European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis



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Abstract

Atherosclerotic stenosis of the internal carotid artery is an important cause of stroke. The aim of this guideline is to analyse the evidence pertaining to medical, surgical and endovascular treatment of patients with carotid stenosis. These guidelines were developed based on the ESO standard operating procedure and followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The working group identified relevant questions, performed systematic reviews and meta-analyses of the literature, assessed the quality of the available evidence, and wrote recommendations. Based on moderate quality evidence, we recommend carotid endarterectomy (CEA) in patients with \geq 60–99% asymptomatic carotid stenosis considered to be at increased risk of stroke on best medical treatment (BMT) alone. We also recommend CEA for patients with \geq 70–99% symptomatic stenosis, and we suggest CEA for patients with 50-69% symptomatic stenosis. Based on high quality evidence, we recommend CEA should be performed early, ideally within two weeks of the last retinal or cerebral ischaemic event in patients with >50–99% symptomatic stenosis. Based on low guality evidence, carotid artery stenting (CAS) may be considered in patients < 70 years old with symptomatic $\ge 50-99\%$ carotid stenosis. Several randomised trials supporting these recommendations were started decades ago, and BMT, CEA and CAS have evolved since. The results of another large trial comparing outcomes after CAS versus CEA in patients with asymptomatic stenosis are anticipated in the near future. Further trials are needed to reassess the benefits of carotid revascularisation in combination with modern BMT in subgroups of patients with carotid stenosis.

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Introduction

Atherosclerotic carotid artery disease is one of the major causes of ischaemic stroke and transient ischaemic attack (TIA), accounting for about 10–15% of cases, depending on the method of aetiological classification and the patient population studied.¹ Atherosclerotic carotid stenosis mostly occurs at the carotid bifurcation, involving the distal common and the proximal internal carotid artery.² Other sites which are predisposed to develop atherosclerotic stenosis are the origin of the common carotid artery and the cavernous segment of the intracranial carotid artery. The prevalence of atherosclerotic carotid disease increases with age and is higher in men than in women. In Caucasian populations, $\geq 50\%$ stenosis of the carotid artery was identified in 2.3% of men in the sixth decade, in 6.0% in the seventh decade and in 7.5% of men aged 80 years; in women, the corresponding prevalence figures were 2.0%, 3.6% and 5.0% in these age groups, respectively.³

This guideline provides recommendations on the use of carotid endarterectomy (CEA) and carotid artery stenting (CAS) in patients with symptomatic or asymptomatic stenosis of the extracranial carotid bifurcation caused by atherosclerosis. We did not review the available evidence regarding management of proximal common carotid artery or intracranial internal carotid artery stenosis, or non-atherosclerotic causes of stenosis, such as secondary to dissection, fibromuscular dysplasia, arteritis etc. Furthermore, we did not include aspects of diagnostic imaging, peri-procedural management, technical aspects of CEA and CAS, or medical therapy. Guidance on these topics can be found in other guidelines.⁴⁻⁶

Methods

This guideline document was commissioned by the European Stroke Organisation (ESO). A multidisciplinary Module Working Group (MWG) was established, consisting of experts in the field from vascular neurology, vascular surgery and neuroradiology, who are represented as authors of this guideline document. The composition of this group was approved by the ESO Guidelines Board and the ESO Executive Committee, based on a review of the intellectual and financial disclosures of the proposed members.

The guidelines were developed using GRADE methodology⁷ and the ESO Standard Operating Procedure.⁸ In brief, we defined the patient population, the interventions and comparators, the outcomes of clinical interest (PICOs), and the design of studies to be included. The outcomes were rated as critical, important or of limited importance according to the GRADE criteria.^{7,8}

Population

This guideline makes recommendations on treatment of patients with symptomatic or asymptomatic atherosclerotic carotid stenosis. Carotid stenosis was defined as symptomatic if it had caused ischaemic cerebrovascular events in the ipsilateral eye (transient monocular blindness or retinal infarction) or cerebral hemisphere (transient ischaemic attack (TIA) or stroke) in the preceding six months. Asymptomatic carotid stenosis was defined as a stenosis which was not associated with any ocular or cerebral ischaemic events in the ipsilateral carotid territory within the preceding six months.

Patient subgroups. PICO questions were additionally analysed for the following pre-specified patient subgroups when data were available:

- 1. Age (</>270 years)
- 2. Sex
- Degree of stenosis, according to the method used in the NASCET study⁹ or its non-invasive equivalent (mild: <50%, moderate: 50–69%, severe: 70–99%, near occlusion (defined as collapse of the distal lumen))
- 4. Time since most recent ischaemic event (for symptomatic carotid stenosis)
- 5. Type of most recent ischaemic event (for symptomatic carotid stenosis): stroke, transient ischaemic attack, ocular ischaemia (including transient monocular blindness or *amaurosis fugax* and retinal infarction).

Interventions and comparators

Interventions and comparators are CAS, CEA, and contemporary best medical therapy (as defined by the study authors at the time of the study). The guideline does not address carotid revascularisation done as part of acute stroke therapy, or carotid angioplasty without insertion of a stent.

Outcomes

We graded outcomes occurring in the peri-procedural period of carotid artery revascularisation, as well as outcomes occurring in the post-procedural period on a scale of 0–9 to classify them as either critical for decision making (grade 7–9; Table 1); important, but not critical for making a decision (grade 4–6; Table 1); or of limited importance for making a decision (grade 0–3). Critical and important outcomes were included in the evidence profile.

The peri-procedural period was defined as the period between randomisation in the trial and 30 days after treatment, or as the first 30 days after randomisation in patients who did not undergo revascularisation (unless different definitions were used in individual trials in question). Peri-procedural outcomes were included as a measure of treatment safety. Postprocedural outcomes (i.e. outcomes occurring beyond the peri-procedural period) were included as a measure of treatment efficacy.

III

Formation of PICO questions

series of PICO (Population, Intervention, А Comparator, Outcome) questions were developed and subsequently approved by the ESO Guidelines board and the ESO Executive Committee. The PICO questions were based on the peri-procedural and post-procedural outcomes, graded as critical or important for decision making, as well as combinations of these outcomes. We only compared peri-procedural outcomes on their own in trials of CAS versus CEA. This resulted in 4 PICO questions for the comparison of CEA versus medical therapy alone, 4 PICO questions for the comparison of CAS versus medical therapy alone and 11 PICO questions for the comparison of CAS versus CEA in separate trials in patients with asymptomatic carotid stenosis and in patients with symptomatic carotid stenosis. We also formulated one PICO question concerning the risk of restenosis after CAS or CEA which was addressed using combined data from patients with symptomatic and asymptomatic carotid stenosis; these data are reported in the section on symptomatic carotid stenosis. Subgroup analyses for these PICO questions were also performed in the aforementioned pre-specified patient subgroups, where data were available.

Literature search, data extraction and synthesis

Literature searches were restricted to reports of randomised controlled trials (RCTs). We identified three

Peri-procedural outcomes graded as	-Death
critical for decision making	-Any stroke (ischaemic or haemorrhagic), defined as an acute onset of focal neu- rological dysfunction, with symptoms lasting for longer than 24 h or leading to death within 24 h, of non-traumatic vascular aetiology. Retinal infarction with visual loss lasting for longer than 24 h, was included within the definition of stroke.
	-Major stroke, defined as resulting in substantial impairment or disability (measured by a modified Rankin scale ¹⁰ score of >2, typically 30 days or more after the event, if available), or death
Peri-procedural outcomes graded as important for decision making	-Myocardial infarction, according to the definitions used in the individual trials -Cranial nerve injury
Post-procedural outcomes graded as critical for decision making	 -Ipsilateral stroke, occurring in the territory of the anterior or middle cerebral artery on the side of the randomised artery. -Any stroke -Major stroke, defined as resulting in substantial impairment or disability (measured
	by a modified Rankin Scale score ¹⁰ (mRS) of >2, if available), or death
Post-procedural outcomes graded as	-Death
important for decision making	-Severe residual or recurrent stenosis (\geq 70% according to the NASCET method of grading stenosis ⁹ or its non-invasive equivalent) or occlusion of the treated artery.

Table 1. Outcomes.

systematic reviews of RCTs in the Cochrane Database of Systematic Reviews, which were of relevance to this guideline, one comparing CEA with medical therapy alone for asymptomatic carotid stenosis,¹¹ one comparing CEA with medical therapy alone for symptomatic carotid stenosis¹² and one comparing CAS with CEA for asymptomatic or symptomatic carotid stenosis.¹³ For the comparisons of CEA versus medical therapy, and CAS versus CEA, systematic searches of the MEDLINE, EMBASE, and Cochrane databases (from the date of the last search in the Cochrane reviews to 10 August 2020) were conducted by two ESO Guidelines methodologists (AL and MTR) using the same search terms which were defined in the Cochrane reviews. For the comparison of CAS versus best medical therapy, a de novo search of the literature was performed using the MEDLINE, EMBASE and Cochrane databases from their inception until 10 August 2020, using the search terms provided in the Online Appendix. To reduce the number of duplicate references identified, we simultaneously searched for relevant data in patients with asymptomatic and symptomatic carotid stenosis.

For each of the three main comparisons, a group of MWG members (a 'PICO group') was formed to select the studies for inclusion and to evaluate the available evidence. Within each PICO group, two MWG members independently screened the titles and abstracts of publications identified from the searches (first level selection), and subsequently assessed the full text of potentially relevant studies (second level selection). Data were extracted independently by AL and MTR from studies which met criteria for second level selection, separately for patients with asymptomatic and those with symptomatic carotid stenosis. At least one additional MWG member checked the extracted data results for accuracy.

For some PICO questions (PICO 6.1 and 6.9), we included outcomes in pre-defined patient subgroups derived from pooled analyses of individual patient data (IPD) from the *EVA-3S*, *SPACE*, *ICSS* and *CREST* trials which were performed by the *Carotid Stenosis Trialists' Collaboration (CSTC)*.

The risks of selection, performance, detection, attrition and reporting bias in each randomised trial were assessed using the Cochrane Collaboration's tool.¹⁴ Heterogeneity across studies was assessed using Cochran's Q (reported as a p value) and I² statistics.¹⁵ For each PICO question and each outcome, the quality of evidence was rated using the GRADEpro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.) as high, moderate, low or very low.⁸

The relevant PICO group was responsible for analysing the available data and formulating an evidence-based recommendation according to the GRADE evidence profiles and the ESO standard operating procedure. Random-effect metanalyses were conducted and relative intervention effects were summarised as risk ratios (RR) and their 95% confidence interval. The absolute measure of intervention effects was calculated as the difference between the baseline risk of an outcome (patients receiving control intervention) and the risk of outcome after the intervention was applied (risk of an outcome in patients who received an intervention). Absolute effects are based on the relative magnitude of an effect with respect to the baseline risk, which is similar to risk differences. The fewer value represents any value below 1 per 1000 and the more value represents any value more than 1 per 1000.

The wording and the rating of the strength of each recommendation was passed by majority voting by all MWG members. An Expert Consensus Statement, based on voting by all MWG members, was presented where the PICO group considered that there was insufficient evidence available to provide clear evidence-based recommendations for situations in which practical guidance was needed for everyday clinical practice. Importantly, these Expert Consensus Statements should not be regarded as evidence-based recommendations since they only reflect the opinion of the majority of the members of the MWG.

The Guideline document was subsequently reviewed by all MWG members and modified until a consensus was reached. Finally, the guideline document was peerreviewed and approved by external reviewers and members of the ESO Guidelines Board and ESO Executive Committee.

Results

Endarterectomy or medical therapy for asymptomatic carotid stenosis

Description of studies. The Veterans Administration (VA) asymptomatic carotid stenosis cooperative study randomised 444 men with \geq 50% asymptomatic carotid stenosis on angiography to CEA (n = 211) or medical therapy alone (n = 233) between 1983 and 1987.¹⁶ Five percent of patients turned out to have <50% stenosis after centralised analysis of the angiograms. Patients had never experienced any prior ipsilateral cerebrovascular events and were followed up for a mean of 47.9 months. The results were reported in 1993.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) randomly allocated 1662 patients with \geq 60% asymptomatic carotid artery stenosis to CEA (n = 825) or medical therapy alone (n = 834) between 1987 and 1993. Patients were defined as being 'asymptomatic' if they never had cerebrovascular symptoms in the distribution of the 'study' carotid artery or vertebrobasilar territory. Patients with contralateral cerebral hemispheric symptoms within the previous 45 days were excluded. Outcomes after a median follow-up period of 2.7 years were reported in 1995.¹⁷ The definition of haemodynamically-significant carotid stenosis was based on meeting at least one of three prespecified criteria from an ocular pneumoplethysmographic (OPG-Gee) examination, an ultrasound of carotid arteries and/or catheter angiography indicating a diameter stenosis of >60% (NASCET methodology). Patients randomised to surgery on the basis of ultrasound findings, or ultrasound combined with OPG-Gee were also required to have a catheter angiogram prior to CEA. If a post-randomisation angiogram revealed that the contralateral carotid artery was more severely stenosed, that artery then became the allocated 'study artery'.

The Asymptomatic Carotid Surgery Trial (ACST-1) randomised 3120 patients with $\geq 60\%$ asymptomatic carotid stenosis on ultrasound to immediate CEA (n = 1560, median delay one month (IQR: 0.3–2.5)) or initial medical therapy with the option of deferred CEA (n = 1560) between 1993 and 2003.^{18,19} The first ACST-1 report in 2004 provided data on outcomes during follow-up for up to five years (mean 3.4 years) after randomisation.¹⁸ A subsequent report in 2010 included outcomes over a median follow-up period of nine years (IQR 6–11 years) after randomisation.¹⁹

The Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis (AMTEC) study randomised 55 patients with 70–79% carotid stenosis to receive CEA (n = 31) or medical therapy alone (n = 24) between 2009 and 2013.²⁰ Stenosis was graded by ultrasound examinations, but had to be confirmed by computed tomographic or magnetic resonance angiography (CTA/MRA) or catheter angiography. The trial was stopped prematurely by the independent data and safety monitoring board because of a high rate of the primary endpoint in the medical arm after a median follow-up period of 3.3 years (maximum, 5.0 years); results were reported in 2015.

Data from patients with 50–99% asymptomatic carotid stenosis randomly assigned to CEA (n=203) or medical therapy alone (n=113) between 2009 and 2013 in the three-arm *Stent-protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy (SPACE-2)* trial were also included in the present section.^{21,22} A detailed description of the SPACE-2 trial is provided in section 'Stenting or medical therapy for asymptomatic carotid stenosis.

The effects of treatment are presented with medical therapy alone as the reference group. A summary of findings is provided in Table 2.

PICO 1.1: In patients with asymptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or periprocedural death? There is moderate quality evidence that endarterectomy reduces the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death compared with medical therapy alone (RR: 0.73, 95% CI: 0.59–0.90; equivalent to 19 fewer events with CEA per 1000, from 28 fewer to 7 fewer; Figure 1.1).

PICO 1.2: In patients with asymptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of stroke in any territory, including peri-procedural death? There is also moderate quality evidence that endarterectomy reduces the longterm risk of stroke in any territory, including periprocedural death, compared with medical therapy alone (RR: 0.74, 0.59–0.92; 31 fewer events with CEA per 1000 patients; from 48 fewer to 9 fewer; Figure 1.2). Comparison of the data on the estimated number of ipsilateral strokes (PICO 1.1) and strokes in any territory (PICO 1.2) suggests that CEA might also prevent strokes occurring outside the territory supplied by the operated carotid artery.

Subgroup data regarding age, sex and severity of stenosis were derived from ACST-1 only. The effect of CEA is significantly modified by age (interaction p = 0.04): there is moderate evidence of a benefit of CEA in patients younger than 75 years (RR: 0.62, 0.49–0.78; Figure 1.2.2), but no evidence of benefit observed in patients \geq 75 years old (RR: 1.03, 95% CI: 0.68–1.55, low quality evidence). There is no evidence of a modification of the effect of CEA according to sex (Figure 1.2.1) or severity of stenosis (Figure 1.2.3).

PICO 1.3: In patients with asymptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of major stroke, including peri-procedural death? There is moderate quality evidence that endarterectomy reduces the long-term risk of major stroke, including peri-procedural death compared with medical therapy alone (RR: 0.77: 0.61–0.98; 14 fewer events with CEA per 1000; from 24 fewer to 1 fewer; Figure 1.3).

Certaint	Certainty assessment						№ of patients		Effect			
N₀ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endarterectomy	Medical therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO 5	I.I: Long-term Randomised trials	r risk of ipsilateral stroke, Not serious Not serious	eral stroke, i Not serious	n cluding peri- Serious ^a	- procedural s i Not serious	i troke in any te None	PICO 1.1: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death 5 Randomised Not serious Not serious Serious ^a Not serious None 139/2830 190/2764 RR 0.1 trials (4.9%) (6.9%) (0.59–0	orocedural 190/2764 (6.9%)	death RR 0.73 (0.59–0.90)	 fewer per 1000 (from 28 fewer to 7 fewer) 	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 5	1.2: Long-term Randomised trials	PICO 1.2: Long-term risk of stroke in any territory, including peri-procedural death 5 Randomised Not serious Not serious Serious ^a Not serious None trials	e in any territ Not serious	ory, including Serious ^a	g peri-proced Not serious	ural death None	238/2830 (8.4%)	326/2764 (11.8%)	RR 0.74 (0.59–0.92)	31 fewer per 1000 (from 48 fewer to 9 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO -	1.2.1a: Long-te Randomised trials	e rm risk of str Not serious	n risk of stroke in any ter Not serious Not serious	rritory, includ Serious ^a	ling peri-proc Not serious	cedural death. None	PICO 1.2.1a: Long-term risk of stroke in any territory, including peri-procedural death. Subgroup: Men 1 Randomised Not serious Not serious Serious ^a Not serious None 89/1021 trials (8.7%)	134/1023 (13.1%)	RR 0.67 (0.52–0.86)	43 fewer per 1000 (from 63 fewer to 18 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO -	1.2.1b: Long-te Randomised trials	e rm risk of str ı Not serious	m risk of stroke in any ter Not serious Not serious	rritory, inclu d Serious ^a	ling peri-proc Not serious	cedural death. None	PICO 1.2.1b: Long-term risk of stroke in any territory, including peri-procedural death. Subgroup: Women 1 Randomised Not serious Not serious Serious ^a Not serious None 40/539 65/ trials (7.4%) (12	нен 65/537 (12.1%)	RR 0.61 (0.42–0.89)	47 fewer per 1000 (from 70 fewer to 13 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO -	1.2.2a: Long-te Randomised trials	rm risk of stroke in any te Not serious Not serious	oke in any te l Not serious	rritory, includ Serious ^a	ling peri-proc Not serious	edural death. None	PICO 1.2.2a: Long-term risk of stroke in any territory, including peri-procedural death. Subgroup: Age <75 years 1 Randomised Not serious Not serious ^a Not serious None 98/1231 160/1239 1 trials (8.0%) (12.9%)	< 75 years 160/1239 (12.9%)	RR 0.62 (0.49 to 0.78)	49 fewer per 1000 (from 66 fewer to 28 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO -	1.2.2b: Long-te Randomised trials	e rm risk of str i Not serious	n risk of stroke in any te r Not serious Not serious	rritory, includ Serious ^ª	ling peri-proc Serious ^b	cedural death. None	PICO 1.2.2b: Long-term risk of stroke in any territory, including peri-procedural death. Subgroup: Age <75 years 1 Randomised Not serious Not serious Serious ^a Serious ^b None 41/329 39/321 1 trials (12.5%) (12.1%)	< 75 years 39/321 (12.1%)	RR 1.03 (0.68–1.55)	4 more per 1000 (from 39 fewer to 67 more)		CRITICAL
PICO -	1.2.3a: Long-te Randomised trials	e rm risk of str Not serious	n risk of stroke in any ter Not serious Not serious	rritory, includ Serious ^a	ling peri-proc Not serious	cedural death. None	PICO 1.2.3a: Long-term risk of stroke in any territory, including peri-procedural death. Subgroup: <80% Stenosis 1 Randomised Not serious Not serious ^a Not serious None 56/641 86/643 trials (13.4%)	Stenosis 86/643 (13.4%)	RR 0.65 (0.48–0.90)	47 fewer per 1000 (from 70 fewer to 13 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO -	I.2.3b: Long-te Randomised trials	e rm risk of str i Not serious	n risk of stroke in any te r Not serious Not serious	rritory, includ Serious ^a	ding peri-procedur Not serious None	cedural death. None	PICO 1.2.3b: Long-term risk of stroke in any territory, including peri-procedural death. Subgroup: ≥80% Stenosis 1 Randomised Not serious Not serious ^a Not serious None 83/919 113/917 trials (9.0%) (12.3%)	5 Stenosis 113/917 (12.3%)	RR 0.73 (0.56–0.96)	33 fewer per 1000 (from 54 fewer to 5 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 4	1.3: Long-term Randomised trials	PICO 1.3: Long-term risk of major stroke, including peri-procedural death 4 Randomised Not serious Not serious Serious ^a Not serious ¹ trials	stroke, inclu Not serious	ding peri-pro Serious ^a	cedural deat Not serious	None	119/2619 (4.5%)	53/253 (6.0%)	RR 0.77 (0.61–0.98)	14 fewer per 1000 (from 24 fewer to 1 fewer)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 4	1.4: Long-term Randomised trials	PICO 1.4: Long-term risk of death 4 Randomised Not serious Not serious trials	Not serious	Serious ^a	Serious ^b	None	699/2619 (26.7%)	667/2531 (26.4%)	RR 1.02 (0.88–1.20)	5 more per 1000 (from 32 fewer to 53 more)		IMPORTANT

Table 2. Summary of findings for endarterectomy versus medical therapy for asymptomatic carotid stenosis (PICO 1.1-1.4).

CI: confidence interval; RR: risk ratio. ^aEndarterectomy and medical therapy have evolved since the trials contributing the evidence were performed. ^bFew events and wide confidence intervals.

	Endartere	ctomy	Medical th	nerapy		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	om, 95% CI	
VA 1993	17	211	24	233	13.0%	0.78 [0.43, 1.41]	1993			-	
ACAS 1995	33	825	52	834	25.2%	0.64 [0.42, 0.98]	1995			-	
ACST 1 2010	82	1560	108	1560	58.9%	0.76 [0.57, 1.00]	2010			4	
AMTEC 2015	2	31	5	24	1.9%	0.31 [0.07, 1.46]	2015	-		-	
SPACE-2 2019	5	203	1	113	1.0%	2.78 [0.33, 23.53]	2020				
Total (95% CI)		2830		2764	100.0%	0.73 [0.59, 0.90]			•		
Total events	139		190								
Heterogeneity: Tau2 -	0.00: Chr	= 3.17.	df = 4 (P =	0.53); P	= 0%			-		<u> </u>	
Test for overall effect								0.05	0.2 Endarterectomy	Medical thera	20 apy

Figure 1.1. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in endarterectomy versus medical therapy for asymptomatic carotid stenosis.

	Endartere	ctomy	Medical th	nerapy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% CI
VA 1993	25	211	30	233	15.9%	0.92 [0.56, 1.51]	1993	
ACAS 1995	60	825	86	834	31.0%	0.71 [0.51, 0.97]	1995	
ACST 1 2010	143	1560	204	1560	50.1%	0.70 [0.57, 0.86]	2010	
AMTEC 2015	2	31	5	24	1.9%	0.31 [0.07, 1.46]	2015	
SPACE-2 2019	8	203	1	113	1.1%	4.45 [0.56, 35.15]	2020	
Total (95% CI)		2830		2764	100.0%	0.74 [0.59, 0.92]		•
Total events	238		326					÷
Heterogeneity: Tau2 =	0.01; Chr	= 5.15.	df = 4 (P =	0.27); P	= 22%			ahr ala d dah
Test for overall effect:								0.05 0.2 1 5 20 Endarterectomy Medical therapy

Figure 1.2. Long-term risk of stroke in any territory, including peri-procedural death in endarterectomy versus medical therapy for asymptomatic carotid stenosis.

	Endartere	ctomy	Medical th	erapy		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.1 Men							
ACST 1 2010 Subtotal (95% CI)	89	1021 1021	134	1023 1023	100.0% 100.0%	0.67 [0.52, 0.86] 0.67 [0.52, 0.86]	-
Total events Heterogeneity: Not ap	69 plicable		134				
Test for overall effect:	Z = 3.15 (P = 0.00	2)				
1.2.2 Women							
ACST 1 2010 Subtotal (95% CI)	40	539 539	65	537 537	100.0% 100.0%	0.61 [0.42, 0.89] 0.61 [0.42, 0.89]	
Total events Heterogeneity: Not ap	40 Inlicable		65				
Test for overall effect:		P = 0.01)				
						-	
							0.5 0.7 1 1.5 2 Endarterectomy Medical therapy
Test for subgroup diff	ferences: Ch	r ² = 0.13	8, df = 1 (P	= 0.72),	r = 0%		Endarcerectority incurcar therapy

Figure 1.2.1. Long-term risk of stroke in any territory, including peri-procedural death in endarterectomy versus medical therapy for asymptomatic carotid stenosis. Subgroup: Sex.

	Endartere	ctomy	Medical th	nerapy		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Ran	dom, 95% CI	
1.2.1 < 75 years										
ACST 1 2010 Subtotal (95% CI)	98	1231 1231	160	1239 1239		0.62 [0.49, 0.78] 0.62 [0.49, 0.78]		-		
Total events	98		160							
Heterogeneity: Not ap	plicable									
Test for overall effect:		P < 0.00	01)							
1.2.2 ≥ 75 years										
ACST 1 2010 Subtotal (95% CI)	41	329 329	39	321 321	100.0%	1.03 [0.68, 1.55] 1.03 [0.68, 1.55]				
Total events	41	525	39	521	100.0%	1.05 [0.00, 1.55]				
Heterogeneity: Not ap										
Test for overall effect:		P = 0.90	•							
							0.2	0 5	1 1	1
								0.5 Endarterectomy	Medical the	5
Test for subgroup diff	erences: Ch	r = 4.41	. df = 1 (P	= 0.04).	P = 77.3	3×		inuarterectomy	weulcal the	apy

Figure 1.2.2. Long-term risk of stroke in any territory, including peri-procedural death in endarterectomy versus medical therapy for asymptomatic carotid stenosis. Subgroup: Age.

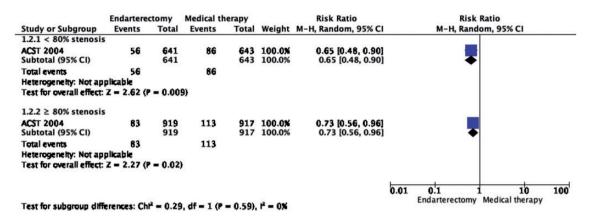


Figure 1.2.3. Long-term risk of stroke in any territory, including peri-procedural death in endarterectomy versus medical therapy for asymptomatic carotid stenosis. Subgroup: Severity of carotid stenosis.

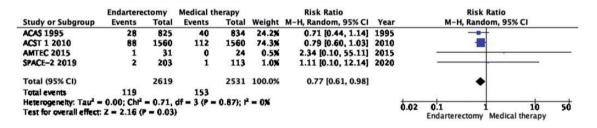


Figure 1.3. Long-term risk of major stroke, including peri-procedural death in endarterectomy versus medical therapy for asymptomatic carotid stenosis.

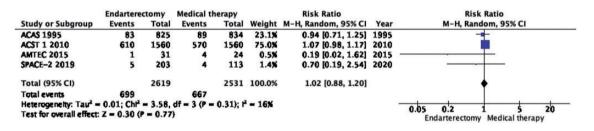


Figure 1.4. Long-term risk of death in endarterectomy versus medical therapy for asymptomatic carotid stenosis.

PICO 1.4: In patients with asymptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of death? There is no difference in long-term risk of death between patients assigned to endarterectomy and those assigned to medical therapy alone (RR: 1.02, 95% CI: 0.88–1.20; 5 more events with CEA per 1000 patients, from 32 fewer to 53 more; low quality evidence; Figure 1.4).

Analysis of current evidence and evidence-based recommendation. Data to assess the benefit of endarterectomy compared with medical therapy alone in patients with asymptomatic carotid stenosis were available from five RCTs which included a total of 5791 patients with mainly $\geq 60\%$ stenosis. We found moderate quality evidence that CEA reduces the risk of ipsilateral stroke and the risk of stroke in any territory in these patients. Based on the results of a single trial, we found no evidence that the benefit of CEA varied significantly between men and women, or according to the severity of the carotid stenosis. We did not find evidence of an increase of the benefit of surgery with increasing degree of asymptomatic carotid stenosis. However, a recent population-based study and systematic review suggested an increase in stroke risk with increasing degrees of asymptomatic carotid stenosis amongst patients receiving contemporary medical therapy.23 Age influenced the effect of surgery in ACST-1, with benefits only observed in patients < 75 years of age. As the effect of age on treatment was only reported in a subgroup analysis of a single trial and taking into account the fact that cardiovascular disease mortality is decreasing and life expectancy is increasing in these patients, we refrained from making recommendations for CEA in patients with asymptomatic carotid stenosis based on fixed age limits.

The two largest trials contributing data were performed two to three decades ago. Best medical management of patients with atherosclerotic disease has evolved since, with more widespread use of statins and other lipid-lowering agents, and stricter control of blood pressure. Annual risks of ipsilateral stroke in more recent observational studies of patients with asymptomatic carotid stenosis range from 0.34 to 1.4%, which is lower than in the medical arms of the RCTs.^{24–26} However, surgical techniques and perioperative management have also improved since these landmark trials were completed. For these reasons, we downgraded the overall quality of evidence for indirectness.

Recommendation

In patients with \geq 60% asymptomatic carotid artery stenosis considered to be at increased risk of stroke on best medical therapy alone, we recommend carotid endarterectomy. Quality of evidence: Moderate $\oplus \oplus \oplus$ Strength of recommendation: Strong for carotid endarterectomy $\uparrow\uparrow$

This recommendation is independent of sex and stenosis severity.

Additional information. The question of whether carotid revascularisation confers additional benefits over modern medical therapy is being investigated in ongoing RCTs: the Second European Carotid Surgery Trial (ECST-2) enrolled 429 patients with asymptomatic or low-to-intermediate risk symptomatic carotid stenosis; follow-up is ongoing.²⁷ The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) includes two parallel trials of stenting vs. medical therapy and endarterectomy vs. medical therapy in patients with \geq 70% asymptomatic carotid stenosis.²⁸

There is debate about whether CEA should only be performed in patients with asymptomatic carotid stenosis who are considered to be at 'higher risk' of stroke on best medical treatment (BMT) alone. The guidelines published by the European Society for Vascular Surgery (ESVS) have proposed that surgery should be considered in selected patients with 60–99% asymptomatic carotid stenosis with one or more imaging or clinical characteristics that may be associated with an increased risk of late ipsilateral stroke.⁴ These characteristics may include, among others, silent infarction on neuroimaging,²⁹ high degree²³ and progression of stenosis,^{30,31} echolucent plaque on ultrasound,^{32,33} intra-plaque haemorrhage on MRI^{34,35} and microemboli²⁴ or reduced cerebrovascular reserve³⁶ on trans-cranial Doppler. This concept is currently being investigated in the *Endarterectomy Combined With Optimal Medical Therapy (OMT) vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-average Risk of Ipsilateral Stroke (ACTRIS)* trial, which is including patients with asymptomatic carotid stenosis who have imaging features believed to confer an increased risk of stroke.

Expert consensus statement.

Expert consensus statement:

12/12 experts concluded that in selected patients 75 years of age or older with \geq 60% asymptomatic carotid artery stenosis and an expected survival of at least five years, who are considered to be at an increased risk of stroke on best medical therapy alone, carotid endarterectomy is suggested after careful consideration of the risks and benefits at a multi-disciplinary team meeting.

Stenting or medical therapy for asymptomatic carotid stenosis

Description of studies. The Stent-protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy (SPACE-2) trial was a randomised multi-centre study in Germany, Austria and Switzerland which aimed to assess the safety and efficacy of CAS or CEA compared with best medical therapy (BMT) alone in patients with asymptomatic >50%common or internal carotid artery stenosis.²² Stenoses were considered asymptomatic if patients had not experienced ipsilateral amaurosis fugax, a TIA or stroke within the preceding 180 days. SPACE-2 started in 2009 as a three-arm trial randomly assigning patients to CEA+BMT, CAS+BMT, or BMT alone in a 3:3:1 ratio, with a target sample size of 3550 patients. For CAS, the use of protection devices was not mandatory. The trial design was changed in 2013 to a two-arm trial of CEA+BMT versus CAS+BMT. Due to slow recruitment, the trial was stopped prematurely in 2014 after 513 patients had been randomised to CEA (n = 203), CAS (n = 197) or BMT (n = 113). This section of the guidelines only includes outcomes of patients in the CAS and BMT groups. Results after one year of follow-up were previously published. The primary efficacy endpoint (the cumulative risk of any stroke or death from any cause within 30 days, plus any ipsilateral ischaemic stroke within five years of followup) is yet to be reported.

We excluded two smaller RCTs because these studies did not report outcomes by symptom status,^{37,38} or patients were treated with primary balloon angioplasty.³⁸ Therefore, the *SPACE-2* data were the only data which could be used to address the PICO questions in this section.

The effects of treatment are presented with medical therapy alone as the reference group. A summary of findings is provided in Table 3.

PICO 2.1: In patients with asymptomatic carotid stenosis, does stenting compared with medical therapy alone reduce the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death? There is very low quality of evidence from *SPACE-2* of a non-significant increase in the risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death with stenting compared with medical therapy alone (RR: 3.44, 95% CI: 0.42–28.23; equivalent to 22 more events with CAS per 1000 patients, from 5 fewer to 241 more; Figure 2.1).

PICO 2.2: In patients with asymptomatic carotid stenosis, does stenting compared with medical therapy alone reduce the long-term risk of stroke in any territory, including peri-procedural death? There is also very low quality evidence from SPACE-2 of a non-significantly higher risk of stroke in any territory, including periprocedural death with stenting compared with medical therapy (RR: 4.59, 0.58–36.22; 32 more events with CAS per 1000 patients, from 4 fewer to 312 more; Figure 2.2).

PICO 2.3: In patients with asymptomatic carotid stenosis, does stenting compared with medical therapy alone reduce the long-term risk of major stroke, including peri-procedural death? Only one such composite event occurred in each of the stenting and medical therapy groups in *SPACE-2* (RR: 0.57, 0.04–9.08; low quality evidence; Figure 2.3).

PICO 2.4: In patients with asymptomatic carotid stenosis, does stenting compared with medical therapy alone reduce the long-term risk of death? There is very low quality of evidence that the long-term risk of death did not differ between patients treated with stenting and medical therapy in *SPACE-2* (RR: 0.29, 0.05– 1.54; Figure 2.4).

Analysis of current evidence and evidence-based recommendations. The evidence from this single, prematurely terminated RCT is very limited. The recruited study population is too small, and the available follow-up period is too short to reliably compare data between treatment groups. We downgraded the evidence for the risk of bias (due to the early termination), imprecision, and indirectness (insufficient length of follow-up), resulting in a very low quality of evidence.

Recommendation

In patients with asymptomatic carotid stenosis, we recommend against carotid artery stenting as a routine alternative to best medical therapy alone. Quality of evidence: Very low \oplus Strength of recommendation: Weak against carotid stenting \downarrow ?

Recommendations regarding the choice between stenting and endarterectomy in patients with asymptomatic carotid stenosis, in whom revascularisation is considered to be appropriate are provided in section "Stenting or endarterectomy for asymptomatic carotid stenosis".

Additional information. Carotid artery stenting versus best medical therapy alone are being compared in one of the two parallel study arms in the ongoing *Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2).*²⁸

Stenting or endarterectomy for asymptomatic carotid stenosis

Description of studies. A single-centre trial in Lexington, Kentucky, USA randomised 85 participants with \geq 80% asymptomatic carotid stenosis to receive either CAS without a cerebral protection device (CPD) or CEA and reported results up to four years after randomisation in 2004.³⁹ A further report in 2014 combined long-term outcomes for up to 10 years in both asymptomatic and symptomatic patients who were enrolled in another trial at the same institution, but the authors did not present separate data according to symptom status.⁴⁰ Therefore, we chose the 2004 report to extract outcome data from patients with asymptomatic stenosis to address our PICO questions.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), a multicentre trial in the USA and Canada, randomised 1321 patients with \geq 50% symptomatic carotid stenosis and 1181 patients with \geq 60% asymptomatic carotid stenosis to CAS or CEA between 2000 and 2008.^{41–48} Interventionists with an experience of < 30 CAS procedures were required to complete a training programme. The use of a CPD was mandatory during stenting. Initial results were published in 2010; the final trial results were published in 2016 with follow-up data for up to 10 years after randomisation (median of 7.4 years). Only data from asymptomatic patients were extracted for our analyses to address these PICO questions.

Table 3	Table 3. Summary of findings for stenting versus medical	findings fc	or stenting versu		apy for asympt	therapy for asymptomatic carotid stenosis (PICO 2.1–2.4).	tenosis (Pl	CO 2. I–2	.4).			
Certain	Certainty assessment						Nº of patients	ents	Effect			
N⁰ of studies	№ of Study studies design	Risk of bias	Inconsistency	Inconsistency Indirectness Imprecision	Imprecision	Other Medical Relative considerations Stenting therapy (95% CI)	Stenting	Medical Relative therapy (95% CI	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO –	2.1: Long-terr Randomised trials	m risk of Serious ^a	n risk of ipsilateral st r Serious ^a Not serious	oke, includin Serious ^b	g peri-procedural s Very serious ^c None	PICO 2.1: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death 1 Randomised Serious ^a Not serious Serious ^b Very serious ^c None 6/197 1/113 RR 3.44 22 more trials (3.0%) (0.9%) (0.42–28.23) 1000 (from 5 f	any territ 6/197 (3.0%)	tory or p / 13 (0.9%)	eri-procedur RR 3.44 (0.42–28.23)	: per ewer to ore)	⊕⊖⊖⊖ critical Very Low	CRITICAL
PICO –	PICO 2.2: Long-term risk of stroke in any territory , I Randomised Serious ^a Not serious Serious ^b trials	n risk of Serious ^a	n risk of stroke in any Serious ^a Not serious		cluding peri-proced Very serious ^c None	including peri-procedural death Very serious ^c None 8/ (4	197 (%1.	1/113 (0.9%)	RR 4.59 (0.58–36.22)	r 5	⊕⊖⊖⊖ Very low	CRITICAL
PICO –	PICO 2.3: Long-term risk of major stroke, including peri-procedural death I Randomised Serious ^a Not serious Serious ^b Not serious ^c None trials	n risk of Serious ^a	n risk of major stroke Serious ^a Not serious	, including pe Serious ^b	e ri-procedural deat t Not serious ^c None	l death None	1/197 (0.5%)	1/113 (0.9%)	RR 0.57 (0.04–9.08)	1000		CRITICAL
PICO	PICO 2.4: Long-term risk of death I Randomised Serious ^a Not s trials	n risk of Serious ^a	n risk of death Serious ^a Not serious	Serious ^b	Very serious ^c None	None	2/197 (1.0%)	4/113 (3.5%)	RR 0.29 (0.05–1.54)	r per fewer to re)	⊕⊖⊖⊖ Very Low	000 Important Very Low
Cl: confi ^a Trial wa ^b Insuffici	Cl: confidence interval; RR: risk ratio. ^a trial was stopped early. ^b Insufficient length of follow-up to assess long-term effects. ^v Very wide confidence intervals.	R: risk ratic w-up to as ervals.	o. sess long-term ef	fects.								

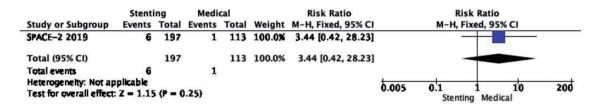


Figure 2.1. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in stenting versus medical therapy for asymptomatic carotid stenosis.

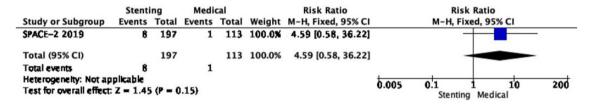


Figure 2.2. Long-term risk of stroke in any territory, including peri-procedural death in stenting versus medical therapy for asymptomatic carotid stenosis.

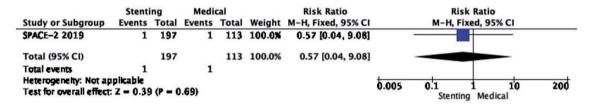


Figure 2.3. Long-term risk of major stroke, including peri-procedural death in stenting versus medical therapy for asymptomatic carotid stenosis.

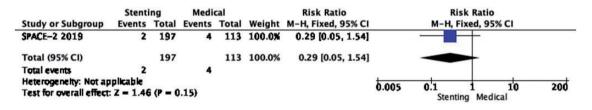


Figure 2.4. Long-term risk of death in stenting versus medical therapy for asymptomatic carotid stenosis.

A single-centre trial in Houston, Texas, USA randomised 60 patients with $\geq 80\%$ asymptomatic carotid stenosis to receive CAS (with mandatory use of a CPD) or CEA. The primary outcome was 'cognitive performance' after treatment; this and other clinical outcome data for up to 6 months after randomisation were reported in 2014.⁴⁹ No data were available for five patients who withdrew consent or were lost to follow-up.

A single-centre trial conducted in Ostrava, Czech Republic, randomised 63 patients with asymptomatic and 87 patients with symptomatic \geq 70% carotid

stenosis to undergo CAS (with the use of a CPD, where possible) or CEA and reported results in 2014.⁵⁰ The primary outcome was the occurrence of new ischaemic brain lesions on magnetic resonance imaging after treatment. Clinical outcome events up to 30 days after treatment were also reported, and these were made available and categorised according to symptom status following correspondence with the investigators.

The Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis (ACT-1) allocated 1453 participants <80 years of age with \geq 70% asymptomatic carotid stenosis in a 3:1 ratio to undergo CAS (with mandatory use of a CPD) or CEA between 2005 and 2013.⁵¹ A prior experience of \geq 25 procedures was required from surgeons and interventionists. The initially planned sample size was 1658 participants, but the study was stopped prematurely due to slow enrolment. Results up to five years after randomisation were previously published.

A single-centre trial at *Carmel Medical Center* in Israel randomised 136 participants with \geq 70% asymptomatic carotid stenosis to receive CAS (with mandatory use of a CPD) or CEA. Results up to five years after randomisation were reported in 2017.⁵² Three patients were lost to follow-up.

Events occurring up to one year after treatment were also extracted from the CAS and CEA groups of the 3-arm *SPACE-2* trial (described in section 'Stenting or medical therapy for asymptomatic carotid stenosis').²²

We did not include data from the multi-centre *Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)* trial conducted in the USA,^{53–55} from one Chinese multi-centre trial,⁵⁶ and two single-centre studies conducted in Beijing, China.^{57,58} Reasons for exclusion of these randomised studies were the inclusion of patients with both asymptomatic and symptomatic carotid stenosis without reporting of separate outcome data according to symptomatic status, inclusion of 'high surgical risk' patients only, or results in the English language only being available as a conference abstract.

The effects of treatment are presented with endarterectomy as the reference group. A summary of findings is provided in Table 4.

PICO 3.1: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death? There is moderate quality evidence that stenting is likely associated with an increased long-term risk of postprocedural ipsilateral stroke, peri-procedural stroke in any territory, or peri-procedural death (RR: 1.25, 95% CI: 0.88–1.79; equivalent to 9 more events with CAS per 1000 patients, from 4 fewer to 28 more; Figure 3.1).

PICO 3.2: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of post-procedural ipsilateral stroke? There is low quality evidence that endarterectomy and stenting do not differ in preventing post-procedural ipsilateral stroke, excluding peri-operative events (RR: 1.12, 0.62–2.00; 3 more events with stenting per 1000 patients, from 8 fewer to 22 more; Figure 3.2).

PICO 3.3: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of stroke in any territory, including peri-procedural death? There is moderate quality evidence that stenting is likely associated with an increased long-term risk of stroke in any territory or peri-procedural death (RR: 1.22, 0.87–1.71; 13 more events with stenting per 1000 patients, from 8 fewer to 42 more; Figure 3.3).

PICO 3.4: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of major stroke, including peri-procedural death? There is low quality evidence that endarterectomy and stenting do not differ in the long-term risk of major stroke or peri-procedural death (RR: 0.99, 0.15–6.68; 0 fewer events with stenting per 1000 patients, from 20 fewer to 20 more; Figure 3.4).

PICO 3.5: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of death? There is low quality evidence that endarterectomy and stenting do not differ in the long-term risk of death (RR: 0.82, 0.31–2.20; 5 fewer events with stenting per 1000 patients, from 18 fewer to 32 more; Figure 3.5).

PICO 3.6: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural stroke? There is moderate quality evidence that stenting is likely associated with an increased risk of peri-procedural stroke (RR: 1.70, 0.99–2.93; 10 more events with stenting per 1000 patients, from 0 fewer to 28 more; Figure 3.6).

PICO 3.7: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural death? There is high quality evidence that endarterectomy and stenting do not differ in the risk of peri-procedural death (RR: 0.33, 0.02–5.33; 1 less event with stenting per 1000 patients, from 1 less to 6 more; Figure 3.7). We did not downgrade the quality of evidence for imprecision because only a single event occurred in each treatment group.

PICO 3.8: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural stroke or death? There is moderate quality evidence that stenting is likely associated with an increased risk of peri-procedural stroke or death as compared to endarterectomy (RR: 1.62, 0.96–2.76; 9 more events per 1000 patients, from 1 less to 27 more; Figure 3.8).

ModelBandleBandleModelModelModelModelModelModelModelModelFIO 11. Daysterm risk of platerial stration.ModelModelModelModelModelModelModelModelModelModelFIO 11. Daysterm risk of platerial stration.Model	Certainty assessment						№ of patients	ents	Effect			
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The peri-procedural deathNot seriousVery seriousNone $2/267$ $2/273$ RR 0.99 0 fewer per 000 Not seriousVery seriousNone (7.3) (0.73) (0.73) $(0.15-6.68)$ 0000 0000 Not seriousVery seriousNone $7/332$ $9/340$ RR 0.82 5 fewer per 0000 Not seriousVery seriousNone $7/332$ $9/340$ RR 0.82 5 fewer per 0000 Not seriousSerious ¹ None 22.056 $9/1317$ RR 1.70 0000 0000 Not seriousSerious ¹ None $52/2056$ $9/1317$ RR 1.70 0000 0000 Not seriousNot seriousNone $52/253$ (1.43) $(0.99-2.93)$ $(0000$ 0000 Not seriousNot seriousNone $52/2056$ $9/1317$ RR 1.70 0000 0000 Not seriousNot seriousNone $52/2056$ 0.130 $0.02-5.33$ 0000 0000 Not seriousSerious ³ None $52/2056$ 0.1320 $0.02-5.33$ 0000 0000 Not seriousSerious ³ None $53/2058$ $20/1320$ $0.92-2.93$ 0000 0000 Not seriousSerious ³ None $53/2058$ 0.1320 $0.02-5.33$ 0000 0000 Not seriousSerious ³ None $53/2058$ 0.1320 $0.92-2.75$ 0.000 0000 Not seriousSerious ³ None $53/205$	PICO 3.3. Long-ter 5 Randomised trials	m risk of stroke Not serious	in any territor Not serious	y, including F Not serious	peri-procedura Serious ^a	I death None	68/929 (7.3%)	55/928 (5.9%)	RR 1.22 (0.87–1.71)	13 more per 1000 (from 8 fewer to 47 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
Not serious hVery serious bNone7/3329/340RR 0.82 ($3.1-2.20$)5 fewer per (1000 $\Theta \Theta \circ$ (1000 Not seriousSerious ^a None7/3329/1317RR 1.70 $0.31-2.20$) 1000 $\Theta \Theta \circ$ (1000 Not seriousSerious ^a None $55/2056$ $9/1317$ RR 1.70 $0.09-2.93$) 1000 $\Theta \Theta \circ$ Not seriousNot seriousNot seriousNone $1/1462$ $1/730$ RR 0.33 1000 $\Theta \Theta \odot$ Not seriousNot seriousNone $1/1462$ $1/730$ RR 0.33 $16wer to$ $\Theta \oplus \odot$ Not seriousSerious ^a None $53/2058$ $20/1320$ RR 0.33 $16wer permore)$ $\Theta \oplus \odot$ Not seriousSerious ^a None $53/2058$ $20/1320$ RR 1.62 9000 9000 Not seriousSerious ^a None $53/2058$ $20/1320$ RR 1.62 9000 9000 Not seriousSerious ^a None $53/2058$ $20/1320$ RR 1.62 9000 9000 Not seriousSerious ^a None $53/2058$ $20/1320$ RR 1.62 9000 9000 Not seriousSerious ^a None $53/2058$ $20/1320$ 8000 9000 9000 Not seriousSerious ^a None $53/2058$ $20/1320$ 8000 9000 9000 Not seriousSerious ^a None $53/2058$ $20/1320$ 9000 9000 9000	PICO 3.4. Long-ter 3 Randomised trials	m risk of major Not serious	stroke, includi Not serious	ng peri-proce Not serious	edural death Very serious ^b	None	2/267 (0.7%)	2/273 (0.7%)	RR 0.99 (0.15–6.68)	0 fewer per 1000 (from 20 fewer to		CRITICAL
Not serious Serious ¹ None 52/2056 19/1317 RR 1.70 10 more per 0000 Not serious Not serious Not serious None 52/2056 19/1317 RR 1.70 10 more per 0000 Not serious Not serious Not serious None 1/1462 1/730 RR 0.33 1 fewer tot 0000 Not serious Not serious Not serious None 1/1462 1/730 RR 0.33 1 fewer tot 0000 Not serious Serious ³ None 53/2058 20/1320 RR 1.62 0000 MODEATIC Not serious Serious ³ None 53/2058 20/1320 RR 1.62 0000 MODEATIC Not serious Serious ³ None 53/2058 20/1320 RR 1.62 0000 MODEATIC Not serious Serious ³ None 53/2058 20/1320 0.056-2.76) 0000 MODEATIC Not serious Serious ³ None 53/2058 20/1320 0.056-2.76) 0000 MODEATIC	PICO 3.5: Long-ter 4 Randomised trials	m risk of death Not serious	Not serious	Not serious	Very serious ^b	None	7/332 (2.1%)	9/340 (2.6%)	RR 0.82 (0.31–2.20)	20 more) 5 fewer per 1000 (from 18 fewer to		IMPORTANT
Not serious Not serious None 1/1462 1/730 R. 0.33 I fewer per 0000 Not serious Not serious None 1/1462 1/730 R. 0.33 I fewer per 0000 Not serious Serious ^a None 53/2058 20/1320 R. 1.62 9 more per 000 Not serious Serious ^a None 53/2058 20/1320 R. 1.62 9 more per 000 2.6 %) (1.5 %) (0.96-2.76) 1000 MODERATE 000	PICO 3.6: Risk of p 7 Randomised trials	i eri-procedural s Not serious	troke Not serious	Not serious	Serious ^a	None	52/2056 (2.5%)	19/1317 (1.4%)	RR 1.70 (0.99–2.93)	32 more) 10 more per 1000 (from 0 fewer to	⊕⊕⊕⊖ MODERATE	CRITICAL
Not serious Serious ^a None 53/2058 20/1320 RR 1.62 9 more per ⊕⊕⊕○ (2.6%) (1.5%) (0.96–2.76) 1000 MODERATE 27 more) 27 more)	PICO 3.7: Risk of p 6 Randomised trials	i eri-procedural d Not serious	leath Not serious	Not serious	Not serious	None	1/1462 (0.1%)	1/730 (0.1%)	RR 0.33 (0.02–5.33)	Lo more) L fewer per 1000 (from I fewer to 6 more)	0000 HIGH	CRITICAL
	PICO 3.8: Risk of p 7 Randomised trials	eri-procedural s Not serious	troke or death Not serious		Serious ^a	None	53/2058 (2.6%)	20/1320 (1.5%)	RR 1.62 (0.96–2.76)	9 more per 1000 (from I fewer to 27 more)	⊕⊕⊕⊖ MODERATE	CRITICAL

XIV

Certaint	Certainty assessment						No of patients	ents	Effect			
No of Study studies design	№ of Study studies design	Risk of bias	Inconsistency	Inconsistency Indirectness Imprecision	Imprecision	Other considerations	Stenting	Other considerations Stenting Endarterectomy (95% CI)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO :	PICO 3.9: Risk of peri-procedural major stroke or death 5 Randomised Not serious Not serious Not ser	i-procedural n Not serious	procedural major stroke or Not serious Not serious	r death Not serious Serious ^a	Serious ^a	None	8/1776	3/1033	RR 1.54	2 more per	O	CRITICAL
	trials						(0.5%)	(0.3%)	(0.39–6.07)	0001	MODERATE	
										(from 2 fewer to 15 more)		
PICO	PICO 3.10: Risk of peri-procedural myocardial infarction	ri-procedural	myocardial inf	arction								
7	Randomised	Not serious	Not serious Not serious Serious	Serious ^c	Serious ^a	None	12/2041	12/2041 16/1304	RR 0.53	6 fewer per		IMPORTANT
	trials						(%9.0)	(1.2%)	(0.25–1.15)	0001	LOW	
										(from 9 fewer to 2		
PICO	PICO 3.11: Risk of peri-procedural cranial nerve injury	ri-procedural	cranial nerve i	injury								
ъ	Randomised	Not serious	Not serious Not serious Not serious	Not serious	Not serious	Very strong	2/1823	36/1092	RR 0.09	30 fewer per		IMPORTANT
	trials					association ^d	(0.1%)	(3.3%)	(0.03–0.28)	1000 (from 32 fewer to 24 fewer)	HIGH	
CI: conf	CI: confidence interval: RR: risk ratio.	SR: risk ratio.										

Table 4. Continued.

CI: confidence interval; RR: risk ratio. ^aFew events, wide confidence intervals. ^bVery wide confidence intervals. ^cDefinition of myocardial infarction differed across trials. ^dVery large effect.

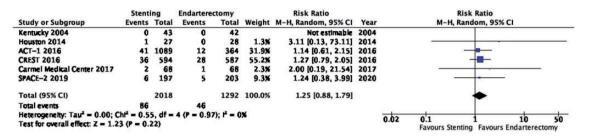


Figure 3.1. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in stenting versus endarterectomy for asymptomatic carotid stenosis.

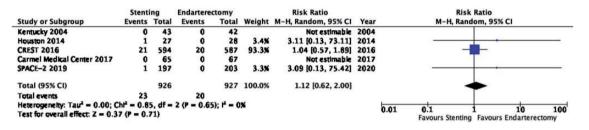


Figure 3.2. Long-term risk of post-procedural ipsilateral stroke in stenting versus endarterectomy for asymptomatic carotid stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	om, 95% CI		
Kentucky 2004	0	43	0	42		Not estimable	2004					
Houston 2014	1	27	0	28	1.1%	3.11 [0.13, 73.11]	2014		-			
CREST 2016	62	594	51	587	92.3%	1.20 [0.84, 1.71]	2016			-		
Carmel Medical Center 2017	2	68	1	68	2.0%	2.00 [0.19, 21.54]	2017		-			
SPACE-2 2019	3	197	3	203	4.5%	1.03 [0.21, 5.04]	2020					
Total (95% CI)		929		928	100.0%	1.22 [0.87, 1.71]				•		
Total events	68		55									
Heterogeneity: Tau ² = 0.00; C	ht² = 0.5	5, df =	3 (P = 0.9)	1); 1 ² = 0	×			-	A.1.		-	-
Test for overall effect: Z = 1.1								0.02	0.1 Favours Stenting	Favours Enda	rterecto	50 omy

Figure 3.3. Long-term risk of stroke in any territory, including peri-procedural death in stenting versus endarterectomy for asymptomatic carotid stenosis.

	Stent	ing	Endartere	ctomy		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95%	CI
Kentucky 2004	0	43	0	42		Not estimable	2004		
Houston 2014	1	27	0	28	36.5%	3.11 [0.13, 73.11]	2014		
SPACE-2 2019	1	197	2	203	63.5%	0.52 [0.05, 5.64]	2020		
Total (95% CI)		267		273	100.0%	0.99 [0.15, 6.68]			_
Total events	2		2						
Heterogeneity: Tau2 -	- 0.00; Cl	ht² = 0.	79, df = 1	(P = 0.3	7); 1 ² = 0;	x		aba a'r	10 50
Test for overall effect								0.02 0.1 1 Favours Stenting Favours	10 50 Endarterectomy

Figure 3.4. Long-term risk of major stroke, including peri-procedural death in stenting versus endarterectomy for asymptomatic carotid stenosis.

	Stent	ing	Endartere	ctomy		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	om, 95% CI	
Kentucky 2004	0	43	0	42		Not estimable	2004				
Houston 2014	1	27	0	28	9.7%	3.11 [0.13, 73.11]	2014		10 -		18
Carmel Medical Center 2017	4	65	4	67	53.7%	1.03 [0.27, 3.95]	2017				
SPACE-2 2019	2	197	5	203	36.6%	0.41 [0.08, 2.10]	2020			_	
Total (95% CI)		332		340	100.0%	0.82 [0.31, 2.20]					
Total events	7		9								
Heterogeneity: $Tau^2 = 0.00$; C Test for overall effect: $Z = 0.3$			2 (P = 0.40	3);	X			0.01	0.1	1 10	100
test ist stermine incet. z = 0.5	- u.								Favours Stenting	Favours Endar	terectomy

Figure 3.5. Long-term risk of death in stenting versus endarterectomy for asymptomatic carotid stenosis.

	Stent	ing	Endartere	ctomy		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	lom, 95% CI	
Kentucky 2004	0	43	0	42		Not estimable	2004				
CREST 2011	15	594	8	587	41.1%	1.85 [0.79, 4.34]	2011		-		
Houston 2014	0	27	0	28		Not estimable	2014				
Ostrava 2014	0	38	0	25		Not estimable	2014				
ACT-1 2016	30	1089	5	364	33.7%	2.01 [0.78, 5.13]	2016		-		
Carmel Medical Center 2017	2	68	1	68	5.3%	2.00 [0.19, 21.54]	2017				
SPACE-2 2019	5	197	5	203	19.9%	1.03 [0.30, 3.50]	2020				
Total (95% CI)		2056		1317	100.0%	1.70 [0.99, 2.93]				•	
Total events	52		19								
Heterogeneity: Tau ² = 0.00; C	cht² = 0.8	2, df =	3 (P = 0.84	4); 1 ² = 0	*			0.01	A		100
Test for overall effect: Z = 1.9	1 (P = 0.	06)						0.01	0.1 Favours Stenting	Favours Endartere	100 ectomy

Figure 3.6. Risk of peri-procedural stroke in stenting versus endarterectomy for asymptomatic carotid stenosis.

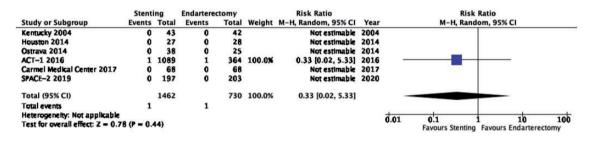


Figure 3.7. Risk of peri-procedural death in stenting versus endarterectomy for asymptomatic carotid stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	om, 95% CI		
Kentucky 2004	0	43	0	42		Not estimable	2004					
CREST 2010	15	594	8	587	38.8%	1.85 [0.79, 4.34]	2010		-			
Houston 2014	0	29	0	31		Not estimable	2014					
Ostrava 2014	0	38	0	25		Not estimable	2014					
ACT-1 2016	31	1089	6	364	37.4%	1.73 [0.73, 4.11]	2016		-	-		
Carmel Medical Center 2017	2	68	1	68	5.0%	2.00 [0.19, 21.54]	2017				_	
SPACE-2 2019	5	197	5	203	18.7%	1.03 [0.30, 3.50]	2020					
Total (95% CI)		2058		1320	100.0%	1.62 [0.96, 2.76]				•		
Total events	53		20									
Heterogeneity: Tau ² = 0.00; ($Cht^{2} = 0.6$	7. df =	3 (P = 0.8	8); r ² = 0	*						-	-
Test for overall effect: Z = 1.7			22					0.01	0.1 Favours Stenting	Favours En	darterect	100 omy

Figure 3.8. Risk of peri-procedural stroke or death in stenting versus endarterectomy for asymptomatic carotid stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Random, 95% CI
Kentucky 2004	0	43	0	42		Not estimable	2004		
CREST 2010	3	594	2	587	59.0%	1.48 [0.25, 8.84]	2010		
Houston 2014	0	29	0	31		Not estimable	2014		
Ostrava 2014	0	38	0	25		Not estimable	2014		
ACT-1 2016	5	1072	1	348	41.0%	1.62 [0.19, 13.85]	2016		
Total (95% CI)		1776		1033	100.0%	1.54 [0.39, 6.07]			
Total events	8		3						
Heterogeneity: Tau ² -	. 0.00; CI	ht² = 0.	00, df = 1	(P = 0.9	5); 1 ² = 0;	x			مع مات ا
Test for overall effect								0.01	0.1 1 10 100 Favours Stenting Favours Endarterectomy

Figure 3.9. Risk of peri-procedural major stroke or death in stenting versus endarterectomy for asymptomatic carotid stenosis.

PICO 3.9: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural major stroke or death? There is moderate quality evidence that stenting is likely associated with a slight increase of the risk of major peri-procedural stroke or death (RR: 1.54, 0.39–6.07; 2 more events with

stenting per 1000 patients, from 2 fewer to 15 more; Figure 3.9).

PICO 3.10: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural myocardial infarction? There is low quality evidence that stenting is likely associated with a

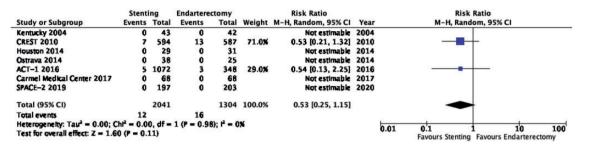


Figure 3.10. Risk of peri-procedural myocardial infarction in stenting versus endarterectomy for asymptomatic carotid stenosis.

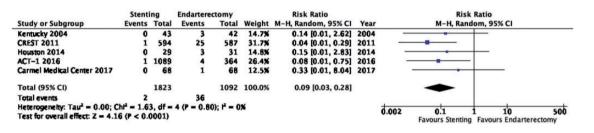


Figure 3.11. Risk of peri-procedural cranial nerve injury in stenting versus endarterectomy for asymptomatic carotid stenosis.

lower risk of peri-procedural myocardial infarction as compared to endarterectomy (RR: 0.53, 0.25–1.15; 6 fewer events with stenting per 1000 patients, from 9 fewer to 2 more; Figure 3.10). We additionally downgraded the quality of evidence for indirectness because all extracted events originated from the CREST and ACT-1 trials, where screening with ECG and cardiac enzymes of all patients was performed before and after treatment; the definition of myocardial infarction included elevation of cardiac enzymes alone, or in combination with ECG changes only (without clinical symptoms).

PICO 3.11: In patients with asymptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural cranial nerve injury? There is high quality evidence that stenting is associated with a lower risk of peri-procedural cranial nerve injury than endarterectomy (RR: 0.09, 95% CI: 0.03–0.28; 30 fewer events per 1000 patients with stenting, from 32 fewer to 24 fewer; Figure 3.11). We upgraded the quality of evidence by two levels for strength of effect.

Analysis of current evidence and evidence-based recommendation. Data comparing the short-term risks and longterm effects between stenting and endarterectomy for asymptomatic carotid stenosis were available from seven trials including a total of 3373 patients. Most studies required patients to have $\geq 60\%$ carotid stenosis for inclusion. Duration of follow-up in the largest trials was for five years or more. The risks of most outcome events were low, which led us to downgrade the level of evidence for imprecision. Low event rates also precluded meaningful subgroup analyses. Overall, we found no clear evidence of statistically significant differences in outcomes between endarterectomy or stenting that were rated as critical for decision making when treating patients with asymptomatic carotid stenosis (low to moderate quality evidence). As the available evidence is not sufficient to recommend stenting as an alternative to endarterectomy, carotid endarterectomy presently remains the treatment of choice for patients with asymptomatic carotid stenosis considered to require revascularisation.

Recommendation

In patients with asymptomatic carotid stenosis in whom revascularisation is considered to be appropriate, we suggest endarterectomy as the current treatment of choice. Quality of evidence: Moderate $\oplus \oplus \oplus$ Strength of recommendation: Weak for carotid endarterectomy \uparrow ?

Additional information. The Asymptomatic Carotid Surgery Trial-2 (ACST-2) has recently completed recruitment of 3.638 patients with asymptomatic carotid stenosis who were randomly assigned to CAS or CEA.⁵⁹ First results are expected in late 2021 and will considerably increase the evidence base, which may lead to updates to the above recommendation.

Expert consensus statements.

Expert consensus statement:

12/12 experts concluded that in patients with asymptomatic

carotid stenosis in whom revascularisation is considered to be appropriate and who are less suitable for surgery, stenting may be suggested. We recommend careful consideration of the risks and benefits at a multi-disciplinary team meeting.

Expert consensus statement:

12/12 experts concluded that the independently assessed risk of in-hospital stroke or death following endarterectomy or stenting for asymptomatic carotid stenosis should be as low as possible, ideally below 2%.⁶

Endarterectomy or medical therapy for symptomatic carotid stenosis

Description of studies. There are three RCTs which randomly assigned patients with symptomatic carotid artery stenosis to CEA or medical therapy alone in a 1:1 ratio. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) separately reported results in patients with severe (70-99%), moderate (50-69%) or mild (<50%) symptomatic carotid stenosis.⁹ The first report in 1991 included outcomes in 659 patients with severe stenosis who had experienced a hemispheric or retinal transient ischaemic attack (TIA) or a non-disabling stroke within the 120 days before enrolment.⁶⁰ The second report in 1998 included outcomes in 858 patients with moderate stenosis and 1368 patients with mild stenosis with a transient ischaemic attack or non-disabling stroke within 180 days before study entry.⁶¹ The 1998 report also provided long-term follow-up data for up to eight years in patients with severe stenosis included in the first report.

The *MRC European Carotid Surgery Trial (ECST)* reported results in 778 patients with severe (70–99%) and 374 patients with very mild (0–29%) symptomatic carotid stenosis in 1991,^{62,63} the results in 1599 patients with mild to moderate (30–69%) symptomatic carotid stenosis in 1996, and the final results with follow-up for up to eight years in all 3024 patients with symptomatic carotid stenosis in 1998.⁶⁴ Eligible patients had a non-disabling ischaemic stroke, TIA or retinal infarction attributable to the carotid stenosis in the preceding six months. In the publication from which data for the current guideline were extracted, degrees of stenosis had been re-measured according to the method used in the NASCET trial.¹²

The Veterans Affairs Cooperative Studies Program (VACSP) symptomatic carotid stenosis trial included 189 patients with >50% symptomatic carotid stenosis and followed them up for a maximum of 33 months.⁶⁵ Eligible patients had an ischaemic stroke, TIA or transient monocular blindness in the preceding 120 days. Results were reported in 1991.

The effects of treatment are presented with medical therapy alone as the reference group. A summary of findings is provided in Table 5.

PICO 4.1: In patients with symptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or periprocedural death? The reduction in the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death, with endarterectomy is strongly dependent on the degree of the symptomatic stenosis and the time interval between the index neurological event and randomisation. There is very low quality evidence for a benefit of CEA if data from all symptomatic patients, regardless of the severity of their stenosis, are grouped and analysed together (RR: 0.83, 95% CI: 0.61-1.14; equivalent to 26 fewer events with CEA per 1000 patients, from 59 fewer to 21 more; Figure 4.1). The level of evidence was additionally downgraded for inconsistency due to statistical heterogeneity between trials. Stratifying results by degree of stenosis, there is high quality evidence of a meaningful benefit of CEA in patients with 70-99% stenosis (RR: 0.37, 0.27-0.50; 169 fewer events per 1000 patients, from 196 fewer to 134 fewer; Figure 4.1.4); low quality evidence of potential benefit in an overall population of patients with 50-69% stenosis (RR: 0.82, 0.58–1.15; 29 fewer events per 1000 patients, from 67 fewer to 24 more); and no evidence of benefit amongst patients with <50% stenosis (RR: 1.09, 0.64-1.85) or near-occlusion (RR: 1.03, 0.57-1.84; very low grade evidence each). The interaction between degree of stenosis and the effect of CEA was significant (p < 0.0001).

The benefit of CEA in patients with $\geq 50\%$ stenosis was most pronounced amongst patients randomised within two weeks of the index neurological event (RR: 0.41, 0.30–0.58, 174 fewer events per 1000 patients, from 206 fewer to 124 fewer, high quality evidence; Figure 4.1.3), but benefit was still present up to 12 weeks (p = 0.001 for interaction with time).

An individual patient data meta-analysis of all three trials showed that the degree of stenosis and time since the last event modified the effect of CEA in an additive manner. There was a significant 14.8% (95% CI: 6.2-23.4%) absolute reduction in the five-year risk of ipsilateral carotid territory ischaemic stroke or any stroke or death within 30 days of CEA in patients with moderate (50–69%) stenosis who were randomised within 14 days of their index ischaemic event (data not included in SoF table or figure).⁶⁶

There is no evidence that the benefit of CEA differs with age (Figure 4.1.1). Although the reduction

Table 5. Summary o	of findings fo	Summary of findings for endarterectomy versus		edical therapy	medical therapy for symptomatic carotid stenosis (PICO 4.1–4.4).	arotid stenosis (PICO 4.1-	4.4).			
Certainty assessment						№ of patients		Effect			
Nº of Study studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endarterectomy	Medical therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO 4.1: Long-term risk of ipsilateral stroke, including 3 Randomised Not serious Serious ^a Serious ^b trials	n risk of ipsilateral st Not serious Serious ^a	l ateral stroke, Serious ^a	including per Serious ^b	i-procedural s Serious ^c	peri-procedural stroke in any territory or peri-procedural death (30-99% stenosis) Serious ^c None 394/3336 415/2754 RR 0.83 26 few (11.8%) (15.1%) (0.61–1.14) 1000 (from 5) (15.1%) (51–1.14) 1000	ory or peri-proce 394/3336 (11.8%)	edural deat 415/2754 (15.1%)	t h (30-99% st RR 0.83 (0.61–1.14)	enosis) 26 fewer per 1000 (from 59 fewer to	⊕⊖⊖⊖ VERY LOW	CRITICAL
PICO 4.1.1a: Long-term risk of ipsilateral stroke, including 2 Randomised Not serious Not serious Serious ^b trials	erm risk of i _l Not serious	psilateral strol Not serious		peri-procedur Not serious	peri-procedural stroke in any territory or peri-procedural death (50-99% stenosis): Age < 65 years Not serious None $86/731$ 93/550 RR 0.70 51 fewer per $\oplus \oplus \oplus \bigcirc$ (11.8%) (16.9%) (0.53-0.92) 1000 MODERA (from 79 fewer to	ritory or peri-pr 86/731 (11.8%)	rocedural d 93/550 (16.9%)	eath (50-99% RR 0.70 (0.53–0.92)	 21 more) 5 stenosis): Age 51 fewer per 1000 (from 79 fewer to 	< 65 years ⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 4.1.1b: Long-term risk of ipsilateral stroke, including 2 Randomised Not serious Not serious Serious ^b trials	erm risk of ip Not serious	psilateral stro l Not serious	ke, including F Serious ^b	peri-procedur Not serious	peri-procedural stroke in any territory or peri-procedural death (50-99% stenosis): Age \geq 65 years Not serious None 89/743 151/694 RR 0.57 94 fewer per $\oplus \oplus \oplus \bigcirc$ (12.0%) (21.8%) (0.44-0.73) 1000 MODERAT (from 122 fewer	ritory or peri-pr 89/743 (12.0%)	rocedural d 151/694 (21.8%)	eath (50-99 % RR 0.57 (0.44-0.73)	14 tewer) 6 stenosis): Age 94 fewer per 1000 (from 122 fewer	≥ 65 years ⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 4.1.2a. Long-term risk of ipsilateral stroke, including 2 Randomised Not serious Not serious Serious ^b trials	e rm risk of i _l Not serious	rm risk of ipsilateral strol Not serious Not serious	ke, including F Serious ^b	peri-procedur Not serious	peri-procedural stroke in any territory or peri-procedural death (50-99% stenosis): Men Not serious None 112/1013 184/873 RR 0.54 97 fewer per (11.1%) (21.1%) (0.44-0.67) 1000 (from 118 fewer	ritory or peri-pr 112/1013 (11.1%)	rocedural d 184/873 (21.1%)	eath (50-99 % RR 0.54 (0.44-0.67)	to 59 tewer) 5 stenosis): Men 97 fewer per 1000 (from 118 fewer	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 4.1.2.b.: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death (50-9% stenosis): Women 2 Randomised Not serious Not serious Serious ^b Serious ^c None 63/461 60/371 RR 0.85 24 fewer per AAD trials (16.2%) (0.58–1.23) 1000 LOV (16700 B fewer to 637 control of 16.2%) (0.58–1.23) 1000 LOV (16700 B fewer to 637 control of 16700 B fewer to 637 control of 16700 CON control of 18.7%) (16.2%) (0.58–1.23) 1000 LOV (16700 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 LOV (16700 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 LOV (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 LOV (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7%) (16.2%) (16.2%) (0.58–1.23) 1000 CON (1000 B fewer to 637 control of 18.7\%)	term risk of Not serious	ipsilateral str Not serious	oke, including Serious ^b	g peri-procedu Serious ^c	iral stroke in any te None	erritory or peri-p 63/46I (I3.7%)	procedural 60/371 (16.2%)	death (50-99 RR 0.85 (0.58–1.23)	to /U rewer) % stenosis): Wor 24 fewer per 1000 (from 68 fewer to 37 more)	men LOW	CRITICAL
PICO 4.1.3a: Long-term risk of ipsilateral stroke, including ischaemic event 2 Randomised Not serious Not serious Serious ^b trials	erm risk of i _l Not serious	rm risk of ipsilateral strol Not serious Not serious		peri-procedur Not serious	peri-procedural stroke in any territory or peri-procedural death (50-99% stenosis): <2 weeks since most recent	ritory or peri-pr 40/325 (12.3%)	rocedural d 88/299 (29.4%)	eath (50-99% RR 0.41 (0.30-0.58)	s stenosis): <2 w 174 fewer per 1000 (from 206 fewer	eeks since mo ##### HIGH	st recent CRITICAL
PICO 4.1.3b: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death (50-99% stenosis): 2-4 weeks since most recent ischaemic event 2 Randomised Not serious Not serious ^b Not serious None 31/268 44/215 RR 0.58 86 fewer per $\oplus \oplus \oplus \bigcirc$ CRITICAL trials (from 133 fewer to 4 fewer)	erm risk of i , Not serious	rm risk of ipsilateral stro l Not serious Not serious	ke, including _F Serious ^b	peri-procedur Not serious	al stroke in any ter None	ritory or peri-pr 31/268 (11.6%)	rocedural d 44/215 (20.5%)	leath (50-99 % RR 0.58 (0.35–0.98)	to 1.24 rever) 5 stenosis): 2–4 vy 86 fewer per 1000 (from 133 fewer to 4 fewer)	veeks since m ⊕⊕⊕⊖ MODERATE	ost recent CRITICAL

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nty assessment Study Risk Inconsistency Indirectness design of bias Inconsistency Indirectness 4.1.3.c: Long-term risk of ipsilateral stroke, including aemic event Randomised Not serious Not serious Serious ^b trials 4.1.4.3. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.3. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.3. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.3. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.3. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.4. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.4. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.1. Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious ^b trials 4.1.4.1. Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious ^b trials 4.1.4.1. Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious ^b trials 4.2.1.1.4.1. Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious ^b trials	Try ansertient Model Not patients Metal Metal<													
	Bandy and standomical bandomical standomica	Certaint	ty assessment						№ of patients		Effect		1	
 ICO 4.1.3c: Long-term risk of ipsilateral stroke, including is chaemic event Randomised Not serious Not serious Serious^b trials ICO 4.1.3d: Long-term risk of ipsilateral stroke, including is chaemic event Randomised Not serious Not serious Serious^b trials ICO 4.1.4a: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4a: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4b: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4c: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4d: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4d: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4d: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials ICO 4.1.4d: Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious^b trials ICO 4.2.1 a: Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious^b trials 	 (CO 4.1.3c Long-term risk of lpaliateral stroke, including peri-procedural stroke in any territory or peri-procedural death (50.4% stensels), ±-12 weeks since most between the monoment. In the distance of the monoment is stroke in any territory or peri-procedural death (50.4% stensels), ±-12 weeks since most between the monoment. In the distance of the monoment is stroke. In the distance of the monoment is stroke. In the distance of the monoment is stroke in any territory or peri-procedural death (50.4% stensels); ±12 weeks since most is diadoning lower to a monoment. Note actions is very serious. Note a track of the intervet and the distance of the monoment is stroke. In the distance of the monoment is stroke. In the distance of the monoment is stroke. In the distance of the distance of the monoment is stroke. In the distance of the distan	N⁰ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endarterectomy	Medical therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Construction Not serious Not serious Serious ^b Indomised Not serious Not serious Serious ^b Ischaemic event Not serious Not serious Serious ^b Randomised Not serious Not serious Serious ^b Indomised Not serious Serious ^b Serious ^b Indomised Not	Tandonised trains Not serious (1.3%) Not serious (1.4%) Not ser	PICO 4 ischa	4.1.3c: Long-t	erm risk of i	psilateral strok			al stroke in any te	rritory or peri-pr	ocedural d	leath (50-99%	stenosis): 4–12	weeks since 1	most recent
 Trials CO 4.1.3d: Long-term risk of ipsilateral stroke, including ischaemic event Randomised Not serious Not serious Serious^b trials CO 4.1.4a: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials CO 4.1.4b: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials CO 4.1.4b: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials CO 4.1.4c: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials CO 4.1.4c: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials CO 4.1.4d: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious Serious^b trials CO 4.1.4d: Long-term risk of ipsilateral stroke, including Randomised Not serious Not serious^a Serious^b trials CO 4.1.4d: Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious^b trials CO 4.2.1.a: Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious^b trials CO 4.2.1.a: Long-term risk of stroke in any territory, including Randomised Not serious Not serious Serious^b trials 	Transaction for the first of the first		Bandomised	Not serious		Sarious ^b	Not serious	Anna	63/560	81/49R	RR 0.70	40 fawar nar		
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Randomised Not serious Serious ^b Very serious ^d None 11/22 Rt I/01 Imore per Tento Tento Consisting Traids Not serious Very serious ^d None 24/157 (13.4%) (0.64-1.57) 1000 Very Low Consisting Not serious Very serious ^d Very serious ^d None 24/157 (14.9%) (0.57-1.84) 1000 Very Very Mode Consisting Not serious Not serious Very serious ^d None 24/157 (14.9%) (0.57-1.84) 1000 Very Not Serious ^d Consisting Not serious Not serious Not serious Not serious None 0.5753 (14.9%) (0.57-1.84) 1000 Very Not Not Consisting Not serious Not serious None (70.14,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 (70.04,050 <t< td=""><td>Randomised Net serious Serious¹ Very serious⁴ Note 41/321 31/322 RR 1.01 Immore per (rent size) 0000 very territory or peri-procedural death: Near occlusion 0000 very vertiony 0000 vertion 00000 vertion 00000 vertion <t< td=""><td>PICO 4 ischa</td><td>4.1.3d: Long-t temic event</td><td>erm risk of i</td><td>ipsilateral strol</td><td></td><td></td><td>al stroke in any te</td><td>rritory or peri-pr</td><td>rocedural c</td><td>leath (50-99%</td><td><pre>% stenosis): >12</pre></td><td>weeks since n</td><td>nost recent</td></t<></td></t<>	Randomised Net serious Serious ¹ Very serious ⁴ Note 41/321 31/322 RR 1.01 Immore per (rent size) 0000 very territory or peri-procedural death: Near occlusion 0000 very vertiony 0000 vertion 00000 vertion 00000 vertion <t< td=""><td>PICO 4 ischa</td><td>4.1.3d: Long-t temic event</td><td>erm risk of i</td><td>ipsilateral strol</td><td></td><td></td><td>al stroke in any te</td><td>rritory or peri-pr</td><td>rocedural c</td><td>leath (50-99%</td><td><pre>% stenosis): >12</pre></td><td>weeks since n</td><td>nost recent</td></t<>	PICO 4 ischa	4.1.3d: Long-t temic event	erm risk of i	ipsilateral strol			al stroke in any te	rritory or peri-pr	rocedural c	leath (50-99%	<pre>% stenosis): >12</pre>	weeks since n	nost recent
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	(128%) (13.4%) (0.66-1.57) 1000 VERY LOW Pert-procedural stroke in any territory or pert-procedural death: Near occlusion 76 more) 76 more) 76 more) Very serious ⁴ None 24/157 17/114 R.R.1.03 4 more per ⊕OO VERY LOW Very serious ⁴ None 24/157 17/114 R.R.1.03 4 more per ⊕OO VERY LOW Very serious ⁴ None (15.3%) (14.9%) (0.57-1.84) 1000 VERY LOW Pert-procedural stroke in any territory or pert-procedural death: Severe (70-9%) stenosis 11/144 R.R.1.03 4 more per ⊕⊕OO CR Pert-procedural stroke in any territory or pert-procedural death: Moderate (50-6%) stenosis 1000 LOM CR Serious ⁵ None 1010/694 R.082 29 fewer to 124 more) Pert-procedural stroke in any territory or pert-procedural death: Moderate (50-6%) stenosis CR 000 VERY LOW Serious ⁵ None (10.6694 R.082 29 fewer to 124 more) Pert-procedural stroke in any territory or pert-procedural death: Mild (50%) stenosis 1000 VERY LOW 000		Randomised	Not serious	Not serious	Serious ^b	Very serious ^d	None	41/321	31/232	RR 1.01	I more per	000⊕	CRITICAL
Interiment of the second service of the service of t	peri-procedural stroke in any territory or peri-procedural death: Near occlusion $(1000 \text{ Very LOW} \text{ Very LOW} \text{ (from 64 fewer to 125 more)}$ Very serious ⁴ None $24/157$ $17/114$ $\mathbb{R} \text{ I}$ ($0.37-1.84$) $0000 \text{ very LOW} \text{ Very LOW}$ Peri-procedural stroke in any territory or peri-procedural death: Severe ($70-9\%$) stenosis 125 more) 0.5618 $117/436$ \mathbb{R} ($0.37-0.50$) 1000 very terr \mathbb{CR} Not serious Strong association ⁴ $50/518$ $117/436$ \mathbb{R} ($0.37-0.50$) $1000 \text{ mer per } \oplus \oplus \oplus$ \mathbb{CR} Not serious None 0.7%) 2.63% $0.27-0.50$) $1000 \text{ mer per } \oplus \oplus \oplus$ \mathbb{CR} Not serious ⁵ None $117/436$ \mathbb{R} ($0.37-0.50$) $1000 \text{ mer per } \oplus \oplus \oplus$ \mathbb{CR} Serious ⁵ None $110/694$ \mathbb{R} ($0.32-0.50\%$) stenosis \mathbb{CR} \mathbb		trials						(12.8%)	(13.4%)	(0.66–1.57)	1000		
peri-procedural death: Near occlusion Very serious ⁴ None $24/157$ $17/114$ RR R.0.00 VERY LOW Very serious ⁴ None $24/157$ $17/114$ R.R 100 VERY LOW Very serious ⁴ None $24/157$ $17/114$ R.R 1000 VERY LOW (15.3%) (14.9%) (0.57-1.84) 1000 VERY LOW Peri-procedural stroke in any territory or peri-procedural death: Severe (70-9%) stenosis $117/436$ R.0.37 169 fewer 0000 HIGH Not serious Strong association ⁴ $50/518$ $117/436$ R.0.037 169 fewer 0000 1000 Peri-procedural stroke in any territory or peri-procedural death: Moderate (50-69%) stenosis 1000 $116/64$ R.0.02 29 fewer to Peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	peri-procedural death: Near occlusion Very serious ⁴ None $24/157$ $17/114$ R.R. 1.03 4 more per $\oplus \bigcirc \bigcirc \bigcirc$ CR Very serious ⁴ None $24/157$ $17/114$ R.R. 1.03 4 more per $\oplus \bigcirc \bigcirc \bigcirc$ CR Peri-procedural stroke in any territory or peri-procedural death. Severe (70–99%) stenosis 125 more) Net serious 505/518 $11/7/436$ R.0.37 169 fewer to CR Not serious Strong association ⁴ 50/518 $11/7/436$ R.0.37 169 fewer to CR Not serious Strong association ⁴ 50/518 $11/7/436$ R.0.37 169 fewer to CR Not serious ⁵ None $10/1008$ $110/694$ R.0.82 29 fewer to CR Serious ⁵ None $10/1008$ $110/694$ R.0.82 29 fewer to CR Serious ⁵ None $12/502$ $11/64/14$ R.R.0.82 29 fewer to CR Serious ⁶ None $12/502$ $10/64/1413$ R.R.0.82 29 fewer to CR Serious ⁶ None $12/64/163$ $10.64/1413$ R.R.0											(Irom 43 lewer u 76 more)	0	
wery serious Value $(1,3,\%)$ $(1,1,7,\%)$ $(0,1,1,3,\%)$ $(1000$ VERY LOW Peri-procedural stroke in any territory or peri-procedural death: $(1,3,\%)$ $(1,4,\%)$ $(0,27-1,3,4)$ 1000 VERY LOW Peri-procedural stroke in any territory or peri-procedural death: $(1,3,\%)$ $(2,7,6)$ $(2,6,8\%)$ $(0,27-0,50)$ 1000 VERY LOW Not serious $5rrong$ association ⁴ $50/518$ $117/436$ RR 0.37 169 fewer 6000 HGH Peri-procedural stroke in any territory or peri-procedural death: 0000 1000 1000 1000 1000 Peri-procedural stroke in any territory or peri-procedural death: 1006 1006 1000 <td>wery serious None (5.3%) (14.9%) (0.57-1.84) 1000 VEN LOW (from 64 fewer to 1.25 more) (5.3%) (14.9%) (0.57-1.84) 1000 VEN LOW (from 64 fewer to 1.25 more) (70.99%) stenois (70.99%) stenois (7.7%)</td> <td>PICO</td> <td>4.1.4a: Long-t</td> <td>erm risk of i</td> <td>psilateral strok</td> <td>ke, including</td> <td>peri-procedur</td> <td>al stroke in any te</td> <td>rritory or peri-pr</td> <td>rocedural d</td> <td>leath: Near o</td> <td>occlusion</td> <td></td> <td></td>	wery serious None (5.3%) (14.9%) (0.57-1.84) 1000 VEN LOW (from 64 fewer to 1.25 more) (5.3%) (14.9%) (0.57-1.84) 1000 VEN LOW (from 64 fewer to 1.25 more) (70.99%) stenois (70.99%) stenois (7.7%)	PICO	4.1.4a: Long-t	erm risk of i	psilateral strok	ke, including	peri-procedur	al stroke in any te	rritory or peri-pr	rocedural d	leath: Near o	occlusion		
peri-procedural stroke in any territory or peri-procedural death: Severe (70-9%) stenosis (from 64 fewer to 125 more) peri-procedural stroke in any territory or peri-procedural death: Severe (70-9%) stenosis (from 196 fewer per ⊕⊕⊕ Not serious Strong association ^d 50/518 117/436 RR 0.37 169 fewer per ⊕⊕⊕ Peri-procedural stroke in any territory or peri-procedural death: Moderate (50-6%) stenosis 0000 HIGH peri-procedural stroke in any territory or peri-procedural death: Moderate (50-6%) stenosis 0000 LOW peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	peri-procedural stroke in any territory or peri-procedural death: Severe (70–9%) stenosis Not serious Strong association ⁴ 50/518 11/1/436 RR 0.37 169 fewer per $\Theta \oplus \Theta \oplus$ Peri-procedural stroke in any territory or peri-procedural death: Moderate (50–9%) stenosis Serious ⁵ None 101/808 110/694 RR 0.82 29 fewer per $\Theta \oplus \odot$ Peri-procedural stroke in any territory or peri-procedural death: Moderate (50–9%) stenosis Serious ⁵ None 101/808 110/694 RR 0.82 29 fewer per $\Theta \oplus \odot$ Peri-procedural stroke in any territory or peri-procedural death: Moderate (50–9%) stenosis Serious ⁶ None 212/1762 164/1413 RR 1.09 1000 LOW (12.0%) (11.6%) (0.64–1.85) 1000 VERY LOW Not serious None 386/3336 584/2754 RR 0.85 32 fewer per $\Theta \oplus \odot$ Not serious ⁶ None 32/157 (11.6%) (0.64–1.85) 1000 VERY LOW Very serious ⁶ None 32/157 (11.6%) (0.64–1.85) 1000 VERY LOW (from 47 fewer to 13 fewer to 14 firm 47 fewer to 13 fewer to 13 fewer to 14 firm 47 fewer to 13 fewer to 13 fewer to 13 fewer to 14 firm 47 fewer to 13 fewer to 14 firm 47 fewer to 14 firm 47 fewer to 15 fewer to 15 fewer to 16 firm 47 fewer to 17 fewer to 17 fewer to 13 fewer to 13 fewer to 13 fewer to 13 fewer to 14 firm 47 fewer to 13 fewer to 14 firm 47 fewer to 15 fewer to 15 fewer to 15 fewer to 16 fewer to 17 fewer to 17 fewer to 17 fewer to 18 fewer to 19 fewer to 10 fewer to 13 fewer to 14 fewer to 13 fewer to 14 fewer to 15 fewer to 13 fewer to 13 fewer to 14 fewer to 15 fewer to 13 fewer to 14 fewer to 15 fewer to 15 fewer to 16 fewer to 17 fewer to 17 fewer to 18 fewer to 19 fewer to 10 fewer	٧	trials	INOU SELIOUS	INOL SERIOUS	serious	very serious	INORE	24/13/ (15.3%)	(14.9%)	0.57–1.84) (0.57–1.84)	4 more per 1000	VERY LOW	CNIICAL
125 more) 125 more) peri-procedural stroke in any territory or peri-procedural death: Severe (70-9%) stenosis 117/436 R 0.37 169 fewer per ⊕000 9.7%) 0.26.8%) 0.27-0.50 1000 HIGH 9.7%) 26.8%) 0.27-0.50 1000 HIGH Peri-procedural stroke in any territory or peri-procedural death: Moderate (50-69%) stenosis 101/694 R 0.82 29 fewer per ⊕000 Peri-procedural stroke in any territory or peri-procedural death: Moderate (50-69%) stenosis 10000 LOW Peri-procedural stroke in any territory or peri-procedural death: Mild (50%) stenosis 24 more) 24 more) Peri-procedural stroke in any territory or peri-procedural death: Mild (50%) stenosis 24 more) 24 more) None 212/1762 164/1413 R 1.09 10 more per ⊕000 Not serious ⁶ None 212/1762 164/1413 R 1.09 10 more per to 24 more) Not serious ⁶ None 212/1762 164/1413 R 1.09 10 more per to 24 more) Not serious ⁶ None 212/1762 164/1413 R 1.09 10 more per to 24 more) Not serious ⁶	125 more) peri-procedural stroke in any territory or peri-procedural death: Severe (70-9%) stenosis Not serious Strong association (7.7%) 50/518 117/436 RR 0.37 160 fewer per 0000 HIGH Not serious Strong association (7.7%) (2.6.8%) (0.27-0.50) 1000 HIGH 000 Peri-procedural stroke in any territory or peri-procedural death: Moderate (50-69%) stenosis 101/808 110/694 RR 0.82 29 fewer CR Serious ⁶ None 101/808 110/694 RR 0.82 29 fewer to 24 24 24 24 24 24 24 26 27 26 27 26 27 26 27 26 27 27 26 27 27 26 27 27 26 27 26 27									-		(from 64 fewer to		
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Not serious Jung association	Not serious Orong association 0.07% (2.6.8%) (0.27-0.50) 1000 HIGH Constrained Constrained HIGH Constrained HIGH Constrained HIGH Constrained Constrained Constrained Constrained Constrained Constrained HIGH Constrained Constrained <thconstrained< th=""> Constrained Const</thconstrained<>	PICO ,	4.1.4b: Long-t Bandomised	erm risk of i	ipsilateral strol			al stroke in any te	rritory or peri-pr	rocedural c	leath: Severe	(70–99%) stend	osis AAAAA	
The series The series <ththe series<="" th=""> The series The series<td>(7.7.6) $(2.0.5.6.5)$ $(0.2.7.0.30)$ 1000 1000 peri-procedural stroke in any territory or peri-procedural death: Moderate (50-9%) stenosis $(10.1808$ $110(694$ RR 0.82 29 fewer 29 CR Serious⁶ None $101/808$ $110(694$ RR 0.82 29 fewer 29 CR Peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis</td> 24 more) 24 more) CR peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis</ththe>	(7.7.6) $(2.0.5.6.5)$ $(0.2.7.0.30)$ 1000 1000 peri-procedural stroke in any territory or peri-procedural death: Moderate (50-9%) stenosis $(10.1808$ $110(694$ RR 0.82 29 fewer 29 CR Serious ⁶ None $101/808$ $110(694$ RR 0.82 29 fewer 29 CR Peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	۲		INOT SERIOUS		Serious	INOT SERIOUS	strong association		()/430		107 Tewer per		CRITCAL
peri-procedural stroke in any territory or peri-procedural death: Moderate (50-6%) stenosis Serious ^c None 101/808 110/694 RR 0.82 29 fewer per 000 LOW Serious ^c None 101/808 110/694 RR 0.82 29 fewer to 000 LOW peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	peri-procedural stroke in any territory or peri-procedural death: Moderate (50.6%) stenosis to 134 fewer) Serious ^c None 101/808 110/694 RR 0.82 29 fewer per ⊕⊕ CR Peri-procedural stroke in any territory or peri-procedural death: Moderate (50%) stenosis 24 more) 24 more) CR Peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis		trials						(%1.%)	(%8.07)	(nc:n-/7:n)	1000 /from 196 fewer	HGH	
peri-procedural stroke in any territory or peri-procedural Serious NoneNone10/694RR 0.8229 fewer per (12.5%) Senois (12.5%) Serious Serious NoneNone10/1808110/694RR 0.8229 fewer per $(17000 67$ 000 LOWperi-procedural stroke in any territory or peri-procedural death:Mild (<50%) stenosis 24 more)24 more) 000 UNperi-procedural stroke in any territory or peri-procedural death:Mild (<50%) stenosis $0.64-1.85$) $0.64-1.85$) 000 VERY LOWng peri-procedural death(11.6%)(0.64-1.85) 1000 VERY LOW $0.64-1.85$) 000 VERY LOWng peri-procedural death(30-99% stenosis) $584/2754$ RR 0.85 32 fewer to 9 more) 99 more) 99 more) 99 more)ng peri-procedural death:Not seriousNone $584/2754$ RR 0.85 32 fewer to 91 more) 99 more) 000 $VERY LOWnding peri-procedural death:None32/157(21.2\%)(0.77-0.94)10000 fewer to13 fewer)0.64-1.810.00very seriousd None32/15725/114RR 1.000 fewer per0.64-2.210.000 fewer per0.00$	peri-procedural stroke in any territory or peri-procedural death: Mode: ate (50-69%) stemosis Serious ⁵ None 10/808 110/694 RR 0.82 29 fewer per ####################################											to 134 fewer)		
Serious ^c None 101/808 110/694 RR 0.82 29 fewer per @@ peri-procedural stroke in any territory or peri-procedural death: Mild (<50%)	Serious ^c None 101/808 110/694 RR 0.82 29 fewer per Hell R R R Hell H	PICO 4	4.1.4c: Long-t	erm risk of i	psilateral strok			al stroke in any te	rritory or peri-pr	ocedural d	leath: Moder	ate (50–69%) ste	enosis	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	(12.5%) (15.9%) (0.58-1.15) 1000 LOW peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	2	Randomised	Not serious			Serious ^c	None	101/808	110/694	RR 0.82	29 fewer per	00	CRITICAL
(from 6/ fewer to 24 more) peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	Peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis		trials						(12.5%)	(15.9%)	(0.58–1.15)	1000	LOW	
peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis	peri-procedural stroke in any territory or peri-procedural death: Mild (<50%) stenosis Serious ^c None 212/1762 164/1413 RR 1.09 10 more per $\oplus \bigcirc \bigcirc$ CR (from 42 fewer to 0.64-1.85) 1000 VERY LOW (from 42 fewer to 99 more) ng peri-procedural death (30-99% stenosis) 584/2754 RR 0.85 32 fewer per $\oplus \oplus \oplus \bigcirc$ CR (from 42 fewer to 17.6%) (0.77-0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 13 fewer) 13 fewer to 13 fower) 13 fewer to 1000 fewer fewer to 1000 VERY LOW (for 0.64-2.21) fool 76 fewer to 1000 VERY LOW (fewer to											(from 67 fewer to	0	
Serious ^c None 212/1762 164/1413 R.1.09 10 Once per $\oplus \bigcirc \bigcirc$ ng peri-procedural death (30-99% stenosis) (11.6%) (0.64–1.85) 1000 VERY LOW ng peri-procedural death (30-99% stenosis) 584/2754 R.0.85 32 fewer to 99 more) Not serious None 586/3336 584/2754 R.0.85 32 fewer to Not serious None 586/3346 (0.77–0.94) 1000 MODERATE (17.6%) (21.2%) (0.77–0.94) 1000 MODERATE uding peri-procedural death: Near-occlusion 25/114 R.1.00 0 fewer per $\oplus \bigcirc \bigcirc \bigcirc$ Very serious ^d None 32/157 25/114 R.1.00 0 fewer per $\oplus \bigcirc \bigcirc \bigcirc$	Serious ^c None 212/1762 164/1413 R 1.09 10 more per $\oplus \bigcirc \bigcirc$ CR ng peri-procedural death (30-99% stenosis) (11.6%) (0.64–1.85) 1000 VENY LOW VENY LOW ng peri-procedural death (30-99% stenosis) 584/2754 R 0.85 32 fewer to 99 more) 99 more) CR Not serious None 586/3336 584/2754 R 0.855 32 fewer to 99 more) CR Not serious None 586/3336 584/2754 R 0.855 32 fewer to 99 more) CR Very serious ⁶ None 32 fewer per $\oplus \oplus \oplus \bigcirc$ 13 64/16 CR Very serious ⁶ None 32/157 25/114 R 1.00 0 fewer per $\oplus \bigcirc \bigcirc \bigcirc$ CR	PICO 4	4.1.4d: Long-t	erm risk of i	bsilateral strok			al stroke in anv te	rritorv or peri-pr	ocedural d	leath: Mild (<	∠4 more) <50%) stenosis		
(11.6%) (0.64–1.85) 1000 VERY LOW (from 42 fewer to 99 more) 584/2754 RR 0.85 32 fewer per ⊕⊕⊕ (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕○○○ (21.9%) (0.46–2.21) 1000 VERY LOW	(11.6%) (0.64–1.85) 1000 VEYY LOW (from 42 fewer to 99 more) 584/2754 RR 0.85 32 fewer per ⊕⊕⊕○ CR (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕○○○ CR (21.9%) (0.46–2.21) 1000 VERY LOW	5	Randomised	Not serious	Serious ^a			None	212/1762	164/1413	RR 1.09	10 more per		CRITICAL
(from 42 fewer to 99 more) 584/2754 RR 0.85 32 fewer per ⊕⊕⊕ (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕ ○○ (21.9%) (0.46–2.21) 1000 VERY LOW	(from 42 fewer to 99 more) 584/2754 RR 0.85 32 fewer per ⊕⊕⊕ (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕ ○○○ CR (21.9%) (0.46–2.21) 1000 VERY LOW		trials						(12.0%)	(11.6%)	(0.64–1.85)	0001		
584/2754 RR 0.85 32 fewer per ⊕⊕⊕ (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕ ○○○ (21.9%) (0.46–2.21) 1000 VERY LOW	584/2754 RR 0.85 32 fewer per ⊕⊕⊕ (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕ ○○○ CR (21.9%) (0.46–2.21) 1000 VERY LOW											(from 42 fewer to 99 more)	0	
584/2/54 RK 0.85 32 fewer per ⊕⊕⊕ () (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) (25/114 RR 1.00 0 fewer per ⊕ ()() (21.9%) (0.46–2.21) 1000 VERY LOW	584/2/54 RK 0.85 32 fewer per ⊕⊕ ⊕() CF (21.2%) (0.77–0.94) 1000 MODERATE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕()() CR (21.9%) (0.46–2.21) 1000 VERY LOW	PICO 4	4.2: Long-terr	n risk of stro	oke in any terri	tory, includi	ng peri-proced	ural death (30-995	% stenosis)					
(21.2%) (0.7.7–0.37) 1000 FROLENALE (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕○○○ (21.9%) (0.46–2.21) 1000 VERY LOW	(21.2%) (0.7.7–0.34) (from 49 fewer to (from 49 fewer to 13 fewer) 25/114 RR 1.00 0 fewer per ⊕OOO CR (21.9%) (0.46–2.21) 1000 VERY LOW	m	Randomised		Not serious	Serious		None	586/3336	584/2754	RR 0.85	32 fewer per		CRITICAL
25/114 RR 1.00 0 fewer per	25/114 RR 1.00 0 fewer per ⊕ CR (21.9%) (0.46–2.21) 1000 VERY LOW		u iais						(%0.71)	(%7.17)	(+4.0-11.0)	(from 49 fewer to 13 fewer)		
Not serious Not serious Serious ^b Very serious ^d None $32/157$ 25/114 RR 1.00 0 fewer per $\oplus \bigcirc \bigcirc$	Not serious Not serious Serious ^b Very serious ^d None 32/157 25/114 RR 1.00 0 fewer per $\oplus \bigcirc \bigcirc \bigcirc$ CR (20.4%) (0.46–2.21) 1000 VERY LOW	PICO 4	4.2.1a: Long-t	erm risk of s	stroke in any te	srritory, inclu	uding peri-proc	sedural death: Ne	ar-occlusion					
(20.4%) (21.9%) (0.46–2.21) 1000	(20.4%) (21.9%) (0.46–2.21) 1000 VERY LOW	7	Randomised		Not serious	Serious ^b			32/157	25/114	RR 1.00	0 fewer per		CRITICAL
	Continue		trials						(20.4%)	(21.9%)	(0.46–2.21)	0001	VERY LOW	

Table 5. Continued.

Certainty assessment	essment					№ of patients		Effect			
№ of Study studies design	ły Risk gn of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endarterectomy	Medical therapy	Relative (95% CI)	Absolute (95% CI)	– Certainty	Importance
									(from 118 fewer to 265 more)		
PICO 4.2.11 Ran tu	2.1b: Long-term risk of stroke in . Randomised Not serious Serious ^a trials	f stroke in any t u Is Serious ^a	erritory, inclu Serious ^a	uding peri-pro Not serious	PICO 4.2.1b: Long-term risk of stroke in any territory, including peri-procedural death: Severe (70–99%) stenosis 2 Randomised Not serious Serious ^a Serious ^a Not serious Strong association ^d 84/518 143/ trials (16.2%) (32.8	sre (70–99%) ste l 84/518 (16.2%)	nosis 143/436 (32.8%)	RR 0.48 (0.29–0.81)	171 fewer per 1000 (from 233 fewer	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 4.2.1c 2 Ran tr	2.1c: Long-term risk of st Randomised Not serious trials	f stroke in any te Is Not serious	e rritory, inclu Serious ^b	uding peri-pro . Not serious	PICO 4.2.1c: Long-term risk of stroke in any territory, including peri-procedural death: Moderate (50–69%) stenosis 2 Randomised Not serious Not serious ^b Not serious None 144/808 165/694 trials (17.8%)	erate (50–69%) s 144/808 (17.8%)	stenosis 165/694 (23.8%)	RR 0.77 (0.63–0.94)	to 62 fewer) 55 fewer per 1000 (from 88 fewer to	⊕⊕⊕⊖ MODERATE °	CRITICAL
ICO 4.2.1 Ran ti	2.1d: Long-term risk o Randomised Not seriou trials	erm risk of stroke in any te Not serious Not serious	erritory, inclu Serious ^b	uding peri-pro Serious ^c	PICO 4.2.1d: Long-term risk of stroke in any territory, including peri-procedural death: Mild (<50%) stenosis 2 Randomised Not serious Not serious Serious ⁵ Serious ^c None 318/1762 trials (18.0%)	(<50%) stenosis 318/1762 (18.0%)	244/1413 (17.3%)	RR 1.09 (0.89–1.34)	14 fewer) 16 more per 1000 (from 19 fewer to	° ℃ € € 0 %	CRITICAL
PICO 4.3: L Ran ti	3: Long-term risk of m Randomised Not seriou trials	n risk of major stroke, inclu Not serious Not serious	uding peri-pr Serious ^b	rocedural deat Serious ^c	PICO 4.3: Long-term risk of major stroke, including peri-procedural death (30-99% stenosis) 3 Randomised Not serious Not serious Serious ^b Serious ^c None trials	150/3336 (4.5%)	l 52/2754 (5.5%)	RR 0.79 (0.51–1.22)	59 more) 12 fewer per 1000 (from 27 fewer to 12 more)	COW °	CRITICAL
PICO 4.3.1 a Ran tu	la: Long-term risk of ndomised Not seriou trials	f major stroke, i Is Not serious	ncluding per i Serious ^b	i-procedural de Very serious ^d	PICO 4.3.1a: Long-term risk of major stroke, including peri-procedural death: Near-occlusion 2 Randomised Not serious Not serious Serious ^b Very serious ^d None I trials (n 12/157 (7.6%)	7/114 (6.1%)	RR 1.33 (0.35–5.08)	20 more per 1000 (from 40 fewer to 251 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
PICO 4.3.11 Ran tu	 B: Long-term risk of Randomised Not seriou trials 	e rm risk of major stroke, i Not serious Not serious	ncluding peri Serious ^b	i-procedural d Not serious	PICO 4.3.1b: Long-term risk of major stroke, including peri-procedural death: Severe (70–99%) stenosis 2 Randomised Not serious Not serious ^b Not serious Strong association ^d 22/518 trials (4.2%)	%) stenosis 22/518 (4.2%)	53/436 (12.2%)	RR 0.35 (0.22–0.57)	79 fewer per 1000 (from 95 fewer to	0 HIGH	CRITICAL
PICO 4.3.1 c Ran tu	l c: Long-term risk of ndomised Not seriou trials	f major stroke, ir Is Not serious	ncluding peri Serious ^b	l -procedural d Serious ^c	PICO 4.3.1 c: Long-term risk of major stroke, including peri-procedural death: Moderate (50–69%) stenosis 2 Randomised Not serious Not serious Serious ⁵ Serious ^c None 35/808 trials (4.3%)	-69%) stenosis 35/808 (4.3%)	39/694 (5.6%)	RR 0.73 (0.41–1.27)	52 fewer) 15 fewer per 1000 (from 33 fewer to		CRITICAL

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Certain	Certainty assessment						N⁰ of patients		Effect			
N₀ of Study studies design	N≙ of Study studies design	Risk of bias	Inconsistency Indirectness	Indirectness	Imprecision	Other considerations	Medical Relative Endarterectomy therapy (95% CI)	Medical Relative therapy (95% CI)		Absolute (95% CI)	Certainty	Certainty Importance
PICO (1.3.1d: Long-t	erm risk of n	najor stroke, i	including per	-i-procedural	PICO 4.3.1d: Long-term risk of major stroke, including peri-procedural death: Mild (<50%) stenosis	stenosis					
2	Randomised trials	Not serious	Randomised Not serious Not serious Serious ^b trials	Serious ^b	Serious ^c	None	79/1762 (4.5%)	50/1413 (3.5%)	RR 1.24 (0.82–1.87)	8 more per 1000		CRITICAL
										(from 6 fewer to 31 more)		
PICO (4.4: Long-tern	n risk of deat	PICO 4.4: Long-term risk of death (30-99% stenosis)	nosis)								
ε	Randomised	Not serious	Randomised Not serious Not serious Serious ^b trials	Serious ^b	Serious ^c	None	738/3335 (77.1%)	576/2758 (70.9%)	576/2758 RR I.00 (20.9%) (0.85–1.19)	0 fewer per 1000		IMPORTANT

CI: confidence interval: RR: risk ratio. ^aSignificant heterogeneity, $l^2 > 70\%$. ^bEndarterectomy and medical therapy have evolved since the trials contributing the evidence were performed. ^cFew events, wide confidence intervals. ^dLarge effect. in the combined outcome was not statistically significant in women (Figure 4.1.2), this was likely due to the low number of women included in the trials (n = 832).

PICO 4.2: In patients with symptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of stroke in any territory, including peri-procedural death? Amongst patients with all degrees of stenosis combined, there is moderate quality of evidence that CEA reduced the long-term risk of stroke in any territory, including periprocedural death, compared with medical therapy alone (RR: 0.85, 95% CI: 0.77-0.94; 32 fewer events per 1000 patients, from 49 fewer to 13 fewer; Figure 4.2). The evidence for a beneficial effect of CEA was of moderate quality in patients with 70-99% stenosis (RR: 0.48, 95% CI: 0.29-0.81; 171 fewer events per 1000 patients, from 233 fewer to 62 fewer; Figure 4.2.1) and in patients with 50-59% stenosis (RR: 0.77, 95% CI: 0.63-0.94; 55 fewer events per 1000 patients, from 88 fewer to 14 fewer). Comparing the number of events prevented between PICO 4.1 and PICO 4.2 within each stenosis category, it can be inferred that CEA mainly prevents ipsilateral stroke.

PICO 4.3: In patients with symptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of major stroke, including peri-procedural death? Amongst patients with all degrees of stenosis combined, endarterectomy did not significantly reduce the long-term risk of major stroke, including peri-procedural death (RR: 0.79, 95% CI: 0.51-1.22; 12 fewer events per 1000 patients, from 27 fewer to 12 more; low quality evidence; Figure 4.3). However, once again, the benefit of CEA varies according to the degree of stenosis. In patients with 70–99% stenosis, there is high quality evidence of benefit (RR: 0.35, 95% CI: 0.22-0.57; 79 fewer events per 1000 patients, from 95 fewer to 52 fewer; Figure 4.3.1). Conversely, there was low quality evidence of potential benefit in patients with 50-69% stenosis (RR: 0.73, 95% CI: 0.41-1.27; 15 fewer events per 1000 patients, from 33 fewer to 15 more), low quality evidence of harm in patients with <50% stenosis (RR: 1.24, 95%) CI: 0.82–1.87), and very low quality evidence of harm in patients with near occlusion (RR: 1.33, 95% CI: 0.35-5.08).

PICO 4.4: In patients with symptomatic carotid stenosis, does endarterectomy compared with medical therapy alone reduce the long-term risk of death? Endarterectomy does not reduce the long-term risk of

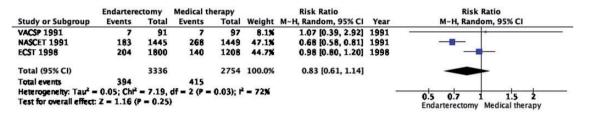


Figure 4.1. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in endarterectomy versus medical therapy for 30–99% symptomatic carotid stenosis.

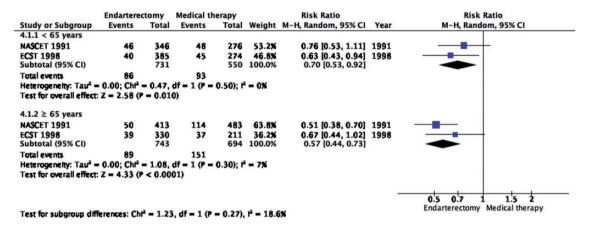


Figure 4.1.1. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in endarterectomy versus medical therapy for 50–99% symptomatic carotid stenosis. Subgroup: Age.

	Endartere	ctomy	Medical th	nerapy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
4.1.1 Men								
NASCET 1991	65	509	124	540	62.7%	0.56 [0.42, 0.73]	1991	
ECST 1998	47	504	60	333	37.3%	0.52 [0.36, 0.74]	1998	
Subtotal (95% CI)		1013		873	100.0%	0.54 [0.44, 0.67]		◆
Total events	112		184					
Heterogeneity: Tau ² =	.0.00; Chl ²	- 0.10,	df = 1 (P =	0.75); P	- 0%			
Test for overall effect:	z = 5.53 (P < 0.00	001)					
4.1.2 Women								
NASCET 1991	31	250	38	219	55.3%	0.71 [0.46, 1.11]	1991	_
ECST 1998	32	211	22	152	44.7%	1.05 [0.63, 1.73]	1998	
Subtotal (95% CI)		461		371	100.0%	0.85 [0.58, 1.23]		
Total events	63		60					
Heterogeneity: Tau2 =	0.02; Chr	= 1.27.	df = 1 (P =	0.26); #	= 21%			
Test for overall effect:	Z = 0.87 (= 0.39	}					
							-	0.5 0.7 1 1.5 2
								Endarterectomy Medical therapy
Test for subgroup diff	ferences: Ch	P = 4.1	5, df = 1 (P	= 0.04).	P = 75.	9%		choancerectority Medical therapy

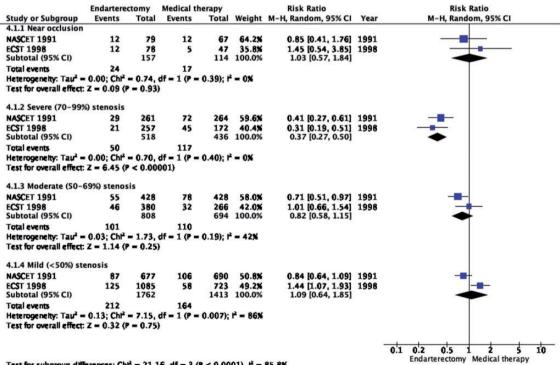
Figure 4.1.2. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in endarterectomy versus medical therapy for 50–99% symptomatic carotid stenosis. Subgroup: Sex.

death compared with medical therapy alone (RR: 1.00, 95% CI: 0.85–1.19; 0 fewer events per 1000 patients, from 31 fewer to 40 more; low quality of evidence; Figure 4.4).

Analysis of current evidence and evidence-based recommendation. Evidence of the effect of CEA compared with medical therapy alone for symptomatic carotid stenosis was available from three trials, which included 6098 patients. Symptomatic carotid stenosis was defined by the occurrence of ischaemic ocular or cerebral events attributable to the stenosis within four to six months before enrolment, depending on the trial and the severity of stenosis. The evidence provided relates to the time when these trials were performed three decades ago. Medical treatment of

	Endartere	ctomy	Medical th	nerapy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events		Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
4.1.1 < 2 Weeks								
NASCET 1991	27	213	62	224	67.9%	0.46 [0.30, 0.69]	1991	
ECST 1998	13	112	26	75	32.1%	0.33 [0.18, 0.61]	1998	
Subtotal (95% CI)		325		299	100.0%	0.41 [0.30, 0.58]		•
Total events	40		66					
Heterogeneity: Tau ² =	0.00; Chr2	= 0.72,	df = 1 (P =	0.40); P	- 0%			
Test for overall effect:	Z = 5.10 (F	< 0.00	001)					
4.1.2 2-4 Weeks								
NASCET 1991	14	132	31	134	54.9%	0.46 [0.26, 0.82]	1991	
ECST 1998	17	136	13	81				
Subtotal (95% CI)		268			100.0%			
Total events	31		44					
Heterogeneity: Tau ² =	0.04; Chr2	= 1.38,	df = 1 (P =	0.24); P	= 27%			
Test for overall effect:	Z = 2.05 (F	= 0.04)					
4.1.3 4-12 Weeks								
NASCET 1991	34	289	50	282	57.9%	0.66 [0.44, 0.99]	1991	
ECST 1998	29	271	31	216	42.1%			
Subtotal (95% CI)		560			100.0%			-
Total events	63		81					-
Heterogeneity: Tau ² =	0.00; Chr2	- 0.13.	df = 1 (P =	0.71); 1	- 0%			
Test for overall effect:	Z = 2.30 (F	= 0.02)					
4.1.4 > 12 Weeks								
NASCET 1991	21	125	19	119	58.7%	1.05 [0.60, 1.86]	1991	
ECST 1998	20	196	12	113	41.3%	0.96 [0.49, 1.89]	1998	
Subtotal (95% CI)		321			100.0%		1000	-
Total events	41		31					
Heterogeneity: Tau ² =	0.00; Chr2	- 0.04,	df = 1 (P =	0.84); P	- 0%			
Test for overall effect:								
								0.2 0.5 1 2 5
								Endarterectomy Medical therapy
Test for subgroup diff	erences: Chi	P = 10.5	6, df = 3 (P = 0.01), F = 72	.6%		citizanterectority metrical therapy

Figure 4.1.3. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in endarterectomy versus medical therapy for 50-99% symptomatic carotid stenosis. Subgroup: Time since last ischaemic event.



Test for subgroup differences: $Chl^2 = 21.16$, df = 3 (P < 0.0001), $l^2 = 85.8\%$

Figure 4.1.4. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in endarterectomy versus medical therapy for symptomatic carotid stenosis. Subgroup: Severity of stenosis.

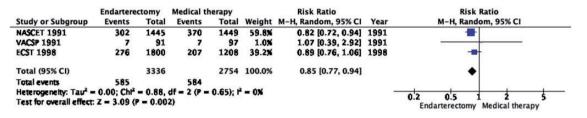


Figure 4.2. Long-term risk of stroke in any territory, including peri-procedural death in endarterectomy versus medical therapy for 30–99% symptomatic carotid stenosis.

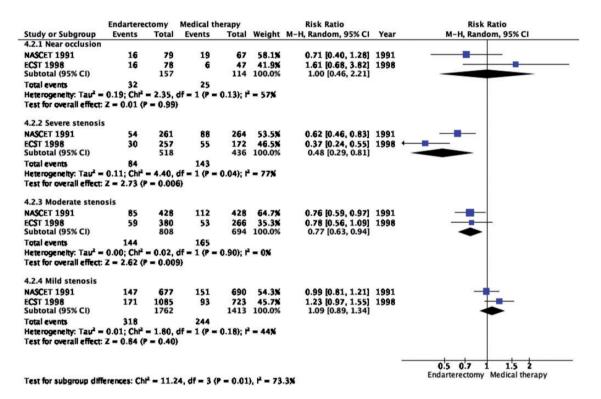


Figure 4.2.1. Long-term risk of stroke in any territory, including peri-procedural death in endarterectomy versus medical therapy for symptomatic carotid stenosis. Subgroup: Severity of stenosis.

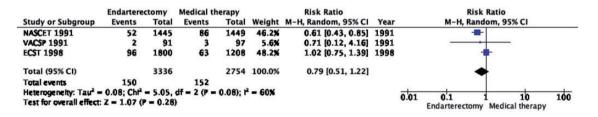


Figure 4.3. Long-term risk of major stroke, including peri-procedural death in endarterectomy versus medical therapy for 30–99% symptomatic carotid stenosis.

patients with atherosclerotic carotid stenosis has improved, with widespread use of statins, the availability of better antiplatelet treatment regimens and stricter control of blood pressure. However, surgical techniques and perioperative management have also improved since these trials were completed. We therefore downgraded the overall quality of evidence for indirectness.

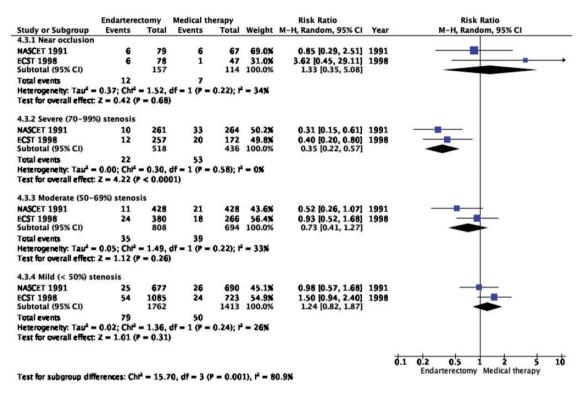


Figure 4.3.1. Long-term risk of major stroke, including peri-procedural death in endarterectomy versus medical therapy for symptomatic carotid stenosis.

Subgroup: Severity of Stenosis.

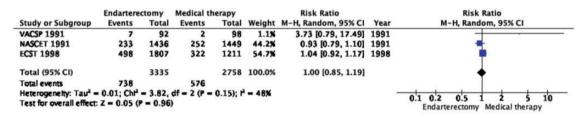


Figure 4.4. Long-term risk of death in endarterectomy versus medical therapy for 30-99% symptomatic carotid stenosis.

The benefits of CEA in patients with symptomatic carotid stenosis strongly depends on the degree of stenosis. Amongst patients with severe (70-99%) stenosis, there is high quality evidence that CEA prevents ipsilateral stroke, moderate quality evidence that it prevents stroke in any territory, and high quality evidence that it prevents major stroke, taking into account the combined risks of peri-operative stroke or death. In patients with moderate (50-69%) carotid stenosis, there is low quality evidence that CEA prevents ipsilateral stroke and major stroke, and moderate quality evidence for prevention of stroke in any territory, again taking into account the peri-operative stroke or death risk, if patients are operated upon within 14 days of their presenting cerebrovascular event. There is no evidence that CEA prevents stroke in patients with mild (<50%) stenosis or near-occlusion of the carotid artery. However, the definition of nearocclusion in the early endarterectomy trials depended on intra-arterial angiography, and there are no widelyaccepted standardised criteria for near-occlusion on ultrasound or non-invasive angiography.⁶⁷ We therefore could not make any clear recommendations on the treatment of carotid near-occlusion in this guideline. The benefit of CEA also strongly depends on the timing of treatment, with the greatest reduction in stroke risk achieved if surgery is performed <14 days of the index event. We found no evidence that the benefit of CEA varies substantially between men and women or between older and younger patients.

The optimal management of patients with distal tandem stenosis is uncertain. In NASCET, patients who had 85–99% extracranial ICA stenosis and any degree of co-existing, ipsilateral intracranial atherosclerotic disease (IAD) had an increased risk of ipsilateral stroke over three years if they were treated with best medical therapy alone compared with those without IAD (45.7% vs. 25.3%, relative risk 1.8, 95% CI: 1.1–3.2).⁶⁸ However, the three-year risk of ipsilateral stroke in surgically-treated patients with 85–99% extracranial ICA stenosis was similar in those with and those without IAD (8.6% vs. 10%, relative risk 0.9; 95% CI: 0.2–3.0). Therefore, IAD should not deter one from proceeding to CEA in suitable patients, whilst acknowledging that only a very small number of patients with severe stenosis were included in this subgroup analysis of the NASCET data.

Recommendations:

In patients with severe (70–99%) symptomatic carotid artery stenosis, we recommend carotid endarterectomy. Quality of evidence: High $\oplus \oplus \oplus \oplus$

Strength of recommendation: Strong for carotid endarterectomy $\uparrow\uparrow$

In patients with moderate (50–69%) symptomatic carotid artery stenosis, we suggest carotid endarterectomy.

Quality of evidence: Low $\oplus \oplus$

Strength of recommendation: Weak for carotid endarterectomy $\ensuremath{\uparrow}$

In patients with mild (<50%) symptomatic carotid artery stenosis, we recommend against carotid endarterectomy.

Quality of evidence: Very low \oplus

Strength of recommendation: Strong against carotid endarterectomy $\downarrow \downarrow$

In patients with 50–99% symptomatic carotid stenosis in whom surgery is considered appropriate, we recommend early endarterectomy, ideally within two weeks of the first neurological event.

Quality of evidence: High $\oplus \oplus \oplus \oplus$

Strength of recommendation: Strong for carotid endarterectomy $\uparrow\uparrow$

These recommendations are independent of sex and age.

Additional information. The Second European Carotid Surgery Trial (ECST-2) is comparing optimised medical therapy (OMT) alone versus OMT and carotid revascularisation in patients with symptomatic carotid stenosis estimated to be at low or intermediate risk of stroke using 'clinical risk modelling', and in patients with asymptomatic carotid stenosis. ECST-2 discontinued recruitment after inclusion of 429 patients in its pilot phase and results are awaited (www.ecst2.com, last accessed 2 February 2021).

Stenting or medical therapy for symptomatic carotid stenosis

Description of studies. We identified no RCTs comparing stenting versus medical therapy alone in patients with

symptomatic carotid stenosis that fulfilled our inclusion criteria. We excluded two small RCTs because these studies did not report outcomes according to symptom status,^{37,38} or patients were treated with primary balloon angioplasty.³⁸

Stenting or endarterectomy for symptomatic carotid stenosis

Description of studies. A single-centre trial in Lexington, Kentucky, USA randomised 104 patients with \geq 70% symptomatic carotid stenosis to receive either CAS without a cerebral protection device (CPD) or CEA and reported results up to two years after randomisation in 2001.⁶⁹

The French multi-centre Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial randomised 527 patients with >60% symptomatic carotid stenosis to undergo CAS or CEA between 2000 and 2005.70-75 Interventionists were required to have performed at least 12 CAS procedures, or at least 35 stenting procedures in the supra-aortic trunks, of which at least 5 involved the carotid artery. The use of CPDs during stenting was made mandatory after an interim analysis raised safety concerns amongst patients treated without CPDs. The trial was stopped early for safety and futility reasons. Initial results were published in 2006, and final results with available data over a median follow-up period of 7.1 years were reported in 2014.

The multi-centre Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy (SPACE) trial randomised 1214 patients with \geq 50% symptomatic carotid stenosis between CAS and CEA in Germany, Austria, and 2006.76-78 Switzerland between 2001 and Interventionists had to show proof of at least 25 successful, consecutive percutaneous transluminal angioplasty or stent procedures in the carotid artery. The use of a CPD was not mandatory. The trial was stopped early for reasons of futility and lack of funding. Initial results were published in 2006 and final results up to two years after randomisation were published in 2008.

A single-centre trial in Regensburg, Germany, randomised 87 patients with \geq 70% symptomatic carotid stenosis to undergo CAS without a CPD or CEA between 1999 and 2002.⁷⁹ Recruitment was stopped when the multi-centre *SPACE* trial, which had a similar study design, was commenced. Results over a median follow-up period of >5 years were published in 2008.

The multi-centre International Carotid Stenting Study (ICSS) randomised 1713 patients with \geq 50%

symptomatic carotid stenosis to receive either CAS or CEA in Europe, Australia, New Zealand, and Canada between 2001 and 2008.^{80–83} Eligible patients had symptoms attributable to their carotid stenosis within 12 months before randomisation; however, only 4% had symptoms which occurred more than 6 months before randomisation. Interventionists were required to have carried out at least 50 stenting procedures, at least 10 of which were in the carotid artery. Use of CPDs was recommended but not mandatory. Initial results were published in 2011 and final results with data over a median follow-up period of 4.2 years were reported in 2015.

The single-centre *Basel Carotid Artery Stenting Study (BACASS)* randomised 20 patients with \geq 50% symptomatic carotid stenosis to CAS with routine use of a CPD or CEA between 1998 and 2002.⁸⁴ Recruitment was stopped when the centre started recruiting patients in ICSS. Results including follow-up data over a median of four years after randomisation were published in 2008.

We also extracted relevant outcomes in symptomatic patients from the Ostrava and CREST trials, which are described in results section 'Stenting or endarterectomy for asymptomatic carotid stenosis'. Furthermore, we included outcomes in pre-defined patient subgroups derived from pooled analyses of individual patient data (IPD) from the EVA-3S, SPACE, ICSS and CREST trials which were performed by the Carotid Stenosis Trialists' Collaboration (CSTC).^{85–87}

We excluded one industry-funded multi-centre randomised trial because the results were only reported in a conference abstract,⁸⁸ and also excluded one single-centre and one multicentre randomised trial in which the majority of patients in the endovascular group were treated with primary balloon angioplasty.^{89,90}

The effects of treatment are presented with endarterectomy as the reference group. A summary of findings is provided in Table 6.

PICO 6.1: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death? There is moderate quality of evidence that endarterectomy is superior to stenting in preventing the combined outcome of post-procedural ipsilateral stroke, peri-procedural stroke in any territory, or peri-procedural death (RR: 1.43, 95% CI: 1.17–1.75; equivalent to 31 more events with stenting per 1000 patients, from 12 more to 54 more; Figure 6.1). In a pooled IPD analysis from the *EVA-3S*, *SPACE*, *ICSS* and *CREST* trials, the relative risk of this outcome varied with age⁸⁷: this analysis provided moderate quality evidence that CEA was superior to CAS in patients aged 65–74 years (hazard ratio (HR): 1.67, 95% CI: 1.23–2.27) and \geq 75 years (HR: 1.85, 95% CI: 1.35–2.53), and low quality evidence that there was no difference in outcomes between stenting and endarterectomy amongst patients <65 years old (HR: 0.83, 95% CI: 0.56–1.21), with a significant interaction between age and treatment effect (p = 0.003; data not shown in figure). There was no evidence of an interaction with sex or severity of stenosis.

PICO 6.2: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of post-procedural ipsilateral stroke? There is moderate quality of evidence that stenting and endarterectomy do not differ in their ability to prevent longterm post-procedural ipsilateral stroke (RR: 1.06, 95% CI: 0.74–1.51; equivalent to 1 more event with stenting per 1000 patients, from 6 fewer to 12 more; Figure 6.2).

PICO 6.3: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of stroke in any territory, including peri-procedural death? There is moderate quality of evidence that endarterectomy is superior to stenting in preventing the combined long-term outcome of stroke in any territory or peri-procedural death (RR: 1.34, 95% CI: 1.08–1.66; 35 more events with stenting per 1000 patients, from 8 more to 68 more; Figure 6.3).

PICO 6.4: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of major stroke, including peri-procedural death? There is low quality of evidence that endarterectomy and stenting do not differ in the long-term risk of major stroke or peri-procedural death (RR: 1.19, 95% CI: 0.88–1.62; 12 more events with stenting per 1000 patients, from 8 fewer to 39 more; Figure 6.4).

PICO 6.5: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of death? There is low quality of evidence that endarterectomy and stenting do not differ in the long-term risk of death (RR: 1.09, 95% CI: 0.94–1.27; 13 more events with stenting per 1000 patients, from 9 fewer to 38 more; Figure 6.5).

PICO 6.6: In patients with asymptomatic or symptomatic carotid stenosis, do endarterectomy and stenting differ in the long-term risk of severe restenosis? For the analysis of restenosis, we combined the data from trials including patients with asymptomatic carotid stenosis, symptomatic stenosis, or both. There is very low

Table 6. Summary of findings for stenting or endarterectomy for symptomatic carotid stenosis (PICO 6.1–6.12).	rotid stenosis (PICO 6.	.1–6.12).				
Certainty assessment	N ^o of patients	ents	Effect			
	tions Stenting	Endarterectomy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO 6.1: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death 7 Randomised Not serious Not serious ^a Not serious None 261/2499 177/2466 trials (10.4%) (7.2%)	any territory or peri-F 261/2499 (10.4%)	or peri-procedural deat 261/2499 177/2466 (10.4%) (7.2%)	h RR I.43 (1.17–1.75)	31 more per 1000 (from 12 more to	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.1.1a: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Age < 65 years 4 IPD of rando- Not serious Not serious ^a Serious ^b None HR 0.83 mised trials (0.56-1.21)	e in any territory or pe	ri-procedural de	eath: Age < 6 HR 0.83 (0.56-1.21)	5 years		CRITICAL
PICU 6.1.1 b: Long-term risk of ipsliateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Age 65–74 years 4 IPD of rando- Not serious Not serious Serious ^a Not serious None mised trials	e in any territory or pe	ri-procedural do	eath: Age 65- HR 1.67 (1.23–2.27)	- /4 years	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.1.1c: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Age ≥ 75 years 4 IPD of rando- Not serious Not serious ^a Not serious None mised trials (1.35–2.53)	e in any territory or pe	ri-procedural de	eath: Age ≥ 7 HR 1.85 (1.35–2.53)	75 years	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.1.2a: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Men 4 IPD of rando- Not serious Not serious ^a Not serious None mised trials (1.23–1.95	e in any territory or pe	ri-procedural de	a th: Men HR 1.54 (1.23–1.95)		⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.1.2b: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Women 4 IPD of rando- Not serious Not serious ^a Serious ^b None mised trials (0.90–1.74)	e in any territory or pe	ri-procedural d	ath: Womer HR 1.25 (0.90–1.74)	F		CRITICAL
PICO 6.1.3a: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Severe (70-99%) stenosis 4 IPD of rando- Not serious Not serious ^a Not serious None mised trials (1.20–1.81)	e in any territory or pe	ri-procedural de	HR 1.48	(70-99%) stenosis	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.1.3b: Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death: Moderate (50-69%) stenosis 4 IPD of rando- Not serious Not serious ^a Serious ^b None — (0.84–2.10) mised trials — (0.84–2.10)	e in any territory or pe	ri-procedural de	eath: Modera HR 1.33 (0.84-2.10)	ite (50-69%) steno	sis 0000 LOW	CRITICAL
PICO 6.2: Long-term risk of post-procedural ipsulateral stroke 6 Randomised Not serious Not serious Serious ^a Not serious None trials	62/2429 (2.6%)	58/2408 (2.4%)	RR 1.06 (0.74–1.51)	l more per 1000 (from 6 fewer to 12 more)	⊕⊕⊕() MODERATE	CRITICAL
 PICO 6.3. Long-term risk of stroke in any territory, including peri-procedural death Randomised Not serious Not serious Serious^a Not serious None trials 	ath 352/2435 (14.5%)	247/2411 (10.2%)	RR 1.34 (1.08–1.66)	35 more per 1000 (from 8 more to 68 more)	⊕⊕⊖ MODERATE	CRITICAL
						(continued)

Certainty assessment					Nº of patients	ints	Effect			
№ of Study F studies design c	Risk of bias Inconsistency Indirectness	Indirectness	Imprecision	Other considerations	Stenting	Endarterectomy	Relative (95% Cl)	Absolute (95% CI)	Certainty	Importance
PICO 6.4. Long-term r 3 Randomised D trials	PICO 6.4. Long-term risk of major stroke, including peri-procedural death 3 Randomised Not serious Not serious Serious ^a Serious ^b Nc trials	l uding peri-p i Serious ^a	rrocedural dea Serious ^b	a th None	84/I117 (7.5%)	71/1125 (6.3%)	RR 1.19 (0.88–1.62)	12 more per 1 000 (from 8 fewer to 39 more)		CRITICAL
PICO 6.5. Long-term risk of death 5 Randomised Not serious trials	risk of death Not serious Not serious	Serious ^ª	Serious ^b	None	278/1778 (15.6%)	251/1762 (14.2%)	RR 1.09 (0.94–1.27)	13 more per 1000 (from 9 fewer to 38 more)		IMPORTANT
PICO 6.6: Long-term r 9 Randomised D trials	PICO 6.6: Long-term risk of severe restenosis 9 Randomised Not serious Serious ^c trials	Serious ^a	Serious ^b	None	212/3077 (6.9%)	l 66/3 47 (5.3%)	RR 1.37 (0.89–2.10)	20 more per 1000 (from 6 fewer to 58 more)	⊕⊖⊖⊖ Very Low	IMPORTANT
PICO 6.7: Risk of peri-procedural stroke 7 Randomised Not serious Not ser trials	I- procedural stroke Not serious Not serious	Serious ^a	Not serious	None	l 68/2495 (6.7%)	101/2472 (4.1%)	RR 1.64 (1.24–2.17)	26 more per 1000 (from 10 more to 48 more)	000erate	CRITICAL
PICO 6.8: Risk of peri-procedural death 8 Randomised Not serious Not se trials	-procedural death Not serious Not serious	Serious ^a	Very serious ^d None	None	22/2538 (0.9%)	14/2514 (0.6%)	RR 1.45 (0.73–2.87)	3 more per 1000 (from 2 fewer to 10 more)	⊕⊖⊖⊖ Very Low	CRITICAL
PICO 6.9: Risk of peri- 7 Randomised N trials	PICO 6.9: Risk of peri-procedural stroke or death 7 Randomised Not serious Not serious Ser trials	s ath Serious ^a	Not serious	None	172/2495 (6.9%)	101/2470 (4.1%)	RR 1.68 (1.20–2.34)	e to	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.9.1 a: Risk of pe 6 Randomised D trials	PICO 6.9.1a: Risk of peri-procedural stroke or death: Age 6 Randomised Not serious Not serious Serious ^a trials	•	< 70 years Serious ^b	None	56/1247 (4.5%)	49/1206 (4.1%)	RR 1.10 (0.75–1.60)	ver to		CRITICAL
PICO 6.9.1b: Risk of pe 6 Randomised N trials	PICO 6.9.1b: Risk of peri-procedural stroke or death: Age 6 Randomised Not serious Not serious Serious ^a trials		≥ 70 years Not serious	Strong association ^e	122/1195 (10.2%)	58/1213 (4.8%)	RR 2.10 (1.55–2.84)	53 more per 1000 (from 26 more to 88 more)	⊕⊕⊕⊕ HIGH	CRITICAL
										(continued)

Table 6. Continued.

Certainty assessment					№ of patients	ints	Effect			
N⁰ of Study studies design	Risk of bias Inconsiste	Inconsistency Indirectness	Imprecision	Other considerations	Stenting	Endarterectomy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO 6.9.2a: Risk of 6 Randomised trials	PICO 6.9.2a: Risk of peri-procedural stroke or death: Men 6 Randomised Not serious Not serious Serious ^a trials	e or death: Men ous Serious ^a	Not serious	None	121/1695 (7.1%)	70/1700 (4.1%)	RR 1.76 (1.09–2.85)	31 more per 1000 (from 4 more to	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.9.2b: Risk of 6 Randomised trials	PICO 6.9.2b: Risk of peri-procedural stroke or death: Women 6 Randomised Not serious Not serious Serious ^a Seri trials	e or death: Won ous Serious ^a	nen Serious ^b	None	57/747 (7.6%)	36/719 (5.0%)	RR 1.45 (0.94–2.23)	76 more) 23 more per 1000 (from 3 fewer to		CRITICAL
PICO 6.9.3a: Risk of 3 IPD of rando- mised trials	PICO 6.9.3a: Risk of peri-procedural stroke or death: Severe (70–99%) stenosis 3 IPD of rando- Not serious Not serious Serious ^a Not serious None mised trials	e or death: Seve bus Serious ^a	s re (70–99%) st Not serious	tenosis None	132/1393 (9.5%)	86/1381 (6.2%)	RR 1.52 (1.17–1.98)	32 more per 1000 (from 11 more to 61 more)	000 BRATE	CRITICAL
PICO 6.9.3b: Risk of 3 IPD of rando- mised trials	PICO 6.9.3b: Risk of peri-procedural stroke or death: Moderate (50–69%) stenosis 3 IPD of rando- Not serious Not serious Serious ^a Serious ^d None mised trials	e or death: Mod bus Serious ^a	lerate (50–69 % Serious ^d) stenosis None	21/332 (6.3%)	l 3/327 (4.0%)	RR 1.59 (0.81–3.12)	23 more per 1000 (from 8 fewer to 84 more)		CRITICAL
PICO 6.9.4a: Risk of 4 IPD of rando- mised trials	PICO 6.9.4a: Risk of peri-procedural stroke or death: ≤ 4 IPD of rando- Not serious Not serious Serious ^a mised trials	e or death: ≤ 7 d bus Serious ^a	days since mo : Not serious	7 days since most recent ischaemic event Not serious Very strong association ^e 24/287 (8.4%)	ent 24/287 (8.4%)	3/226 (1.3%)	RR 6.30 (1.92–20.66)	70 more per 1000 (from 12 more to 261 more)	⊕⊕⊕⊕ HIGH	CRITICAL
PICO 6.9.4b: Risk of 4 IPD of rando- mised trials	PICO 6.9.4b: Risk of peri-procedural stroke or death:>7 d 4 IPD of rando- Not serious Not serious ^a mised trials	e or death:>7 da ous Serious ^a	ays since most rece l Not serious None	lays since most recent ischaemic event Not serious None (7 (7	nt 129/1798 (7.2%)	65/1815 (3.6%)	RR 2.00 (1.50–2.68)	36 more per 1000 (from 18 more to 60 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
PICO 6.9.5a: Risk of 3 IPD of rando- mised trials	PICO 6.9.5a: Risk of peri-procedural stroke or death: Hemispheric stroke as most recent ischaemic event 3 IPD of rando- Not serious Not serious ^a Not serious None 85/813 55 mised trials (10.5%) (6	e or death: Hem ous Serious ^a	ispheric stroke as n Not serious None	e as most recent ischa None	lemic ever 85/813 (10.5%)	t 52/797 (6.5%)	RR 1.60 (1.15–2.23)	39 more per 1000 (from 10 more to	000 C C C C C C C C C C C C C C C C C C	CRITICAL
PICO 6.9.5b: Risk of 3 IPD of rando- mised trials	PICO 6.9.5b: Risk of peri-procedural stroke or death: TIA 3 IPD of rando- Not serious Not serious Serious ^a mised trials		as most recen Not serious	as most recent ischaemic event Not serious None	53/589 (9.0%)	31/601 (5.2%)	RR 1.74 (1.14–2.68)	ou more) 38 more per 1000 (from 7 more to 87 more)	⊕⊕⊕⊖ MODERATE	CRITICAL
										(continued)

Table 6. Continued.

Certainty assessment						No of patients	ents	Effect			
No of Study studies design	Risk of bias I	Inconsistency Indirectness	Indirectness	Imprecision	Other considerations	Stenting	Stenting Endarterectomy (95% Cl)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PICO 6.9.5c: Risk of 3 IPD of rando- mised trials	. 9.5c: Risk of peri-procedural stroke or death: R IPD of rando- Not serious Not serious Serious ^a mised trials	al stroke or Not serious	death: Retin Serious ^a	ral ischaemia as mo Very serious ^d None	PICO 6.9.5c: Risk of peri-procedural stroke or death: Retinal ischaemia as most recent ischaemic event 3 IPD of rando- Not serious Not serious ^a Very serious ⁴ None 15/310 mised trials (4.8%)	mic event 15/310 (4.8%)	14/297 (4.7%)	RR 1.03 (0.50–2.09)	ier to	⊕⊖⊖⊖ VERY LOW	CRITICAL
PICO 6.10: Risk of peri-procedural major stroke or death 7 Randomised Not serious Not serious Serious ^a trials	eri-procedural major strol Not serious Not serious	I major strol Not serious	ke or death Serious ^a	Serious ^b	None	81/2495 (3.2%)	60/2470 (2.4%)	RR 1.33 (0.96–1.85)	er to		
PICO 6.11: Risk of peri-procedural myocardial infarction 6 Randomised Not serious Not serious Serious ^a trials	eri-procedural myocardial infarcti c Not serious Not serious Serious ^a	l myocardial Not serious	infarction Serious ^a	Serious ^b	Strong association ^e	11/1878 (0.6%)	23/1874 (1.2%)	RR 0.48 (0.24–0.98)	21 more) 6 fewer per 1000 (from 9 fewer to 0	⊕⊕⊕⊖ MODERATE	IMPORTANT
PICO 6.12: Risk of peri-procedural cranial nerve injury 6 Randomised Not serious Not serious Serious ^a trials	eri-procedural cranial ner Not serious Not serious	l cranial ner Not serious	ve injury Serious ^a	Not serious	Very strong association ^e 7/1892 (0.4%)	7/1892 (0.4%)	103/1877 (5.5%)	RR 0.10 (0.05-0.20)	rewer) 49 fewer per 1000 (from 52 fewer to 44 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
CI: confidence interval; RR: risk ratio. ³ Stenting and endarterectomy have evolved since the time of the contributing trials. ^b Few events, wide confidence intervals. ^c Significant heterogeneity, $1^2 > 60\%$. ^d Very wide confidence intervals. ^e Large effect.	RR: risk ratio. cctomy have evol idence intervals. cy, I ² > 60%. intervals.	lved since the	time of the c	ontributing trial	ý						

Table 6. Continued.

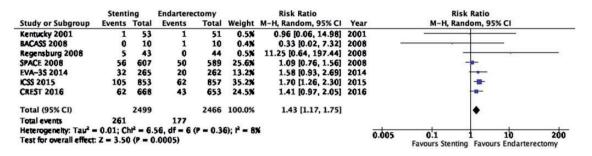


Figure 6.1. Long-term risk of ipsilateral stroke, including peri-procedural stroke in any territory or peri-procedural death in stenting versus endarterectomy for symptomatic carotid stenosis.

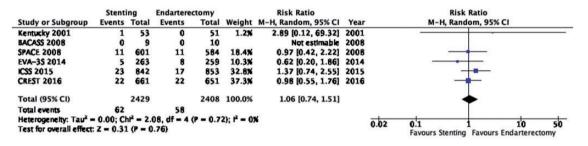


Figure 6.2. Long-term risk of post-procedural ipsilateral stroke in stenting versus endarterectomy for symptomatic carotid stenosis.

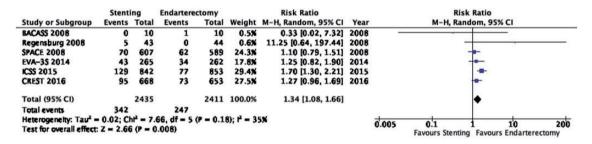


Figure 6.3. Long-term risk of stroke in any territory, including peri-procedural death in stenting versus endarterectomy for symptomatic carotid stenosis.

	Stent	ing	Endartere	ctomy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
BACASS 2008	0	10	0	10		Not estimable	2008	
EVA-35 2014	22	265	17	262	25.0%	1.28 [0.70, 2.35]	2014	
CSS 2015	62	842	54	853	75.0%	1.16 [0.82, 1.65]	2015	
Total (95% CI)		1117		1125	100.0%	1.19 [0.88, 1.62]		-
Total events	84		71					
Heterogeneity: Tau ²	- 0.00; Cl	ht² = 0.	.07, df = 1	(P = 0.7	9); 1 ² = 0	×	13	
Test for overall effect								0.2 0.5 1 2 5 Favours Stenting Favours Endarterectomy

Figure 6.4. Long-term risk of major stroke, including peri-procedural death in stenting versus endarterectomy for symptomatic carotid stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	ar M-H, Random, 95% CI
BACASS 2008	1	10	1	10	0.3%	1.00 [0.07, 13.87]	2008	8
Regensburg 2008	0	43	0	44		Not estimable	2008	8
SPACE 2008	32	607	28	589	9.2%	1.11 [0.68, 1.82]	2008	8
EVA-35 2014	92	265	93	262	41.6%	0.98 [0.78, 1.23]	2014	4 🗕 🗕
CSS 2015	153	853	129	857	48.9%	1.19 [0.96, 1.48]	2015	5 +
Total (95% CI)		1778		1762	100.0%	1.09 [0.94, 1.27]		•
Total events	278		251					
Heterogeneity: Tau2 -	- 0.00; Cl	ht² = 1.	53, df = 3	(P = 0.6	7); 12 = 0	×		ما م ما م ما م ما م
Test for overall effect					1010			0.1 0.2 0.5 1 2 5 10 Favours Stenting Favours Endarterectomy

Figure 6.5. Long-term risk of death in stenting versus endarterectomy for symptomatic carotid stenosis.

quality evidence that endarterectomy and stenting do not differ in the long-term risk of severe restenosis (RR: 1.37, 95% CI: 0.89–2.10; Figure 6.6). We additionally downgraded the evidence for inconsistency, as there was evidence of substantial heterogeneity between trials ($I^2 = 57\%$).

PICO 6.7: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural stroke? There is moderate quality of evidence that stenting is associated with a higher risk of peri-procedural stroke than endarterectomy (RR: 1.64, 95% CI: 1.24–2.17; 26 more events with stenting per 1000 patients, from 10 more to 48 more; Figure 6.7). PICO 6.8: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural death? There is very low quality of evidence that stenting and endarterectomy do not differ in the risk of peri-procedural death (RR: 1.45, 95% CI: 0.73–2.87; 3 more events per 1000 patients with stenting, from 2 fewer to 10 more; Figure 6.8).

PICO 6.9: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural stroke or death? There is moderate quality evidence that stenting is associated with a higher risk of peri-procedural stroke or death than endarterectomy overall (RR: 1.68, 95% CI: 1.20–2.34; 28 more events with stenting per 1000 patients, from

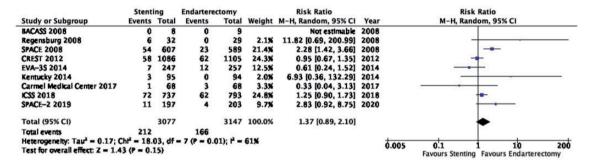


Figure 6.6. Long-term risk of severe restenosis in stenting versus endarterectomy for symptomatic or asymptomatic carotid stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio			Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	dom, 95% CI	
Kentucky 2001	0	53	0	53		Not estimable	2001				
EVA-35 2006	24	265	9	262	12.6%	2.64 [1.25, 5.56]	2006				
SPACE 2006	44	607	37	589	31.1%	1.15 [0.76, 1.76]	2006		-	-	
BACASS 2008	0	10	1	10	0.8%	0.33 [0.02, 7.32]	2008		-		
CREST 2010	37	668	21	653	22.6%	1.72 [1.02, 2.91]	2010				
KSS 2010	62	853	32	857	31.8%	1.95 [1.28, 2.95]	2010				
Ostrava 2014	1	39	1	48	1.1%	1.23 [0.08, 19.05]	2014		-	-	
Total (95% CI)		2495		2472	100.0%	1.64 [1.24, 2.17]				•	
Total events	168		101							100	
Heterogeneity: Tau2 =	0.02: CI	nt² = 5.	96. df = 5	P = 0.3	1): F = 16	*			<u></u>	1 10	
Test for overall effect								0.01	0.1 Favours Stenting	1 10 Favours Endartere	100 ctomy

Figure 6.7. Risk of peri-procedural stroke in stenting versus endarterectomy for symptomatic carotid stenosis.

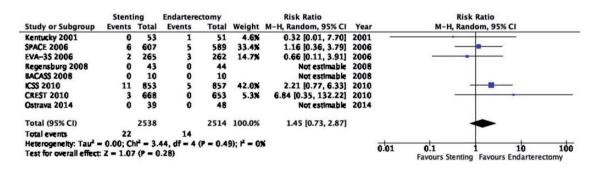


Figure 6.8. Risk of peri-procedural death in stenting versus endarterectomy for symptomatic carotid stenosis.

8 more to 55 more; Figure 6.9). However, these results vary with age. Amongst patients \geq 70 years, there is high quality evidence that CAS is associated with a higher risk of this composite outcome compared with CEA (RR: 2.10, 95% CI: 1.55–2.84; 53 more events with stenting per 1000 patients, from 26 more to 88 more; Figure 6.9.1). Amongst patients <70 years, there is low quality evidence that the risk of this combined outcome does not differ between the two treatment modalities (RR: 1.10, 95% CI: 0.75–1.60; 4 more events with stenting per 1000 patients, from 10 fewer to 24 more). The interaction between age and treatment effect is significant (p = 0.009). There is no evidence of an interaction with sex (Figure 6.9.2).

A pooled analysis of IPD from *EVA-3S*, *SPACE* and *ICSS* provides no evidence for a modification of the effect of CAS versus CEA on the risk of periprocedural stroke or death by the severity of stenosis (Figure 6.9.3) or type of most recent ischaemic event (hemispheric stroke, transient ischaemic attack or ocular ischaemia; Figure 6.9.5).⁸⁵

Another pooled analysis of IPD from *EVA-3S*, *SPACE*, *ICSS and CREST* provides high-quality evidence of an increased risk of peri-procedural stroke or death with CAS compared with CEA amongst patients treated <7 days after their most recent ischaemic event (RR: 6.30, 95% CI: 1.92– 20.66; 70 more events with CAS per 1000 patients, from 12 more to 261 more; Figure 6.9.4), and moderate quality evidence for this difference amongst patients treated >7 days after the event (RR: 2.00, 95% CI: 1.50–2.68; 36 more events with stenting per 1000 patients, from 18 more to 60 more).⁸⁶ The unadjusted *p*-value for the interaction between timing and treatment effect was 0.07, the adjusted *p*-value in the original publication was 0.06.

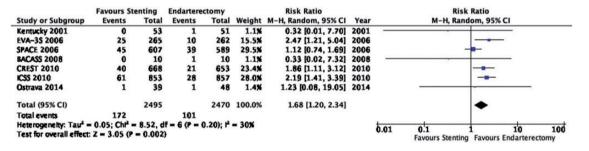


Figure 6.9. Risk of peri-procedural stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Random, 95% CI
6.9.1 < 70 years									
EVA-35 2006	10	127	6	106	14.9%	1.39 [0.52, 3.70]	2006		
SPACE 2006	17	347	22	333	37.9%	0.74 [0.40, 1.37]	2006		
BACASS 2008	0	4	0	2		Not estimable	2008		
ICSS 2010	20	395	14	404	32.0%	1.46 [0.75, 2.85]	2010		
CREST 2010	9	351	6	327	13.7%	1.40 [0.50, 3.88]	2010		
Ostrava 2014	0	23	1	34	1.4%	0.49 [0.02, 11.44]	2014	-	
Subtotal (95% CI)		1247		1206	100.0%	1.10 [0.75, 1.60]			•
Total events	56		49						
Heterogeneity: Tau ² -	= 0.00; Cl	ht² = 2.	96, df = 4	(P = 0.5	6); 1 ² = 0	ĸ			
Test for overall effect	: Z = 0.48	8 (P = C	.63)						
6.9.2 ≥ 70 years									
EVA-35 2006	17	138	5	156	9.7%	3.84 [1.46, 10.14]	2006		
SPACE 2006	28	260	17	256	27.5%	1.62 [0.91, 2.89]	2006		+
BACASS 2008	0	6	1	8	1.0%	0.43 [0.02, 9.00]			
CREST 2010	31	317	15	326	25.7%	2.13 [1.17, 3.86]	2010		
CSS 2010	45	458	20	453	35.2%	2.23 [1.34, 3.71]	2010		
Ostrava 2014	1	16	0	14	0.9%	2.65 [0.12, 60.21]	2014		
Subtotal (95% CI)		1195		1213	100.0%	2.10 [1.55, 2.84]			•
Total events	122		58						
Heterogeneity: Tau ² -	- 0.00; Cl	ht² = 3.	38, df = 5	(P = 0.6	4); 12 = 0	ĸ			
Test for overall effect	Z = 4.75	9 (P < 0	.00001)						
								0.01	0.1 1 10 10
								0.01	Favours Stenting Favours Endarterectomy
Test for subgroup diff	ferences:	Cht2 =	6.84. df =	1 (P = 0.	.009), P -	85.4%			ravours stenting ravours Endarterectomy

Figure 6.9.1. Risk of peri-procedural stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis. Subgroup: Age.

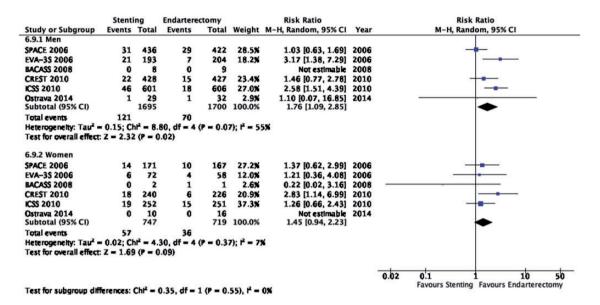


Figure 6.9.2. Risk of peri-procedural stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis. Subgroup: Sex.

	Stenti	ng	Endartere	ctomy		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.9.1 Severe (70% to	99%) ste	nosis					
CSTC 2010 Subtotal (95% CI)	132	1393 1393	86	1381 1381	100.0% 100.0%	1.52 [1.17, 1.98] 1.52 [1.17, 1.98]	
Total events Heterogeneity: Not ap Test for overall effect:		i (P = (86 1.002)				
6.9.2 Moderate (50%	to 69%)	stenos	is				
CSTC 2010 Subtotal (95% CI)	21	332 332	13	327 327	100.0% 100.0%	1.59 [0.81, 3.12] 1.59 [0.81, 3.12]	
Total events Heterogeneity: Not ap Test for overall effect:		(P = 0	13 0.18)				

Figure 6.9.3. Risk of peri-procedural stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis. Subgroup: Severity of stenosis.

	Stenti	ing	Endartere	ctomy		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
6.9.1 Treated ≤ 7 day	ys							
CSTC 2017 Subtotal (95% CI)	24	287 287	3	226	100.0% 100.0%	6.30 [1.92, 20.66] 6.30 [1.92, 20.66]		
Total events Heterogeneity: Not ap Test for overall effect:		(P = 0	3					
6.9.2 Treated > 7 da	vs							
CSTC 2017 Subtotal (95% CI)	129	1798 1798	65		100.0% 100.0%	2.00 [1.50, 2.68] 2.00 [1.50, 2.68]		
Total events Heterogeneity: Not ap			65					
Test for overall effect:	Z = 4.68	8 (P < 0	.00001}					
							0.01	0.1 1 10 100 Favours Stenting Favours Endarterectomy

Test for subgroup differences: $Chi^2 = 3.37$, df = 1 (P = 0.07), $t^2 = 70.4\%$

Figure 6.9.4. Risk of peri-procedural stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis. Subgroup: Time since last ischaemic event.

PICO 6.10: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural major stroke or death? There is low quality of evidence that stenting is likely associated with an increased risk of peri-procedural major stroke or death (RR: 1.33, 95% CI: 0.96–1.85; 8 more events with stenting per 1000 patients, from 1 fewer to 21 more; Figure 6.10).

Total Eve 813 813	52 797	Weight		-
	797			
	797			
813		100.0%	1.60 [1.15, 2.23]	
	52			
(P = 0.005))			
k				
589	31 601	100.0%	1.74 [1.14, 2.68]	
589	601	100.0%	1.74 [1.14, 2.68]	●
	31			
(P = 0.01)				
310	14 297	100.0%	1.03 [0.50, 2.09]	
310	297	100.0%	1.03 [0.50, 2.09]	
	14			
(P = 0.94)				
	589 (P = 0.01) 310 310	589 31 601 589 31 601 31 (P = 0.01) 310 14 297 310 297	589 31 601 100.0% 589 31 601 100.0% 31 (P = 0.01) 310 14 297 100.0% 310 14 297 100.0% 14	589 31 601 100.0% 1.74 [1.14, 2.68] 589 601 100.0% 1.74 [1.14, 2.68] 31

Figure 6.9.5. Risk of peri-procedural stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis. Subgroup: Type of last ischaemic event.

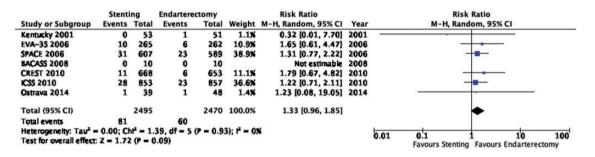


Figure 6.10. Risk of peri-procedural major stroke or death in stenting versus endarterectomy for symptomatic carotid stenosis.

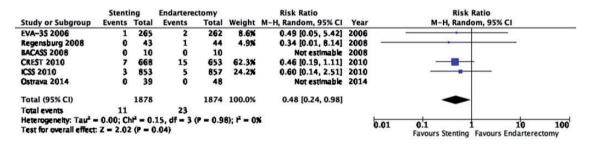


Figure 6.11. Risk of peri-procedural myocardial infarction in stenting versus endarterectomy for symptomatic carotid stenosis.

PICO 6.11: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural myocardial infarction? There is moderate quality of evidence that stenting is associated with a lower risk of peri-procedural myocardial infarction than endarterectomy (RR: 0.48, 95% CI: 0.24–0.98; 6 fewer events with stenting per 1000 patients, from 9 fewer to 0 fewer; Figure 6.11). Even though the relative effect was large, there were a limited number of clinically relevant cardiac outcome events observed. Furthermore, we had additional concerns about

'indirectness' due to the definition of myocardial infarction used in the CREST trial which contributed to two thirds of the cardiac outcome events included in the aggregate analysis (see results section 'Stenting or endarterectomy for asymptomatic carotid stenosis').

PICO 6.12: In patients with symptomatic carotid stenosis, do endarterectomy and stenting differ in the risk of peri-procedural cranial nerve injury? There is strong evidence that stenting is associated with a lower risk of peri-procedural cranial nerve injury than

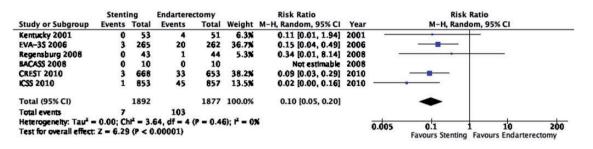


Figure 6.12. Risk of peri-procedural cranial nerve injury in stenting versus endarterectomy for symptomatic carotid stenosis.

endarterectomy (RR: 0.10, 95% CI: 0.05–0.20; 49 fewer events with stenting per 1000 patients, from 52 fewer to 44 fewer; Figure 6.12). We upgraded the quality of the evidence by two levels for strength of effect.

Analysis of current evidence and evidence-based recommendation. Evidence to compare short-term risks and longterm effects of CAS versus CEA for the treatment of symptomatic carotid stenosis was derived from 7 RCTs which included a total of 4893 patients. It is important to note that the available evidence for CAS relates to percutaneous trans-femoral stenting only. There are no available data from RCTs on the safety of transcarotid stenting. As such, all recommendations included in this guideline refer to trans-femoral CAS. All studies included patients with >50% stenosis. Symptomatic carotid stenosis was defined by the occurrence of ischaemic ocular or cerebral events attributable to the stenosis within six months prior to enrolment, except in ICSS where a very small minority of patients were enrolled 6-12 months after symptom onset. Amongst the four largest trials contributing to the evidence, the median duration of follow-up was four to seven years in three studies and two years in one study. When recruitment in these trials started 20 years ago, carotid artery stenting was still at a relatively early stage of technical development, periprocedural medication regimens were not standardised, and there was limited experience with the procedure. In addition, only a minority of patients included in these trials were treated within the recommended 14 days of their index ischaemic event. We therefore downgraded the quality of evidence for indirectness.

Overall, there is moderate quality evidence that endarterectomy is superior to stenting when one considers peri-procedural and post-procedural outcomes that were rated as 'critical' for decision making. The differences between stenting and endarterectomy are mainly apparent in the peri-procedural period: stenting is associated with a higher risk of peri-procedural stroke than endarterectomy (critical for decision making), whereas endarterectomy is associated with higher risks of myocardial infarction and mostly transient cranial nerve palsy (important for decision making).

The risks of peri-procedural stroke or death differ between patient subgroups: there is high quality evidence that stenting is associated with a higher risk of this outcome in patients \geq 70 years, and low quality evidence that the risk of this outcome is similar in patients <70 years. The higher risk of peri-procedural stroke or death after carotid artery stenting compared with endarterectomy is also more evident amongst patients treated within seven days of their index cerebrovascular event. After the peri-procedural period, there is moderate grade evidence that stenting and endarterectomy do not differ in their ability to prevent stroke.

Recommendations

In patients with symptomatic carotid artery stenosis requiring revascularisation, we recommend endarterectomy as the treatment of choice.

Quality of evidence: Moderate $\oplus \oplus \oplus$

Strength of recommendation: Strong for carotid endarterectomy $\uparrow\uparrow$

In patients with symptomatic carotid stenosis <70 years old requiring revascularisation, we suggest that stenting may be considered as an alternative to endarterectomy. Quality of evidence: Low $\oplus \oplus$ Strength of recommendation: Weak for carotid stenting \uparrow ?

Additional information. In light of technical developments in stent design and cerebral protection devices, and alternative (trans-brachial and trans-carotid) access routes which are now available, new trials of stenting in selected patients with symptomatic carotid stenosis are warranted.

Expert consensus statements.

12/12 experts concluded that the suitability of a patient with symptomatic carotid stenosis for carotid endarterectomy versus stenting should also take into account the interval since their last ischaemic cerebrovascular event, as well as anatomical and morphological features, including the atherosclerotic burden of the aortic arch.

11/12 experts concluded that the independently assessed risk of in-hospital stroke or death following endarterectomy or stenting for symptomatic carotid stenosis should not exceed 4%.⁶

12/12 experts concluded that where possible, the indication for carotid endarterectomy or carotid artery stenting should be discussed at a multi-disciplinary team meeting. Consensus decisions can be made in between meetings, in order not to delay urgent revascularisations.

12/12 experts concluded that the establishment of validated local, regional or national registries, including audit systems for carotid interventions to monitor complication rates in patients with asymptomatic and symptomatic carotid stenosis is recommended.

Discussion

This evidence-based guideline was developed following the GRADE process and provides recommendations for the treatment of symptomatic and asymptomatic carotid stenosis by endarterectomy (CEA) or stenting (CAS) versus best medical therapy alone. All recommendations and expert consensus statements are summarised in Tables 7 and 8.

Carotid revascularisation has been studied in randomised clinical trials for more than three decades, providing a wealth of evidence. Observational case series and large-scale registries are important to advance treatments and provide contemporary data on risks in real-world settings, but ultimately, the choice between treatment options should be informed by evidence from high quality RCTs, where such trials are available. We therefore based our recommendations in this guideline document for the choice between medical therapy alone, CEA or CAS on the evidence derived from randomised clinical trials only.

In some areas, particularly for stenting of asymptomatic carotid stenosis, the available evidence from clinical trials is still limited. However, additional data from large trials in asymptomatic carotid stenosis which are currently ongoing are expected in the near future and should provide a stronger evidence base to guide management of these patients.

CAS and CEA differ in treatment-associated risks, such as myocardial infarction and stroke. To fully determine the overall clinical impact of these outcomes in patients, additional measures such as quality of life

Table	7.	Synoptic	table	of all	recommendations.
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Recommendations	Quality of evidence	Strength of recommendation
In patients with \geq 60% asymptomatic carotid artery stenosis considered to be at increased risk of stroke on best medical therapy alone, we recommend carotid endarterectomy.	Moderate $\oplus \oplus \oplus$	Strong for carotid endar- terectomy ↑↑
In patients with asymptomatic carotid stenosis, recommend against carotid artery stenting as a routine alternative to best medical therapy alone.	Very low \oplus	Weak against carotid stenting ↓?
In patients with asymptomatic carotid stenosis in whom revascu- larisation is considered to be appropriate, we suggest endar- terectomy as the current treatment of choice.	Moderate $\oplus \oplus \oplus$	Weak for carotid endar- terectomy ↑
In patients with severe (70–99%) symptomatic carotid artery stenosis, we recommend carotid endarterectomy.	$Moderate \oplus \oplus \oplus$	Strong for carotid endar- terectomy ↑↑
In patients with moderate (50–69%) symptomatic carotid artery stenosis, we suggest carotid endarterectomy.	Low $\oplus \oplus$	Weak for carotid endar- terectomy ↑
In patients with mild (<50%) symptomatic carotid artery stenosis, we recommend against carotid endarterectomy.	Very low \oplus	Strong against carotid endarterectomy ↓↓
In patients with 50–99% symptomatic carotid stenosis in whom surgery is considered appropriate, we recommend early end- arterectomy, ideally within two weeks of the last neurological event.	High ⊕⊕⊕⊕	Strong for carotid endar- terectomy ↑↑
In patients with symptomatic carotid artery stenosis requiring revascularisation, we recommend endarterectomy as the treatment of choice.	Moderate $\oplus \oplus \oplus$	Strong for carotid endar- terectomy ↑↑
In patients with symptomatic carotid stenosis <70 years old requiring revascularisation, we suggest that stenting may be considered as an alternative to endarterectomy.	Low ⊕⊕	Weak for carotid stenting

Table 8. Synoptic table of all expert consensus statements.

Expert consensus statements Based on voting by all MWG members	Voting results
In selected patients 75 years of age or older with ≥60% asymptomatic carotid artery stenosis and an expected survival of at least five years, who are considered to be at an increased risk of stroke on best medical therapy alone, carotid endarterectomy is suggested after careful consideration of the risks and benefits at a multi-disciplinary team meeting.	12/12
In patients with asymptomatic carotid stenosis in whom revascularisation is considered to be appropriate and who are less suitable for surgery, stenting may be suggested. We recommend careful consideration of the risks and benefits at a multi-disciplinary team meeting.	12/12
The independently assessed risk of in-hospital stroke or death following endarterectomy or stenting for asymptomatic carotid stenosis should be as low as possible, ideally below 2%.	12/12
The suitability of a patient with symptomatic carotid stenosis for carotid endarterectomy versus stenting should also take into account the interval since their last ischaemic cerebrovascular event, as well as anatomical and morphological features, including the atherosclerotic burden of the aortic arch.	12/12
The independently assessed risk of in-hospital stroke or death following endarterectomy or stenting for symptomatic carotid stenosis should be as low as possible, ideally below 4%.	11/12
Where possible, the indication for carotid endarterectomy or carotid artery stenting should be discussed at a multi-disciplinary team meeting. Consensus decisions can be made in between meetings, in order not to delay urgent revascularisations.	12/12
12/12 experts concluded that the establishment of validated local, regional or national registries, including audit systems for carotid interventions to monitor complication rates in patients with asymptomatic and symptomatic carotid stenosis is recommended.	12/12

MWG: Module Working Group.

and level of dependency should be systematically assessed in future trials.

We also acknowledge the fact that many of the trials providing the evidence for these guidelines were performed two to three decades ago. There have been important advances in the medical management of patients with atherosclerosis, and technical developments have also improved the safety of CEA and CAS since then. Because we had some concerns – especially in patients with asymptomatic carotid stenosis – that the applicability of the findings obtained in earlier trials may not apply to current clinical practice with contemporary medical and interventional treatment, we reduced the grade of some of the evidence for 'indirectness'.

Any benefit of CEA or CAS is closely related to peri-procedural complication rates. Since the inhospital complication rates of CEA and CAS have improved in recent years, expert consensus statements were prepared which suggested that the independentlyassessed peri-operative stroke and death rates after CEA or CAS should ideally be below 2% in patients with asymptomatic carotid stenosis and below 4% in patients symptomatic carotid stenosis. In randomised trials, about two thirds of these events occurred in the first two days after treatment, when patients were typically still in hospital.⁹¹ Therefore these proposed acceptable in-hospital thresholds of 2% and 4% correspond with the traditionally-recommended 30-day thresholds of 3% and 6% for patients with asymptomatic and symptomatic stenosis, respectively. In-hospital thresholds may be more easily applicable to routine clinical practice because many patients will not be independently assessed by a neurologist or stroke physician 30 days after intervention. Moreover, outcomes following CEA and CAS should ideally be analysed at a local, regional and national level.

With modern medical management aiming for lower targets for lipid and blood pressure control, and more effective antiplatelet regimens (especially in patients with recent symptoms), the risk of stroke in asymptomatic and symptomatic carotid stenosis is expected to be lower than in the medical arms of some prior published trials. Ongoing trials are investigating whether contemporary medical therapy may obviate the need for invasive revascularisation in selected patient groups.

There have been a number of developments in the field of carotid artery stenting since the first trials which compared stenting with endarterectomy were completed, including the design of closed-cell and mesh-design stents,^{92,93} newer approaches to cerebral protection (involving reversal or arrest of blood flow),^{94–105} and alternative access routes which avoid the aortic arch (including trans-brachial and trans-carotid access.^{106–110} In addition, quality assurance programmes for stenting have been introduced in some countries.¹¹¹ For patients with symptomatic stenosis, the restriction to the evidence from past randomised trials may underestimate the role of CAS in experienced centres who are able to maintain low

peri-procedural complication rates. Although stenting using more modern state-of-the-art techniques might reduce the peri-procedural risk of stroke, this needs to be tested in randomised trials of CAS versus CEA. Until further evidence is available, in patients requiring carotid revascularisation, the current weight of evidence is in favour of recommending CEA over CAS in most patient subgroups.

Plain language summary

Carotid stenosis refers to narrowing of a major blood vessel in the neck (the carotid artery) which carries blood to the eye and brain and is caused by fatty and calcium deposits in the blood vessel wall (atherosclerotic plaque). Carotid stenosis may cause a transient ischaemic attack (TIA or 'warning stroke') or a stroke. The narrowing can be removed by a surgical procedure called 'carotid endarterectomy', during which the surgeon opens the artery and removes the carotid plaque. An alternative treatment, called 'carotid artery stenting', involves passing a fine wire and tube through the skin and into the narrowed artery in the neck. A metal tube (stent) is placed inside the carotid artery to open it up with a view to preventing it from narrowing again. In patients who have not experienced recent symptoms (such as stroke, TIA, or ocular (eye) symptoms) from their carotid stenosis ('asymptomatic patients'), but who are still considered to be at risk of stroke on medication alone, we recommend carotid endarterectomy. In patients who have recently experienced these symptoms ('symptomatic patients'), we recommend carotid endarterectomy if the stenosis is severe, and suggest carotid endarterectomy may be considered if the stenosis is moderate. If surgery is recommended, we advise that carotid endarterectomy should be carried out as early as possible after the patient's initial symptoms, preferably within two weeks. Carotid artery stenting can be considered as an option to carotid endarterectomy in patients with symptomatic carotid stenosis, especially in patients younger than 70 years of age.

Name	Conflicts of interest
Leo H Bonati	Co-Principal Investigator of the ECST-2 and ACST-2 trial. Grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the University of Basel and AstraZeneca for research related to carotid artery disease. Consultancy fees from AstraZeneca.
Joachim Berkefeld	Unrelated grants for angiographic imaging research from Siemens.
Gert J de Borst	Member of the writing committee of the ESVS guideline on the management of carotid athero- sclerotic disease; EU Horizon 2020 grant for stratification of carotid disease; consultation fees from BAYER; Steering Committee Member ECST-2, CSTC.
Richard Bulbulia	Co-PI ACST-2, Co-Chair, ESC Position Paper on Carotid Disease
Hans-Henning Eckstein	Steering Committee SPACE-1, Co-PI SPACE-2, CSTC, Co-Investigator ROADSTER 1 and ROADSTER 2, Co-Investigator ACST-2, EU Horizon 2020 grant for stratification of carotid disease
Alison Halliday	PI for the ACST trials, Steering committee member for ECST-2, past TSC member ICSS. Chair-Elect of ESC Council on Stroke, co-author on the ESVS Carotid Guidelines, Co-author ESC Guidelines on Dyslipidaemias, CSTC
Isabelle van Herzeele	Consulting and Research Grants from Silkroad Medical, Medtronic and Impact APV Europe.
Stavros Kakkos	Member of the writing committee of the ESVS guideline on the management of carotid athero- sclerotic disease.
lgor Koncar	EU Horizon 2020 grant for stratification of carotid disease, Member of the writing committee of the ESVS guideline on the management of carotid atherosclerotic disease
Dominick JH McCabe	Prior grant funding from: The Meath Foundation; The Irish Institute of Clinical Neuroscience; The Irish Heart Foundation Stroke Prevention Bursary programme; The Trinity College Dublin Innovation Bursary; The Vascular Neurology Research Foundation, Ireland. Unrestricted edu- cational grant funding from: Biogen Idec, Ireland; Verum Diagnostica, GmbH; Bayer HealthCare, Ireland; and SINNOWA Medical Science & Technology Co., China for unrelated translational research studies. Member of the writing committee for the ESVS guidelines for the management of patients with atherosclerotic carotid and vertebral artery stenosis (2017 and 2022).
Jean-Baptiste Ricco	Grant and consultation fees from BAYER, Member of the writing committee of the ESVS guideline on the management of carotid atherosclerotic disease
Peter Ringleb	Steering Committee Member SPACE-2, CSTC. Unrelated grant from Boehringer Ingelheim (ECASS-4). Unrelated lecture fees from Boehringer Ingelheim, Bayer, Pfizer, Daiichi Sankyo.

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Guarantor

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Contributorship

All listed authors have contributed to the preparation and writing of the manuscript, researched literature and conceived the guideline, were involved in protocol development, reviewed and edited the manuscript and approved the final version of the manuscript. LHB, SK and JB wrote the first draft of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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