

Risk of stroke in the periprocedural period: a literature review comparing carotid endarterectomy and stenting

ORIGINAL RESEARCH

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ABSTRACT

Background: Atherosclerosis of the carotid arteries is a pathophysiological process increasing the risk of stroke. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are two recognised procedures indicated by the National Institute of Clinical Excellence (NICE) guidelines aiming to reduce the risk of stroke. However, both are associated with periprocedural complications (defined as within 30 days), particularly stroke. This review aims to identify which treatment, CAS or CEA, has a lower risk of periprocedural stroke in patients with symptomatic or asymptomatic carotid artery stenosis.

Methods: NICE Evidence Search identified relevant UK guidelines. Search strategies combining free-text terms searched the Cochrane Database of Systematic Reviews, MEDLINE, PubMed, CINAHL, and EMBASE for systematic reviews post-2011, and RCTs from 2015 onwards. Studies were included if they contained a comparison of CEA vs CAS with regards to periprocedural risk of stroke, and if they contained novel studies not seen in the NICE guidance. English language and full-text limits were applied.

Results: Searches identified 202 articles. Two reviewers performed independent screening identifying 3 guidelines, 7 systematic reviews, and 1 randomised control trial eligible for inclusion. Guidelines currently advocate usage of both procedures, unlike Scottish Guidelines (SIGN) who only support CEA. Four appraised systematic reviews found a statistically significant increase in stroke probability with CAS ($p < 0.05$). The remaining reviews and RCT did not show a significantly increased risk with CAS ($p > 0.05$).

Discussion: This review's findings suggest that CAS is associated with an increased risk of periprocedural stroke when compared to CEA. Current UK guidelines by NICE and SIGN may require revisiting and take into account the new evidence not included in the original guidelines. There is a need for ongoing research as stenting technology improves over time.

BACKGROUND

Atherosclerosis is the pathophysiological process of lipid and fibrous tissue deposition within the tunica intima of arteries, leading to plaque formation. These plaques cause luminal narrowing and may rupture, becoming a site for thrombus formation. (1) Plaque formation and subsequent rupture in the carotid arteries can form emboli that migrate to the cerebral vasculature, potentially causing occlusion leading to ischaemia. (2,3) Ischaemic stroke, caused by such an occlusion, is defined as a sudden onset of neurological symptoms lasting more than 24 hours. (4) This form of stroke accounts for 85% of all strokes; the remaining 15% are haemorrhagic. (5)

Stroke is a major cause of morbidity and mortality, responsible for over 40,000 deaths in 2015, making it the 4th largest cause of death that year. (5) Non-lethal strokes have numerous long-term consequences such as loss of movement, speech problems, and life-changing impacts on the patient’s relatives, especially if long-term care is required following the incident. (6)

Carotid artery stenosis is responsible for approximately 20% of all strokes in the UK. (7) There is a recognised need to manage the disease process of carotid atherosclerosis, to prevent adverse events such as stroke. Conservative measures are crucial in targeting modifiable risk factors, particularly in an ageing population where atherosclerosis is of increasing incidence. (8) Table 1 shows the modifiable and non-modifiable risk factors for carotid atherosclerosis.

Table 1 - Modifiable and non-modifiable risk factors for carotid atherosclerosis (8)

Modifiable	Non-Modifiable
Smoking	Age
Blood Cholesterol	Family History
Hypertension	Gender
Obesity	Genetics
Immobility	
Diabetes	

Treatment of established carotid artery stenosis is divided into medical and surgical therapies. (9) Medical therapies aim to reduce the risk of clot formation through agents such as aspirin and clopidogrel. There are two major surgical options: carotid endarterectomy (CEA) and carotid artery stenting (CAS). CEA is an open procedure performed by vascular surgeons, whereby the carotid artery is opened, and the plaque physically removed. Stenting is a minimally invasive procedure performed by interventional radiologists who feed a catheter through a distant

artery, for instance the femoral, and placing a mesh to maintain the patency of the carotid artery lumen. Currently, NICE guidelines acknowledge a lack of evidence to support early stenting. (10) However, it can be performed at the surgeon and patient’s discretion. (11,12) Indications for carotid surgery as mentioned in the NICE TIA and Stroke Guideline CG68 can be found in Table 2. (10)

Table 2 - NICE CG68 Indications for operating (10)

1. Individuals who have a suspected TIA/non-disabling stroke should undergo a clinical assessment and relevant Radiology with surgery potentially to follow.
2. Recognised stable neurological symptoms with associated luminal narrowing of >50% according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria or >70% according to the European Carotid Surgery Trialists' Collaborative Group (ECST) criteria.
3. Surgery within 2 weeks of TIA/Stroke symptoms.

RATIONALE

Interventional radiology has emerged as a field involving minimally invasive surgery associated with lower rates of periprocedural complications, quicker recovery times and smaller scars compared to open surgery. (13) Therefore, it is perhaps expected that CAS could be a safer procedure with fewer complications compared to CEA. Scoping searches identified stroke to be a complication associated with both interventions.

This review was performed to ascertain the relative safety of the two surgical procedures, focussing on periprocedural stroke as the measure of safety, as stroke is the major adverse event that the surgeries are aiming to prevent. Similarly, periprocedural outcomes give a more accurate reflection of the surgery itself than longer-term outcomes which are more likely to be confounded by other factors contributing to the patient’s health.

Patients with symptomatic and asymptomatic carotid stenosis represent the population most likely to receive surgery, therefore representing the population of interest. Symptomatic is defined as patients who have suffered neurological symptoms due to stenosis and asymptomatic as patients picked up incidentally. All author definitions of stenosis were accepted as this review compared periprocedural outcomes, not successful treatment of the stenosis itself. The intervention was CAS; the newer method to treat stenosis. For the comparator, the current established method, endarterectomy, was chosen. With regards to outcome, periprocedural stroke (stroke within 30 days post-procedure) was selected as it is a known complication of both procedures and reflects operational safety.

The Population Intervention Comparator Outcome (PICO) for this review is therefore:

- **Population:** Patients with symptomatic/asymptomatic carotid artery stenosis requiring surgical intervention
- **Intervention:** Carotid artery stenting
- **Comparator:** Carotid endarterectomy
- **Outcome:** Periprocedural stroke (defined as stroke within 30 days post-procedure)
- **Review Question:** Which treatment, CAS or CEA, has a lower risk of periprocedural stroke in patients with symptomatic or asymptomatic carotid artery stenosis?

METHODOLOGY

A literature review was designed following a pre-defined protocol outlined below:

1. Creation of a PICO question
2. Development of inclusion and exclusion criteria
3. Formation of a search strategy for the databases NICE Evidence Search, MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, and PubMed
4. Article selection and appraisal
5. Discussion and conclusion of findings

Search Strategy

UK guidelines were identified using NICE Evidence Search. The electronic databases NICE Evidence Search, MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, and PubMed were searched in parallel for eligible systematic reviews. All the aforementioned databases except NICE Evidence Search were used to identify RCTs. Search terms used for each database were similar, generally including “Carotid stenosis AND stent AND endarterectomy” (Table 3). Variations in search terms were due to differences in the terminology accepted by the individual databases.

Article Selection and Management

Date limits were pre-specified for systematic reviews to identify reviews and RCTs not seen in guidelines. RCTs were limited to find novel trials not in any reviews or guidelines. English language and full-text limits were applied for all searches. Two authors

performed independent title and abstract screening against pre-defined inclusion and exclusion criteria. Disagreements were resolved through consensus agreement with a third reviewer.

Included papers compared carotid endarterectomy and stenting to treat stenosis, with assessment of periprocedural stroke as an outcome. Excluded papers did not compare the procedures, did not feature periprocedural stroke as an outcome, or were reviews/RCTs found in guidelines. EndNote x7 (Clarivate Analytics, USA) managed study records throughout the review process.

Data Extraction

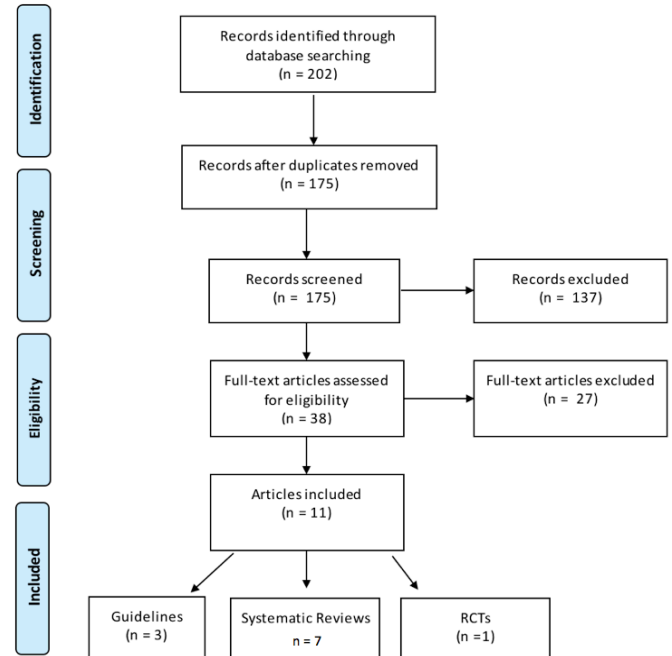
Two authors performed extraction of results comparing the two procedures and their risk of stroke in the periprocedural period. Appraisal of guidelines used the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. (14) Two authors independently appraised the Systematic reviews and the RCT using the appropriate Critical Appraisal Skills Programme (CASP) checklists. (15)

Table 3 – Search terms

Search	Database	Search Terms	Limits applied
Guidelines	NICE Evidence Search	Carotid stenosis AND stent AND endarterectomy	NICE Accredited Guidance
Systematic reviews	Cochrane	Carotid stenosis AND Stents AND Carotid Endarterectomy AND Stroke	Systematic Reviews Year 2011 – current
	MEDLINE	Carotid stenosis AND Stents AND Endarterectomy, Carotid AND Stroke	Systematic Reviews Year 2011 – current English Language
	CINAHL	Carotid endarterectomy AND carotid stenting AND stroke AND periprocedural	Year 2011 – current Systematic review
	PubMed	Carotid stenosis AND Stents AND Endarterectomy, Carotid AND Stroke	Systematic Reviews Year 2011 – current English Language
	EMBASE	Carotid Artery Obstruction AND Stent AND carotid endarterectomy AND cerebrovascular accident	Systematic Reviews Year 2011 – current

Randomised Controlled Trials	MEDLINE	Carotid stenosis AND Stents AND Endarterectomy, Carotid AND Stroke	Randomised Controlled Trials Year 2015 - current
	EMBASE	Carotid Artery Obstruction AND Stent AND carotid endarterectomy AND cerebrovascular accident	Randomised Controlled Trials Year 2015 - current
	PubMed	Carotid stenosis AND Stents AND Endarterectomy, Carotid AND Stroke	Randomised Controlled Trials Year 2015 - current
	CINAHL	Carotid endarterectomy AND carotid stenting AND stroke AND periprocedural	Randomised Controlled Trials Year 2015 - current
	Cochrane	Carotid stenosis AND Stents AND Carotid Endarterectomy AND Stroke	Trials 2015 - current

Figure 1 - Adapted PRISMA flowchart showing review process (16)



Results

From 202 search results a total of eleven eligible papers were found. These included three guidelines, seven systematic reviews and one RCT (Figure 1).

All three guidelines concluded that there is inadequate evidence to assess the efficacy and safety of early CAS (Table 4). (11,12,17) CEA remains the first-line intervention for both scenarios. NICE recommends performing CAS only if a skilled clinician is available and in certain situations (e.g. for research purposes) after patients have consented and been made aware of endarterectomy as an alternative. (11,12) The results of the systematic reviews and RCT are shown in Table 5.

Table 4 - Summary of guidelines

Guideline	Date of publication	Evidence base	Conclusion
Carotid artery stent placement for asymptomatic extracranial carotid stenosis (IPG388) (11) Author: NICE	April 2011 however evidence overview was performed in 2010	2 meta-analyses 2 randomised controlled trials 2 non-randomised controlled studies 3 case series 3 case reports	Stenting for asymptomatic stenosis can be performed by skilled clinicians under special arrangements, such as research, but CEA remains first line
Carotid artery stent placement for symptomatic extracranial carotid stenosis (IPG389) (12) Author: NICE	April 2011 however evidence overview was performed in 2010	2 meta-analyses 4 randomised controlled trials 2 non-randomised controlled studies 5 case series 4 case reports	CEA is first line. Evidence accepts usage of stenting if the specialist and patient choose.
Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention (17) Author: SIGN	December 2008	1 systematic review	Carotid angioplasty and stenting is not recommended without further evidence of its safety and efficacy above CEA.

Table 5 - Systematic review and RCT results (18-25)

Name of Study	Study Design	Number of trials	Total number of patients	Main results (CAS vs CEA)
Bonati LH et al. (2012) (18)	Systematic review	16 RCTs	7,527	OR 1.81, 95% CI: 1.40 to 2.34, P<0.00001 I ² = 12%
Gahramenpour A et al. (2012) (19)	Systematic review	14 RCTs 15 meta-analyses 1 data registry	74,003	No meta-analysis performed.

Paraskevas KI et al. (2016) (20)	Systematic review	21 data registries	Over 1.5 million procedures assessed	No meta-analysis performed.
Raman G et al. (2013) (21)	Systematic review	3 RCTs 7 NRCS	377,361	NRCS RR 1.74 (95% CI: 1.41-2.16)
Zhang L et al. (2015) (22)	Systematic review	12 RCTs 3 Prospective Controlled Studies 20 Retrospective comparative studies	27,525	Studies in 2011-2015 RR 1.50 (95% CI 1.14-1.98 p=0.004) I ² = 0% Studies in 2006-2010 RR was 1.61 (95% CI 1.35-1.91 p< 0.001) I ² = 45% Studies in 2001-2005 RR 1.01 (95% CI 0.64-1.60 p=0.95) I ² = 10%
Ouyang Y et al. (2015) (23)	Systematic review	9 RCTs	6,984	RR=1.62 (95% CI: 1.31-2.00, P<0.0001, I ² =37%)
Vincent S et al. (2015) (24)	Systematic review	8 RCTs	7,091	RR=1.49 (95% CI: 1.11-2.01, P value not stated, I ² =42.2%)
Rosenfield K et al. (2016) (25)	RCT	1 RCT	1,453	CAS 2.8% vs CEA 1.4%, p=0.23)

DISCUSSION

This literature review identified 3 guidelines and 7 systematic reviews and 1 RCT comparing CEA vs CAS and the development of stroke in the periprocedural period. (11,12,17-25) All provided evidence to suggest CEA is associated with a lower risk of periprocedural stroke, some with statistical significance. (11,12,17-25)

Guideline Appraisal

The three eligible guidelines identified were the NICE IPG388 (asymptomatic stenosis) (12) and IPG389 (symptomatic stenosis) (13) along with SIGN 108. (17) NICE IPG388/389 were produced in 2011 and clearly state the PICO and the outcomes to be assessed. (11,12) Outcomes compared patients that had either procedure performed, categorised as ‘efficacy’ (stroke, mortality, and arterial patency) and ‘safety’ (mortality, stroke, myocardial infarction, and other). (11,12) Searches of MEDLINE, CINAHL, EMBASE, Cochrane Database and other specified databases were

performed. (11,12) Searches yielded eligible meta-analyses, RCTs, non-randomised controlled studies (NRCS), case series, and case reports. Due to heterogeneity, NICE did not perform a meta-analysis. (11,12) No mention of inclusion or exclusion criteria was made, and whilst the search strategy for MEDLINE was shown, other databases strategies were not included. (11,12)

Results for the studies used were given as relative risks (RR) and hazard ratios (HR), and significance was defined as a $p < 0.05$. Three of the studies in IPG388 (asymptomatic stenosis) (1 meta-analysis, 1 RCT and 1 NRCS) showed that CEA had a significantly lower rate of periprocedural stroke. (11) IPG389 demonstrated a similar picture in symptomatic patients, with CAS significantly increasing periprocedural stroke in five (2 meta-analyses, 3 RCTS) of the 17 studies, although most studies found no statistically significant difference. (12) Both guidelines acknowledged the use of 'low quality' evidence, concluding endarterectomy remains first-line, but this does not represent a contraindication for stenting to occur. (11,12)

SIGN Guideline 108 was produced in 2008 which recommends against using stenting to treat both symptomatic and asymptomatic stenosis. (17) The basis of this recommendation is entirely from the meta-analysis by Ederle et al. (26) This analysis is also appraised by NICE and it is interesting to note that the conclusion by SIGN differs to NICE despite both using the same meta-analysis. The SIGN guideline, however, lacked the methodological rigour of the NICE guidelines, with no defined search strategy and no explanation of how the evidence was sourced.

Systematic Reviews Appraisal

A total of seven systematic reviews were included (18-24); these vary in the study types featured, but all suggest CAS to be associated with increased risk of periprocedural stroke compared to CEA. (18-24) Three limited their reviews to only RCTs. (18, 23,24) Another three included RCTs along with other study designs such as meta-analyses and retrospective studies. (19,21,22) One review looked at dataset registries in isolation. (20) Due to variation in studies included, only five performed meta-analyses of the data that they collected. (18, 21-24) None of the systematic reviews looked solely at UK populations and were mainly North American in origin. Given the variation in international healthcare systems, there may be questionable applicability to UK populations. Those looking at only RCTs contained the smallest numbers of patients (ranging from 6988 to 7527 patients), while the study looking at dataset registries contained a pool of over 1.5 million procedures. Six out of seven reviews (except Raman et al.) (21) looked at both asymptomatic and symptomatic patients.

Search strategy quality varied across the reviews, with the most comprehensive search strategy performed by Bonati et al. (18) They

searched for RCTs in CENTRAL, MEDLINE, EMBASE, Science Citation Index, and Cochrane Stroke Group Trials Register. Additionally, they searched three registries for ongoing trials, searched reference lists for relevant studies, and contacted experts in the field. Only Bonati et al. (18) and Paraskevas et al. (20) had two independent reviewers perform a title screen of each database. Most of the reviews limited their inclusion criteria to English language only, with two exceptions: Vincent et al. (24) accepted English and French languages, while Bonati et al. (18) did not apply any language limits.

Additionally, Paraskevas et al. (20) was the only study to apply a date limit to their search by excluding pre-2008 studies. They justified this by wanting to exclude historical studies, however, no justification was made as to why 2008 was seen as a cut off. All reviews performed quality assessments of their studies and reviewed for bias, except for Gahramenpour et al. (19) Furthermore, only Bonati et al. supported each of their judgements of bias using quotes from the original trials. (18) Use of a consistent tool allows a reader to critique the authors' bias assessments and ensure that the authors were not biased themselves.

All but Gahramenpour et al. (19) or Paraskevas et al. (20) performed a meta-analysis of the data. Only Paraskevas et al. justified their lack of meta-analysis, stating that baseline patient characteristics and outcomes were reported variably, and there was substantial heterogeneity in the registries used. (20) The five meta-analyses measured heterogeneity using I^2 statistics. The I^2 values varied between 0 and 45% when analysing RCTs, indicating low to moderate heterogeneity as per Cochrane definitions. (27,28)

In reviews where RCTs were used, the most common RCTs were CREST, (29) EVA-3S, (30) SAPPHERE, (31) SPACE, (32) and ICSS. (33) These were large-scale RCTs with the smallest including 334 patients (SAPPHERE (31)) and the largest 2522 (CREST (29)). These five in particular were all considered to have low bias when assessed by two independent reviewers in Bonati et al. (18) Three of the aforementioned RCTs used in the meta-analyses by Bonati et al. (20) and Zhang et al. (22) found a statistically significant difference in our primary outcome of stroke (EVA-3S, (30) ICSS, (33) CREST (29)) and 2 (SAPPHERE (31) and SPACE (32)) did not, however, the cumulative data did point to a significant difference.

Bonati et al. presented their results as odds ratios, finding that in symptomatic patients, CAS had statistically significant increased odds of stroke (OR 1.81, 95% CI: 1.40 to 2.34, $P < 0.00001$). (18) Four studies presented their findings in the form of relative risks (Vincent et al., Ouyang et al., Raman et al. and Zhang et al.). (21-24) Their findings varied between RR=1.49 (95% CI: 1.11-2.01) (Vincent et al. (24)) and RR=1.74 (95% CI: 1.41-2.16) (Raman et al. (21)). A notable abnormality with Ouyang et al. (23) was the lack of correlation of results in the abstract and results sections of

the article.

Interestingly, not all of the studies in Zhang et al. support this conclusion. (22) The authors performed a chronological analysis and found that studies from 2001–2005 showed no statistically significant difference between the procedures. (22) In their discussion, they attribute this to the novelty of the procedure at that time, thus CAS was only used in simple cases. (22)

RCT Appraisal

The ACT-1 trial had a clearly focused PICO, with the aims being well defined. (25) The sample size was large, with 1453 patients randomised at a ratio of 3:1 to receive CAS or CEA. Randomisation was performed with use of a web-based system. (25) Blinding was not possible due to the nature of the interventions; this increases the possibility of bias. A baseline characteristics table is included in the study and shows similar characteristics between the two study arms. Important possible confounders such as age, gender, cigarette smoking, diabetes and previous cardiovascular disease were considered. The presence of two similar groups indicates successful randomisation. Moreover, the study mentions that analysis was by intention to treat (ITT). This refers to analysis with respect to the groups to which participants were originally randomised. The inclusion criteria for ACT-1 was specific; it focused on patients aged 79 years or younger, with severe carotid stenosis who were asymptomatic and not considered to be at high risk of stroke. (25) This specificity may limit applicability to the wider population.

Review Findings

This review identified literature suggesting CAS is associated with increased periprocedural stroke relative to CEA. Given Interventional Radiology and Endovascular Surgery are modern and rapidly advancing fields, it is possible that periprocedural outcomes will change over time as technology improves. Previous evidence has shown that improved operator skill is associated with superior outcomes (34–36) and that the use of different stenting technology has been associated with variations in safety outcomes. (37) Relevant RCTs were included, published after the most recent systematic review to see if contemporary evidence supports the trend seen up until now.

Currently, NICE guidelines withhold from offering any definitive recommendation regarding the use of CAS over CEA. (11,12) They appreciate that CAS is an expanding field and recommend the use of stenting for research purposes. On the other hand, SIGN concluded that stenting was not recommended without further

evidence. The SIGN guidelines were published in 2008, before the results of many important large-scale trials were released. This guideline is in need of an update. (17)

As previously alluded to, our review seems to indicate that the NICE guidelines need updating regarding the safety of carotid stenting versus endarterectomy, however, this review focused on a single outcome. Many of the studies we analysed considered a number of important safety and efficacy outcomes, such as periprocedural myocardial infarction. In order to make a conclusive recommendation, a multitude of periprocedural complications should be looked at to gauge the overall picture of CAS vs CEA. Similarly, factors such as patient preference, specialist availability, and cost effectiveness play a role in national decision-making.

Limitations

A limitation of our review was our exclusion of studies which we were unable to access in full or those which were non-English language. Where information was absent or unclear, a future review could contact study authors to obtain information. Furthermore, we did not search for ongoing or unpublished trials, which could provide relevant up-to-date results reflecting current practice.

CONCLUSION

This review aimed to compare the safety of two procedures, endarterectomy and stenting, to ascertain which is associated with a greater risk of periprocedural stroke. The conclusion, based on available research, suggests stenting is associated with an increased risk of periprocedural stroke in asymptomatic and symptomatic patients when compared to carotid endarterectomy. This may change as surgical practice continues to evolve. Based on the probability of periprocedural stroke, endarterectomy may remain preferable to stenting, until adequate high-impact research can argue to the contrary.

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