><th>Follow-up</th><th>Number lost to follow-up</th><th>Patients free of stroke or fatal stroke[a]</th></tr>
<tr><td>30 day</td><td>0</td><td>0% (0/204)</td></tr>
<tr><td>1 year</td><td>1</td><td>92% (138/150)</td></tr>
<tr><td>5 years</td><td>5</td><td>87% (86/99)</td></tr>
<tr><td>10 years</td><td>35</td><td>-</td></tr>
<tr><td>15 years</td><td>35</td><td>-</td></tr>
<tr><td>20 years</td><td>35</td><td>83% (29/35)</td></tr>
<tr><td>27 years</td><td>46</td><td>-</td></tr>
</table>
[a]The numbers lost to follow-up do not correspond with the total patient number for each year of follow-up. For example the authors do not report what happened to the remaining 53 patients in year 1.

Paper states an overall 5-year mortality of 50% but it is unclear how this figure was calculated.</td><td><u>Deaths after 27-year follow-up</u>: 91% (144/158) (calculated by IP analyst)
<u>Cause of all death</u> (n = 144):
Stroke: 20% (29/144)
Myocardial infarction: 30% (43/144)
Limb ischaemia: 12% (17/144)
Mesenteric embolism: 1% (2/144)
Ruptured aortic aneurysm: 4% (6/144)
Malignancy: 27% (39/144)
Chronic airway disease: 1% (2/144)
Unknown: 4% (6/144)</td></tr>
<tr><td colspan="2">Abbreviations used: ICA, intracranial artery; EC-IC, extracranial to intracranial; TIA, transient ischemic attack.</td></tr>
</table>

Case series reports on adverse events (11 & 12)

Safety
Chiu TL (2011) Retrospective case series – Taiwan **n=85**, mean age 62.8 years (range 23 to 81), patients medically treated for hypertension and with cerebral atherosclerotic disease, but experiencing transient ischemic episodes, ischemic syndrome, reversible ischemic neurological deficits or minor stroke, were recruited were offered EC-IC surgery. Follow-up: mean 64 months (range 15 to 90) The author reports reperfusion injury with cerebral oedema in the MCA territory in 1/85 patient. This happened immediately after EC-IC bypass. The author identifies hypertension, ipsilateral ICA occlusion and contralateral MCA occlusion as being predisposing factors. **Ruh S (2011)** Retrospective case series – Korea n=13, mean age 57 years (range 44-76), 31% (4/13) males, patients treated by EC-IC bypass surgery using RAIG at a single neurosurgical institute between 2003 and 2009. The diseases comprised intracranial aneurysm (n=10), carotid artery occlusive disease (n=2), and delayed stenosis in the donor superficial temporal artery (STA) after previous STA-middle cerebral artery bypass surgery (n=1). Patients were followed clinically and radiographically Bypass surgery was successful in all patients. At a mean follow-up of 53.4 months, the short-term patency rate was 100%, and the long-term rate was 92.3%. Twelve patients had an excellent clinical outcome of Glasgow Outcome Scale (GOS) 5, and one case had GOS 3. Procedure-related complications were a temporary dysethesia on the graft harvest hand (n=1) and a haematoma at the graft harvest site (n=1), and these were treated successfully with no permanent sequelae. In one case, spasm occurred which was relieved with the introduction of mechanical dilators. CONCLUSION: EC-IC bypass using a RAIG appears to be an effective treatment for a variety of cerebrovascular diseases requiring proximal occlusion or trapping of the parent artery.
Abbreviations used: EC-IC, extracranial to intracranial; RAIG, radial artery interposition graft.

Efficacy

Stroke

A systematic review of 2,591 patients (2 randomised controlled trials [RCTs] with follow-up intervals of 56 and 25 months, and 19 non-randomised studies with follow-up not stated) reported no difference in stroke rates (any type) between patients having extracranial to intracranial bypass (EC-IC, plus best medical treatment) and those having medical treatment only (in the RCTs n=1,691; odds ratio [OR] 0.99, 95% confidence interval [CI] 0.79 to 1.23, p = 0.91 and in the non-randomised studies [18 studies], n=881; OR 0.80, 95% CI 0.54 to1.18, p = 0.25). In the same systematic review, ischaemic stroke rate was not statistically significantly different between patients having EC-IC bypass and those having medical treatment only (in the RCTs n=1,573; OR 0.69, 95% CI 0.44 to 1.08, p=0.11and in the non-randomised studies [13 studies], n=640; OR 0.72, 95% CI 0.44 to 1.18, p=0.19). Two RCTs reported a statistically significantly smaller probability of stroke, vascular event or vascular death amongst the patients having EC-IC when compared with patients having medical treatment only (n=1,573; OR 0.68, 95% CI 0.51 to 0.91, p = 0.009). No statistically significant difference was seen in the same systematic review of 2,591 patients (13 non-randomised studies; n=673; OR 0.69, 95% CI 0.45 to 1.04, p=0.079).Two non-randomised studies (n=361) reported no statistically significant difference in intracranial haemorrhage rates between patients having EC-IC when compared with patients having medical treatment only (OR 1.14, 95% CI 0.44 to 2.93, p=0.79) in the same systematic review.[1]

A systematic review of 506 patients reported a statistically significantly lower rate of stroke 12 months after surgery in patients with severe stage I failure (loss of autoregulatory vasodilation) who had EC-IC bypass (1%) than in patients having medical treatment only (19%, 95% CI 1.17 to 4.08, p=0.015). In the same systematic review, stroke rate was not statistically significantly different in patients with stage II failure (autoregulatory failure characterised by decreases of cerebral blood flow and increases of oxygen extraction fraction) who had EC-IC bypass (0%) when compared with patients having medical treatment only (13%, 95% CI 0.89 to 3.63, p=0.10).[2]

In an RCT of 1,377 patients, EC-IC bypass surgery was associated with 14% (90% CI 3 to 34) increased relative risk of fatal and non-fatal stroke (Mantel-Haenszel chi-squared=1.72) at a mean follow-up of 56 months (p value not reported).[3]

). In an RCT (n=195) comparing 97 patients having EC-IC bypass with 98 patients who had medical treatment only, ipsilateral ischaemic stroke rate was not statistically significantly different between groups (rate difference 2%, 95% CI −10 to 14, p=0.81), at 2-year follow-up.[4]

In a case series comparing 128 patients with cerebral blood flow (CBF) less than 90% of normal and cerebral vascular reactivity (CVR) between 10 and 30% (Japanese EC-IC bypass study [JET-2]) to 103 patients CBF less than 80% and CVR less than 10% (Japanese EC-IC bypass study [JET] medical group), reported that the JET medical group was at significantly higher risk of stroke, EC-IC bypass, myocardial infarction and death (17% [17/103]) than the JET-2 group (7% [9/128], p=0.02) and ipsilateral stroke and EC-IC bypass (10% [11/103]) than the JET-2 group (4% [5/128], p=0.04), at 2-year follow-up.[9]

A case series of 204 patients who had EC-IC bypass reported the rate of patients free of stroke or fatal stroke to be 92% (138/150) at 1 year follow-up and 87% (86/99) at 5-year follow-up.[10]

Transient ischaemic attack (TIA) and cerebral haemodynamics

In the systematic review of 2,591 patients, 11 non-randomised studies reported a statistically significantly smaller risk of transient ischaemic attack or amaurosis in patients who had EC-IC bypass when compared with patients who had medical treatment only (n=524; OR, 0.34, 95% CI 0.16 to 0.69, p = 0.003). Three non-randomised studies from the same systematic review reported no statistically significant difference in normalisation of cerebral haemodynamics in patients who had EC-IC bypass and those having medical treatment only (n=56; OR 6.63, 95% CI 1.85 to 23.78).[1]

Graft patency

The RCT of 1,377 patients reported a graft patency rate, assessed by angiography, of 96% (576/600) in patients who had EC-IC bypass, at a median of 32 days post-procedure.[3]

In the RCT of 195 patients, graft failure rate was 2% (2/97) in patients who had EC-IC bypass, at 2 years follow-up.[2]

In the RCT of 195 patients, graft failure rate was 2% (2/97) in patients treated by EC-IC bypass, at 2-years follow-up.[4]

Functional impairment and neurocognitive function

The RCT of 1,377 patients reported higher rates of major functional impairment (inability to function without assistance) in patients who had EC-IC bypass (7% [46/663]) compared to patients treated medically only (5% [36/714]), no p value reported.[3]

In an RCT of 43 patients there was no statistically significantly difference in neurocognitive function (measured by 14 standardised neuropsychological tests and the Centre for Epidemiological Studies depression scale), at 2 year follow-up, between patients who had EC-IC bypass and patients who had medical treatment only (point estimate 0.02, 95% CI, 20.50 to 0.54, p=0.93).[5]

Safety

Postoperative stroke

In an RCT (n=1,377) comparing 663 patients who had EC-IC bypass with 714 patients who had medical treatment, the rate of cerebral and retinal ischaemic events was higher in the EC-IC bypass group (12% [81/663]) than in the medical group (3% [24/714]), within 30 days of surgery or 39 days of randomisation for the medical group), no p value reported. The same RCT reported a higher rate of major stroke, defined as an 'inability to function without assistance', in patients who had EC-IC bypass (3% [20/663]) in comparison with the medical treatment only group (1% [9/714]), within 30 days of surgery or 39 days of randomisation, p value not reported.[3]

A case series of 876 patients with occlusive cerebrovascular disease reported no statistically significantly difference in the rate of post-procedure stroke in asymptomatic patients who had EC-IC bypass (2% [2/123]) when compared with asymptomatic patients who had intracranial stenting (4% [10/243], p=0.341). The same case series reported a statistically significantly higher rate of post-procedure stroke in symptomatic patients who had EC-IC bypass (25% [32/126]) than in symptomatic patients who had intracranial stenting (10% [40/384], p<0.001).[7]

Death

Death from a vascular cause was not statistically significantly different in patients who had EC-IC compared to patients having medical treatment alone ,in 2 randomised controlled trials (RCTs, n=1,691, follow-up of 56 months and 25 months) (odds ratio [OR] 0.96, 95% CI 0.71 to 1.29, p=0.77) and in 19 non-randomised studies (n=900; OR 0.95, 95% CI 0.56 to1.63, p=0.86), reported in the systematic review of 2,591 patients with symptomatic carotid artery occlusion. All-cause mortality was not statistically significantly different in patients having EC-IC bypass compared to patients having medical treatment only,1 RCT (n=1,573; OR 0.94, 95% CI 0.74 to 1.21, p = 0.64) and in 8 non-randomised studies (n=346; OR 0.80 (95% CI: 0.50 to 1.29, p = 0.37) reported in the systematic review of 2,591 patients.[1]

The RCT comparing 663 extracranial to intracranial bypasses with 714 medically treated patients reported a mortality rate of 17% (112/663) in the bypass group and 20% (140/714) in the medical group (mean follow-up 56 months).[3]

All-cause mortality was not statistically significantly different in asymptomatic patients having EC-IC bypass (1.6% [2/123]) when compared to patients having intracranial stenting (ICS, 2.5% [6/243], p=0.8870) in a case series of 876 patients. All-cause mortality was statistically significantly lower in symptomatic patients having EC-IC bypass (4% [5/126]) when compared to patients having ICS (12% [46/384], p=0.015) in the same care series.[7]

Death rates were 1% (5/343) in patients with occlusive cerebrovascular disease without post-procedure stroke and 7% (5/69) in patients with post-procedure stroke in a case series of 415 patients having EC-IC bypass.[8]

Dependency

In the case series of 876 patients with occlusive cerebrovascular disease, asymptomatic patients were no more likely to be transferred to another care facility, rather than home, if they had EC-IC bypass (16% [19/121]) when compared with patients who had intracranial stenting (9% [21/237], p=0.08). Symptomatic patients were statistically significantly more like to be transferred to another care facility, rather than home, if they had EC-IC bypass (66% [80/121]) when compared with patients who had intracranial stenting (53% [180/338], p=0.08).[7]

In a case series of 415 patients who had EC-IC bypass, destination at discharge for patients with post-procedure stroke was home (59% [41/69]), short-term facility (25% [17/69]) and long-term facility (9% [6/69]).[8]

Myocardial infarction

Myocardial infarction rate was not statistically significantly different in patients having EC-IC bypass compared to patients having medical treatment only, in 2 RCTs (n=1522; OR 0.78, 95% CI 0.46 to 1.32, p = 0.35, follow-up of 25 to 56 months) or in 2 non-randomised studies (n=79; OR 2.67, 95% CI 0.41 to 17.60, p = 0.31, unknown follow-up) in the systematic review of 2,591 patients.[1]

Myocardial infarction occurred in 1 patient of 97 at 30 days follow-up in the RCT of 195 patients.[4]

Surgery related safety events

The following adverse events were reported in the RCT of 195 patients who had EC-IC bypass: epidural or subdural haematoma (2% [2/97]), seizures (2% [2/97]), respiratory disorder (1% [1/97]), hypotension (1% [1/97]), and wound infection (1% [1/97]). The following adverse events happened to the same patient: deep vein thrombosis (1% [1/97]), atrial flutter (1% [1/97]), cardiac tamponade (1% [1/97]), pulmonary embolus (1% [1/97]).[4]

Haemorrhage, haematoma complicating the procedure, hydrocephalus, ventriculostomy, mechanical ventilation, deep vein thrombosis, pulmonary embolism and placement of an inferior vena cava filter were reported in the case series of 415 patients who had EC-IC bypass (no frequencies were reported).[8]

Other

Reperfusion injury with cerebral oedema was reported in 1patient in a case series of 85 patients who had EC-IC bypass.[11]

Temporary dysethesia on the graft harvest site (1/13) and haematoma at the graft harvest site (1/13) was reported in a case series of 13 patients who had EC-IC bypass.[12]

Validity and generalisability of the studies

- It is not always possible to understand if there is an association between the intervention and the cause of death. This is particularly true in studies with longer follow-up.[3,10]
- The evidence was reviewed on extracranial to intracranial bypass for patients with cerebral atherosclerosis only. The evidence for different indications might present with different efficacy and safety profiles.

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

- Extracranial to intracranial bypass for intracranial atherosclerosis. NICE interventional procedure guidance 348 (2010). Available from: https://www.nice.org.uk/guidance/ipg348
- High-flow interposition extracranial to intracranial bypass. NICE interventional procedures guidance 73 (2004). Available from: https://www.nice.org.uk/guidance/ipg73
- Endovascular stent insertion for intracranial atherosclerotic disease. NICE interventional procedures guidance 429 (2012). Available from: https://www.nice.org.uk/guidance/ipg429
- Laser-assisted cerebral vascular anastomosis without temporary arterial occlusion. NICE interventional procedures guidance 252 (2008). Available from: https://www.nice.org.uk/guidance/ipg252

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. One

Specialist Advisor Questionnaire for extracranial to intracranial bypass for intracranial atherosclerosis was submitted and can be found on the NICE website

Patient commentators' opinions

NICE's Public Involvement Programme sent xxx questionnaires to xxx NHS trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted if there is no patient commentary

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

Section to be inserted if patient commentators raised no new issues

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Section to be inserted if patient commentators raised new issues

The patient commentators raised the following issues about the safety/efficacy of the procedure, which did not feature in the published evidence or the opinions of specialist advisers, and which the committee considered to be particularly relevant:

Issues for consideration by IPAC

- The EC/IC Bypass Study has been widely quoted in the published literature in the last 24 years and is deemed to be instrumental in reducing the use of extracranial to intracranial bypass to prevent stroke in the US and Europe. The paper received criticisms from different groups (Ausman 1986, Day 1986, Sundt 1987), including the inability to identify and separately analyse a subgroup of patients with impaired cerebral haemodynamics due to occlusive cerebrovascular disease in whom surgical revascularisation could be more beneficial.

- The Carotid occlusion surgery study[4,5] was terminated for futility (in error) and the recruited sample was smaller than prospectively determined in the sample power calculations.

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Appendix A: Additional papers on extracranial to intracranial bypass for intracranial atherosclerosis

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
Britz GW, Agarwal V, Mihlon F et al. (2016) Radial Artery Bypass for Intractable Vertebrobasilar Insufficiency: Case Series and Review of the Literature. World Neurosurgery 85: 106-13.	Case series n=3 FU=6 months, 2 months, 9 months	Surgical revascularization should be considered in the posterior circulation in the rare subset of patients with VBI, who remain symptomatic despite having a protracted course of maximal medical therapy with large- and medium-sized vessel occlusions and poor collateral circulation.	Larger studies included in table 2, no new safety outcomes.
Dong Y, Teoh H L, Chan BP et al (2012) Changes in cerebral hemodynamic and cognitive parameters after external carotid-internal carotid bypass surgery in patients with severe steno-occlusive disease: a pilot study. Journal of the Neurological Sciences 322(1-2): 112-6.	Non-randomised comparative study n=18 (9 intervention, 9 controls) FU=6 months	EC-IC bypass patients had significant improvement in verbal memory (p=0.037) and executive function (p=0.043) and a trend of improvement in visual memory (p=0.052) compared to controls. EC-IC bypass surgery in carefully selected patients could improve cerebral haemodynamics and verbal memory and executive function	Non-randomised, larger studies included in table 2, no new safety outcomes.
Doormaal T, Van Der Zwan , A , Klijn C J, Regli L, and Tulleken C A (2010) Symptomatic carotid artery occlusion treated with a high flow extra-intracranial excimer laser assisted non-occlusive anastomosis (ELANA) bypass. International Journal of Stroke 5: 151	Case series n=24 FU=4 years	Univariate analysis showed that clinical improvement correlated significantly with success of recanalization and with early recanalization within 72 hr. Age, gender, and preoperative Rankin stage did not have influence. Clinical deterioration or death was only associated with perioperative cerebral events and seemed to be time-independent. Multivariate analysis did not have enough statistical power to analyze the impact of different risk factors on outcome after urgent revascularization. In patients who undergo surgery after 72 hr from symptom onset, the risk seems to outweigh the benefit.	Larger studies included in table 2, no new safety outcomes.
Duckworth EA, Rao VY, and Patel A J (2013) Double-barrel bypass	Case series n=10	No intraoperative complications or wound-healing issues occurred. Postoperative computed tomography	Larger studies included in table

for cerebral ischemia: technique, rationale, and preliminary experience with 10 consecutive cases. Neurosurgery 73(1 Suppl Operative), ons30-8; discussion ons37-8.	FU=8 months	perfusion studies all showed improvement, and delayed vascular imaging demonstrated universal graft patency. Nine of 10 patients have been asymptomatic since surgery, whereas 1 patient demonstrated symptoms in a separate vascular distribution. Double-barrel STA-MCA bypass is both feasible and potentially advantageous. In our series, both bypass branches remained patent, augmenting flow to the territories most at need.	2, no new safety outcomes.
Galkin P, Gushcha A, Chechetkin A et al. (2015) Superficial temporal artery to middle cerebral artery bypass with interposed saphenous vein graft in patients with atherosclerotic internal carotid artery occlusive disease and impaired cerebral haemodynamics. *Journal of Neurosurgical* Sciences, 61 (1): 22-32.	Case series n=60 FU=5 months	Bypass patency in these patients was confirmed with repeated DUS up to 42 months period. At mean clinical follow--up of 22.3 months 14 patients (73,7%) reported an improvement of their condition, 4 patients (21%) didn't observe any changes in well-being and 1 patient (5,3%) got worse. Late bypass patency assessment was available and confirmed in 16 patients at mean follow--up of 15.6 months post operation. Average growth of regional cerebral blood flow was 24.1%. Use of interposed SVG bypass for EC--IC revascularization is an effective method that could be applied in patients with cerebral ischemia caused by internal carotid artery occlusive disease and absence of appropriate donor artery.	Larger studies included in table 2, no new safety outcomes.
Gazyakan E, Lee CY, Wu CT et al. (2015) Indications and Outcomes of Prophylactic and Therapeutic Extracranial-to-intracranial Arterial Bypass for Cerebral Revascularization. Plastic and Reconstructive Surgery - Global Open 3(4): e372.	Case series n=28 FU=33 months	The overall patency rate of bypass was 100%, the postoperative stroke rate was zero, and the surgical complication rate was 14.3%. There was no significant difference in the bypass patency rate between the 2 groups or between the high-flow and low-flow bypass patients. Patients who underwent prophylactic bypass had minimal surgical and total complications ($P = 0.03$ and $P < 0.01$, respectively) and a better neurological outcome. Surgical complications were more common in patients who underwent therapeutic bypass (25%). The collaboration of neurosurgeons and plastic surgeons in performing EC-IC bypass can result in excellent outcomes with a high bypass patency rate and few complications, particularly for prophylactic EC-IC bypass.	Larger studies included in table 2, no new safety outcomes.
Hamamura T, Morioka T, Sayama T et al. (2010) Cerebral hyperperfusion syndrome associated with non-convulsive	Case report n=1 FU=	A 77-year-old man developed cerebral hyperperfusion syndrome with temporal deterioration of consciousness and worsening of left hemiparesis on the 6(th) postoperative day following	Larger studies included in table 2, no new safety outcomes.

status epilepticus following superficial temporal artery-middle cerebral artery anastomosis. Case report. Neurologia Medico-Chirurgica 50(12): 1099-104.		superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis for right M(1) occlusion. Electroencephalography (EEG) revealed frequent ictal discharges in the right hemisphere, although convulsive seizures were not apparent. Administration of anticonvulsants was performed based on the diagnosis of non-convulsive status epilepticus (NCSE). Complete recovery from hyperperfusion syndrome was achieved with rapid improvement of EEG findings. The present case demonstrates the pathophysiological mechanism of hyperperfusion syndrome associated with NCSE after STA-MCA anastomosis.	
Inoue T, Ohwaki K, Tamura A et al. (2016) Extracranial-intracranial bypass for internal carotid/middle cerebral atherosclerotic steno-occlusive diseases in conjunction with carotid endarterectomy for contralateral cervical carotid stenosis: clinical results and cognitive performance. Neurosurgical Review 39(4): 633-41.	Case series n=14 FU=8 months	Performance IQ and Average score improvements were statistically significant. Clinical results after EC-IC bypass in conjunction with contralateral CEA were feasible. Based on the group rate analysis, we conclude that successful unilateral EC-IC bypass and contralateral carotid endarterectomy does not adversely affect postoperative cognitive function.	Larger studies included in table 2, no new safety outcomes.
Inoue T, Ohwaki K, Tamura A et al. (2016) Postoperative transient neurological symptoms and chronic subdural hematoma after extracranial-intracranial bypass for internal carotid/middle cerebral atherosclerotic steno-occlusive diseases: negative effect on cognitive performance. Acta Neurochirurgica 158(1): 207-16.	Case series n=14 FU=6 months	Postoperative transient neurological symptoms and/or CSDH might play a significant role in the subtle decline in cognition following an EC-IC bypass. However, this detrimental effect was small, and based on the group rate analysis, we concluded that a successful unilateral EC-IC bypass does not adversely affect postoperative cognitive function.	Larger studies included in table 2, no new safety outcomes.
Kalani MY, Rangel-Castilla L, Ramey Wet al. (2015) Indications and results of direct cerebral revascularization in the modern era. World Neurosurgery 83(3): 345-50.	Case series n=121 (40 patients moyamoya, 54 complex aneurysms) FU=19 months	Although microvascular cerebral revascularization is no longer performed as commonly as in the past, it remains an essential part of the skill set required to treat select vascular pathologies. Complex aneurysms are the single largest indication for direct bypass procedures. Moyamoya disease is by far the largest indication if indirect bypass procedures are included in the analysis. In experienced hands,	Larger studies included in table 2, no new safety outcomes.

		the morbidity and mortality of patients undergoing cerebral revascularization procedures are low and long-term outcomes generally excellent.	
Kimura H, Taniguchi M, Mori T et al. (2016) Clinical Implication of Temporary Hypointense Lesion on Diffusion-Weighted Imaging After Extracranial-Intracranial Bypass Surgery. World Neurosurg 97: 21.	Case report n=1 FU=discharge	An abrupt increase of CBF after bypass installation to the brain with no vascular response and complete disruption of the blood-brain barrier would cause a remarkable increase of extracellular fluid and excessive water molecule diffusion, resulting in excessive vasogenic edema. This was a plausible mechanism for the transient hypointense lesion on DWI with increased apparent diffusion coefficient value.	Larger studies included in table 2, no new safety outcomes.
Lee MK, White RP, Dyde R et al. (2012) Extracranial - Intracranial (EC-IC) bypass surgery for occlusive cerebrovascular disease and its assessment using CT perfusion with acetazolamide challenge. British Journal of Neurosurgery 26(3): 300.	Case report n=1 FU=discharge	A 69-year-old man presented with several episodes of transient weakness involving left lower extremity. Cerebral angiography showed occlusion of the right ACA at the A2 segment. After medical treatment failure, the patient underwent STA-ACA bypass surgery. Subsequent to surgery, there was immediate disappearance of transient ischemic attack and follow-up angiography showed favorable revascularization of the ACA territory. Bypass surgery can be considered in the patients with symptomatic occlusion of the ACA, who have experienced failure in medical treatment.	Larger studies included in table 2, no new safety outcomes.
Low SW, Teo K, Lwin S et al. (2015) Improvement in cerebral hemodynamic parameters and outcomes after superficial temporal artery-middle cerebral artery bypass in patients with severe stenoocclusive disease of the intracranial internal carotid or middle cerebral arteries. Journal of Neurosurgery 123(3): 662-9.	Case series n=112 (46 STA-MCA bypass 31 best medical treatment) FU=34 months	Transcranial Doppler and acetazolamide-challenge repeated at 4 +/- 1 months showed significant improvement in the STA-MCA bypass group. During a mean follow-up of 34 months (range 18-39 months), only 6 (13%) of 46 patients in the bypass group developed cerebral ischemic events, as compared with 14 (45%) of 31 patients receiving medical therapy (absolute risk reduction 32%, p = 0.008). STA-MCA bypass surgery in carefully selected patients with symptomatic severe intracranial stenoocclusive disease of the intracranial ICA or MCA results in significant improvement in hemodynamic parameters and reduction in stroke recurrence.	Larger studies included in table 2, no new safety outcomes. Study sample overlap with Teo (2013) in Appendix A.
Muroi C, Khan N, Bellut et al. (2011) Extracranial-intracranial bypass in atherosclerotic cerebrovascular	Case series n=72 FU=34 months	Stroke recurrence took place in 10 patients (15%) resulting in an annual stroke risk of 5%. Improved cerebral haemodynamics was documented in 81% of revascularised hemispheres. Patients with unchanged or worse	Larger studies included in table 2, no new safety outcomes.

disease: report of a single centre experience. British Journal of Neurosurgery 25(3): 357-62.		haemodynamic parameters had significantly more post-operative TIAs or strokes when compared to those with improved perfusion reserves (30% vs.5% of patients, p<0.05). In conclusion, EC-IC bypass procedure in selected patients with occlusive cerebrovascular lesions associated with haemodynamic impairment has revealed to be effective for prevention of further cerebral ischemia, when compared with a stroke risk rate of 15% reported to date in patients only under antiplatelet agents or anticoagulant therapy.	
Nagm Alhusain, Horiuchi Tetsuyoshi, Ito Kiyoshi, and Hongo Kazuhiro (2016) Relationship Between Successful Extracranial-Intracranial Bypass Surgeries and Ischemic White Matter Hyperintensities. World Neurosurgery 91: 112-20.	Case series n=12 FU=6 months	This study might be considered the first step to find a relationship between successful EC-IC bypass surgeries and the course of ischemic WMHs. It could also open the door for further studies to make more solid conclusions.	Larger studies included in table 2, no new safety outcomes.
Nagm A, Horiuchi T, Yanagawa T et al. (2016) Risky Cerebrovascular Anatomic Orientation: Implications for Brain Revascularization. World Neurosurgery , no pagination.	Case report n=1 FU= discharge	A 71-year-old woman presented with uncontrollable frequent right lower limb transient ischemic attacks (TIAs) attributed to a left cerebral ischemic lesion due to severe left ACA stenosis. She underwent successful left-sided superficial temporal artery-ACA bypass using interposed vascular graft. The patient awoke satisfactory from anaesthesia; however, on postoperative day 1, she developed right-sided hemiparesis. Extensive postoperative investigations disclosed that watershed shift infarction was considered the aetiology for this neurologic deterioration.	Larger studies included in table 2, no new safety outcomes.
Patel HC, McNamara l R, Al-Rawi P G et al. (2010) Improved cerebrovascular reactivity following low flow EC/IC bypass in patients with occlusive carotid disease. British Journal of Neurosurgery 24(2): 179-84.	Case series n=13 FU=NR	About 85% of patients had either an improvement in symptoms or no further symptoms. There was a 93% graft patency and no operative mortality. Low flow EC/IC bypass can improve CVR in patients with symptomatic cerebral ischaemia in the presence of occlusive carotid disease. However, therapy must be individualised, with careful patient selection and minimal surgical morbidity.	Larger studies included in table 2, no new safety outcomes.
Persoon S, Luitse MJ, de Borst GJ, et al. (2011) Symptomatic internal carotid artery	Prospective case series	Recurrent ischaemic stroke occurred in 23 patients, resulting in an annual rate of 2.4% (95% CI 1.5 to 3.6). Risk factors for recurrent ischaemic stroke	Larger studies included in table

occlusion: a long-term follow-up study. Journal of Neurology, and Neurosurgery & Psychiatry 82(5): 521-6.	n=117 (77 had medical treatment, 22 had endarterectomy, 16 had EC-IC bypass) FU=10 years	were age (HR 1.07, 1.02 to 1.13), cerebral rather than retinal symptoms (HR 8.0, 1.1 to 60), recurrent symptoms after documented occlusion (HR 4.4, 1.6 to 12), limb-shaking transient ischaemic attacks at presentation (HR 7.5, 2.6 to 22), history of stroke (HR 2.8, 1.2 to 6.7) and leptomeningeal collaterals (HR 5.2, 1.5 to 17) but not CO(2) reactivity (HR 1.01, 0.99 to 1.02: The prognosis of patients with transient ischaemic attack or minor stroke and ICA occlusion depends on age, several clinical factors and the presence of leptomeningeal collaterals. The long-term risk of recurrent ischaemic stroke is much lower than that of other vascular events.	2, no new safety outcomes.
Quach ET, Gonzalez AA, Shilian P et al. (2015) Posterior circulation cerebral hyperperfusion syndrome after high flow external carotid artery to middle cerebral artery bypass. Journal of Clinical Neuroscience 22(9): 1515-8	Case report n=1 FU=discharge	The patient underwent left cerebral hemisphere revascularization with a high flow external carotid artery to MCA bypass with aneurysm trapping. During skin closure, significant changes were seen in her bilateral upper extremity motor-evoked potentials. The patient's postoperative exam was noted for an intermittent inability to follow commands, bilateral upper extremity weakness, vertical nystagmus, and alogia that all dramatically improved with strict blood pressure control. Postoperative perfusion imaging revealed posterior circulation hyperemia. This patient highlights the potential for hyperaemic complications outside the revascularized arterial territory. Strict blood pressure control is recommended in order to prevent and manage hyperaemia-associated symptoms. Improving our understanding of CHS may assist in identifying at risk patients and at risk arterial territories in order to optimize CHS prevention and management strategies.	Larger studies included in table 2, no new safety outcomes.
Radovnicky T, Vachata P, Bartos R et al. (2016) The masaryk hospital extracranial-intracranial bypass study. Neurosurgical Review, 1-5.	Case series n=93 FU=2 years	The 30-day risk of stroke and death was 7.5 %. It consists of one death, one major ischaemic stroke, two reversible neurological deficits and three TIAs. The 2-year risk of stroke and death was 9.7 %. Extracranial-intracranial bypass is an effective treatment of haemodynamic impairment in patients with internal carotid occlusion. Maintaining low-level morbidity and mortality is possible with a dedicated	Larger studies included in table 2, no new safety outcomes.

		neurovascular team. This is the only way in which we can reduce the risk of stroke and death in patients with bypass compared to patients treated medically.	
Sandow N, von Weitzel-Mudersbach P, Rosenbaum S et al. (2013) Extra-intracranial standard bypass in the elderly: perioperative risk, bypass patency and outcome. Cerebrovascular Diseases 36(3): 228-35.	Case series n=50 FU= 18 months	Perioperative stroke rate was 0% in both groups and mild morbidity occurred in 18.8 and 14.7%, respectively (p = 0.699). One 84-year-old female patient died due to perioperative endocarditis. Initial bypass patency was 93.8% in patients above the age of 70 years and 97.1% in the younger group (p = 0.542). Secondary occlusion rate was low in both groups (>70 years: 0% vs. <70 years 3.7%). No new neurologic deficit occurred in patients with a patent bypass during the follow-up period (median 18 +/- 13.1 months). Two patients with an initially occluded bypass and one with a secondary bypass occlusion suffered from new neurological symptoms. Our data show comparable safety and efficiency of EC-IC bypass surgery in patients under and above the age of 70 years due to a careful preoperative work-up and a strict indication for bypass surgery	Larger studies included in table 2, no new safety outcomes.
Schubert GA, Seiz M, Schmiedek P et al. (2012) Risk of hemorrhage and ischemia after EC/IC bypass surgery-an observational analysis of 204 consecutive revascularization procedures. Journal of Neurosurgery 117(2): A402.	Case series n=99 patients with cerebral atherosclerotic disease (remaining moyamoya) FU=time of discharge	Extra-intracranial bypass surgery remains a treatment option in patients with moyamoya disease, although its use in the context of atherosclerotic disease was recently put into question. Regardless, a detailed characterization of perioperative risk factors is needed to optimize a potential long-term benefit of surgery. At a high-volume center, the complication rate is low independent from the underlying pathology with a high patency rate. Antiplatelet treatment does not increase the risk of hemorrhagic complications, but may improve outcome. Longer follow-up is required to adequately assess the true efficacy of revascularization on stroke prevention.	Larger studies included in table 2, no new safety outcomes.
Sia SF, Davidson AS, Assaad NN et al. (2011) Comparative patency between intracranial arterial pedicle and vein bypass surgery. Neurosurgery 69(2): 308-14.	Case series n=178 intracranial arterial pedicle bypass, 152 intracranial vein bypass (188 for carotid occlusion) FU=2 years	There was no statistically significant difference in early, late, and overall patency between the 2 bypass groups. The surgical complication rate was greater for vein bypass. Both arterial pedicle and vein bypass have good long-term patency.	Larger studies included in table 2, no new safety outcomes.

Sinha AK, Lu S, Sharma V et al.(2010) Acetazolamide challenged HMPAO SPECT plays important role in decision making for superficial temporal artery-middle cerebral artery (STA-MCA) bypass in patients with severe steno-occlusive disease of intracranial internal carotid and middle cerebral artery. European Journal of Nuclear Medicine and Molecular Imaging 37: S394.	Case series n=72 FU=6 months	There were no perioperative complications and during subsequent follow up (mean 10months; range 3 to 28months). Early morning headache and lethargy noted in 16 patients resolved completely. 3(14%) in the surgery group developed new cerebral ischemic event during follow up. Acetazolamide-challenged HMPAO-SPECT repeated at 5+/-2months after STA-MCA bypass surgery revealed significant improvement in CVR in all cases. Patients with symptomatic severe intracranial steno-occlusive disease and impaired vasodilatory reserve carry a high risk of cerebral ischemic events. Assessment of cerebral vasodilatory reserve and quantification of metabolic hypoperfusion by acetazolamide-challenged HMPAO-SPECT may be used to select patients who would benefit from STA-MCA bypass surgery.	Larger studies included in table 2, no new safety outcomes.
Sotoca FJ, Camps-Renom P, Prats-Sanchez L et al. (2015) Delayed hyperperfusion syndrome after extra-intracranial bypass: A case report. International Journal of Stroke 10: 397.	Case report n=1 FU=discharge	Delayed intracerebral haemorrhage due to a reperfusion syndrome is a rare complication after extra-intracranial bypass. Poor BP control, previous stroke and antiplatelet therapy may have contributed to its occurrence in this case.	Larger studies included in table 2, no new safety outcomes.
Teo K, Choy DK, Lwin S et al. (2013) Cerebral hyperperfusion syndrome after superficial temporal artery-middle cerebral artery bypass for severe intracranial steno-occlusive disease: a case control study. Neurosurgery 72(6): 936-42; discussion 942-3.	Case series n=112 (46 STA-MCA bypass 31 best medical treatment) FU=7 days	Symptomatic cerebral HPS is common in the early postoperative period after EC-IC bypass surgery. Early diagnosis and appropriate management might prevent the complications of this syndrome.	Larger studies included in table 2, no new safety outcomes. Study sample overlap with Low (2015) in Appendix A.
Tokugawa J, Nakao Y, Kudo K et al. (2014) Posterior auricular artery-middle cerebral artery bypass: a rare superficial temporal artery variant with well-developed posterior auricular artery-case report. Neurologia Medico-Chirurgica 54(10): 841-4.	Case report n=1 FU=discharge	A 65-year-old man developed mild motor weakness in the right extremities caused by multiple small infarctions. Cerebral angiography showed severe stenosis in the C2 portion of the left internal carotid artery, absence of the parietal branch of the left STA, and a well-developed PAA extending to the parietal area. The patient underwent STA (frontal branch)-MCA and PAA-MCA double anastomosis, and has suffered no stroke or transient ischemic attack. The STA with no bifurcation is known	Larger studies included in table 2, no new safety outcomes.

		as a rare variation. The PAA also occurs with size variations but well-developed PAA is thought to be extremely rare. PAA can be used as a donor artery for MCA territory revascularization if the vessel size is suitable. Preoperative evaluation of the anatomy is mandatory for harvesting the arteries.	
Torihashi K, Chin M, Sadamasa N et al. (2011) Ischemic stroke due to dissection of the middle cerebral artery treated by superficial temporal artery-middle cerebral artery anastomosis--case report. Neurologia Medico-Chirurgica 51(7): 503-6.	Case report n=1 FU=discharge	A 62-year-old man presented with dissection of the right middle cerebral artery Digital subtraction angiography approximately 24 hours after admission revealed a linear contrast defect indicating an intimal flap of the M(1) segment. The diagnosis was dissection of the MCA. His neurological deficits improved gradually. Superficial temporal artery (STA)-MCA anastomosis was performed on the 26th day. Follow-up angiography showed good patency of the STA-MCA anastomosis, repair of the dissection of the M(1) segment, and improvement of the flow in the MCA. The patient was discharged from our hospital with no neurological deficits. Although the dissection in this case was spontaneously repaired, STA-MCA anastomosis was useful to get through a critical time. If the stenosis shows further progression or the infarction size enlarges, STA-MCA anastomosis may be effective.	Larger studies included in table 2, no new safety outcomes.
Weis-Muller BT, Spivak-Dats A, Turowski B et al. (2013) Time is brain? - Surgical revascularization of acute symptomatic occlusion of the internal carotid artery up to one week. Annals of Vascular Surgery 27(4): 424-432.	Case series n=43 FU=3 days	Univariate analysis showed that clinical improvement correlated significantly with success of recanalization and with early recanalization within 72 hr. Age, gender, and preoperative Rankin stage did not have influence. Clinical deterioration or death was only associated with perioperative cerebral events and seemed to be time-independent. Multivariate analysis did not have enough statistical power to analyse the impact of different risk factors on outcome after urgent revascularization. In patients who undergo surgery after 72 hr from symptom onset, the risk seems to outweigh the benefit.	Larger studies included in table 2, no new safety outcomes.
Yamaguchi K, Kawamata T, Kawashima A et al. (2010) Incidence and predictive factors of cerebral hyperperfusion after extracranial-	Case series n=50 FU=perioperative	The incidence of cerebral blood flow-assessed postoperative hyperperfusion after EC-IC bypass for atherosclerotic occlusive cerebrovascular diseases was not rare. Post EC-IC bypass CHS could be reduced by continuous, strict	Larger studies included in table 2, no new safety outcomes.

intracranial bypass for occlusive cerebrovascular diseases. Neurosurgery 67(6): 1548-54; discussion 1554		blood pressure control under sedation.	

Appendix B: Related NICE guidance for Extracranial to intracranial bypass for intracranial atherosclerosis

Guidance	Recommendations
Interventional procedures	**Extracranial to intracranial bypass for intracranial atherosclerosis. Interventional procedure guidance 348 (2010)** 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. **High-flow interposition extracranial to intracranial bypass. NICE interventional procedures guidance 73 (2004)** 1.1 Current evidence on the safety and efficacy of high-flow interposition extracranial to intracranial bypass does not

	appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 This decision relates to the procedure when used for the treatment of diseases of the carotid artery, such as atherosclerosis. No judgement is made regarding its use as one part of a larger operation, such as bypassing an internal carotid artery that has been surgically occluded during resection of a tumour. 1.3 Clinicians wishing to undertake high-flow interposition extracranial to intracranial bypass should take the following actions: • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's *Information for the Public* is recommended. • Audit and review clinical outcomes of all patients having high-flow interposition extracranial to intracranial bypass. 1.4 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence. **Endovascular stent insertion for intracranial atherosclerotic disease. NICE interventional procedures guidance 429 (2012).** 1.1 Current evidence on the efficacy of endovascular stent insertion for intracranial atherosclerotic disease shows no substantial differences in clinical outcomes compared with medical treatment after 1–2 years. Evidence on its safety shows that there is a significant risk of periprocedural stroke and death. Therefore, this procedure should only be used in the context of research. Research should clearly define patient selection and be designed to provide outcome data based on follow-up of at least 2 years. **Laser-assisted cerebral vascular anastomosis without temporary arterial occlusion. NICE interventional procedures guidance 252 (2008)** 1.1 Current evidence on the safety and efficacy of laser-assisted cerebral vascular anastomosis without temporary arterial occlusion is based on very limited numbers of patients. Therefore the procedure should only be used with special arrangements for clinical governance, consent, and audit or research. 1.2 Clinicians wishing to undertake laser-assisted cerebral vascular anastomosis without temporary arterial occlusion should take the following actions. • Inform the clinical governance leads in their Trusts.

	• Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG252publicinfo). • Audit and review clinical outcomes of all patients having laser-assisted cerebral vascular anastomosis without temporary arterial occlusion. 1.3 Selection of patients for this procedure should be carried out in the context of a multidisciplinary team including a neurosurgeon and an interventional neuroradiologist. 1.4 Publication of safety and efficacy outcomes will be useful. The Institute may review the procedure upon publication of further evidence.

Appendix C: Literature search for extracranial to intracranial bypass for intracranial atherosclerosis

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	15/11/2016	Issue 11 of 12, November 2016
HTA database (Cochrane Library)	15/11/2016	Issue 4 of 4, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	15/11/2016	Issue 10 of 12, October 2016
MEDLINE (Ovid)	15/11/2016	1946 to November Week 1 2016
MEDLINE In-Process (Ovid)	15/11/2016	November 14, 2016
EMBASE (Ovid)	15/11/2016	1974 to 2016 Week 46
PubMed	15/11/2016	n/a
BLIC	15/11/2016	n/a

Trial sources searched on 15 11 2016

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

Websites searched on 15 11 2016

- 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.

MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

1 (extracran* adj intracran* adj2 (revascular* or bypass* or by-pass* or circulation)).tw.

2	((high-flow* or high flow*) adj2 (revascular* or bypass* or by-pass* or circulation)).tw.
3	(("EC-IC" or "EC/IC") adj2 (revascular* or bypass* or by-pass* or circulation)).tw.
4	(extra*-intracran* adj2 (revascular* or bypass* or by-pass* or circulation)).tw.
5	EIAB.tw.
6	((Transcranial* or saphenous vein) adj2 (revascular* or bypass* or by-pass* or circulation)).tw.
7	*Cerebral Revascularization/
8	or/1-7
9	Animals/ not Humans/
10	8 not 9
11	(2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016*).ed.
12	10 and 11