CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Prevention of Stroke Evidence Tables

Management of Extracranial Carotid Disease and Intracranial Atherosclerosis

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PREVENTION of STROKE Writing Group

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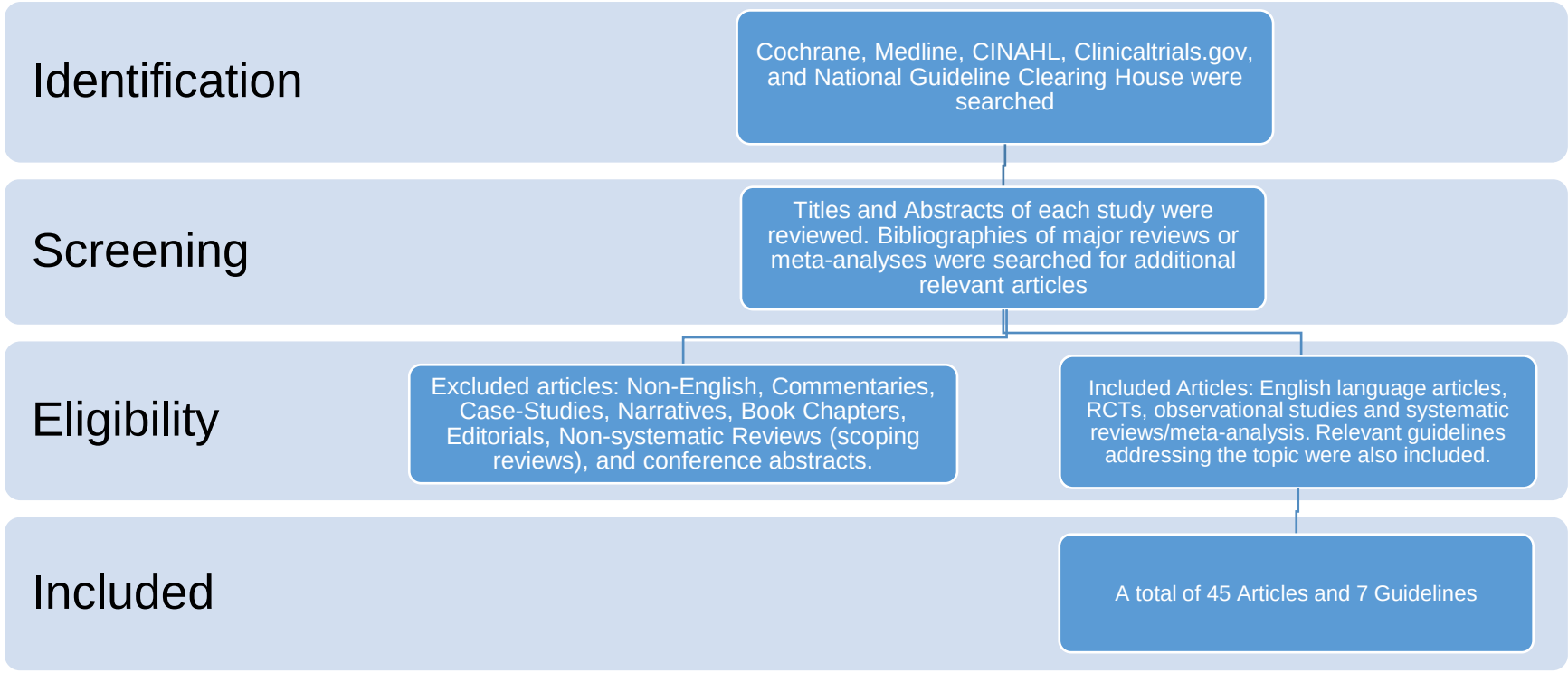
Search Strategy



Cochrane, Medline, CINAHL, National Guideline Clearing House and clinicaltrials.gov were search using the terms (“Carotid Stenosis” OR “Carotid Endarterectomy” OR “Carotid Stenting”; AND “Stroke”). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 45 articles and 6 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical Guidelines for Stroke. 5th Edition 2016, Edinburgh, Scotland	A Following stroke or TIA, the degree of carotid artery stenosis should be reported using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. B People with non-disabling carotid artery territory stroke or TIA should be considered for carotid revascularisation, and if they agree with intervention: − they should have carotid imaging (duplex ultrasound, MR or CT angiography) performed urgently to assess the degree of stenosis; − if the initial test identifies a relevant severe stenosis (greater than or equal to 50%), a second or repeat non-invasive imaging investigation should be performed to confirm the degree of stenosis. This confirmatory test should be carried out urgently to avoid delaying any intervention. C People with non-disabling carotid artery territory stroke or TIA should be considered for carotid revascularisation if the symptomatic internal carotid artery has a stenosis of greater than or equal to 50%. The decision to offer carotid revascularisation should be: − based on individualised risk estimates taking account of factors such as the time from the event, gender, age and the type of qualifying event; − supported by risk tables or web-based risk calculators (e.g. the Oxford University Stroke Prevention Research Unit calculator, www.stroke.ox.ac.uk/model/form1.html) D People with non-disabling carotid artery territory stroke or TIA and a carotid stenosis of less than 50% should not be offered revascularisation of the carotid artery. E Carotid endarterectomy for people with symptomatic carotid stenosis should be: − the treatment of choice, particularly for people who are 70 years of age and over or for whom the intervention is planned within seven days of stroke or TIA; − performed in people who are neurologically stable and who are fit for surgery using either local or general anaesthetic according to the person's preference; − performed as soon as possible and within 1 week of first presentation; − deferred for 72 hours in people treated with intravenous thrombolysis; − only undertaken by a specialist surgeon in a vascular centre where the outcomes of carotid surgery are routinely audited. F Carotid angioplasty and stenting should be considered for people with symptomatic carotid stenosis who are: − unsuitable for open surgery (e.g. high carotid bifurcation, symptomatic re-stenosis following endarterectomy, radiotherapy-associated carotid stenosis); or: − less than 70 years of age and who have a preference for carotid artery stenting. The procedure should only be undertaken by an experienced operator in a vascular centre where the outcomes of carotid stenting are routinely audited. G People who have undergone carotid revascularisation should be reviewed post-operatively by a stroke physician to

Guideline	Recommendations
	optimise medical aspects of vascular secondary prevention. H Patients with atrial fibrillation and symptomatic internal carotid artery stenosis should be managed for both conditions unless there are contraindications. **Cervical artery dissection** A-Any patient suspected of cervical artery dissection should be investigated with CT or MR including angiography. B- Patients with acute ischaemic stroke suspected to be due to cervical arterial dissection should receive alteplase if they are otherwise eligible. C- Patients with acute ischaemic stroke suspected to be due to cervical arterial dissection should be treated with either an anticoagulant or an antiplatelet agent for at least 3 months.
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke 2014*;45:2160-2236.**	**Symptomatic extracranial carotid disease** • For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence A). • For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% (Class I; Level of Evidence B). • When the degree of stenosis is <50%, CEA and CAS are not recommended When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery if there are no contraindications to early revascularization (Class IIa; Level of Evidence B). • CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% (Class IIa; Level of Evidence B). (Revised recommendation) • It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke (Class IIa; Level of Evidence B). (New recommendation) • Among patients with symptomatic severe stenosis (>70%) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable (Class IIa; Level of Evidence B). (Revised recommendation) • CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies (Class I; Level of Evidence B). (Revised recommendation) • Routine, long-term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is

Guideline	Recommendations
	not recommended (Class III; Level of Evidence B). (New recommendation) • For patients with a recent (within 6 months) TIA or ischemic stroke ipsilateral to a stenosis or occlusion of the middle cerebral or carotid artery, EC/IC bypass surgery is not recommended (Class III; Level of Evidence A). • For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational (Class IIb; Level of Evidence C). (New recommendation) • Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke, as outlined elsewhere in this guideline (Class I; Level of Evidence A). • CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% (Class IIa; Level of Evidence B). • It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complication (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke (Class IIa; Level of Evidence B). New recommendation • CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies (Class I; Level of Evidence B). • Routine, long term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended (Class III; Level of Evidence B). New recommendation • For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational (Class IIb; Level of Evidence C). **Intracranial stenosis** • For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable (Class IIb; Level of Evidence B). New recommendation • For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone (Class IIb; Level of Evidence C). New recommendation • For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of systolic BP below 140 mm Hg and high-intensity statin therapy are recommended (Class I; Level of Evidence B). • For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke on medical management and the inherent periprocedural risk of endovascular treatment (Class III; Level of Evidence B). New recommendation • For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an

Guideline	Recommendations
	antithrombotic agent at the time of the stroke or TIA (Class III; Level of Evidence B). New recommendation • For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational (Class IIb; Level of Evidence C). • For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of systolic BP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational (Class IIb; Level of Evidence C). New recommendation • For patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational (Class IIb; Level of Evidence C).
Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. **2011 SA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/ SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease** ***Circulation* 2011;124:489 –532** **(selected)**	**Recommendations for Selection of Patients for Carotid Revascularization** Class I 1. Patients at average or low surgical risk who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70% as documented by noninvasive imaging (Level of Evidence: A) or more than 50% as documented by catheter angiography (Level of Evidence: B) and the anticipated rate of perioperative stroke or mortality is less than 6%. 2. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%. (Level of Evidence: B) 3. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. (Level of Evidence: C) Class IIa 1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low. (Level of Evidence: A) 2. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention.3 (Level of Evidence: B) **Recommendations for Management of Patients with Cervical Artery Dissection** Class IIa Antithrombotic treatment with either an anticoagulant (heparin, low-molecular-weight heparin, or warfarin) or a platelet inhibitor (aspirin, clopidogrel, or the combination of extended-release dipyridamole plus aspirin) for at least 3 to 6 months is reasonable for patients with extracranial carotid or vertebral arterial dissection associated with ischemic

Guideline	Recommendations
	stroke or TIA. (Level of Evidence: B) Class IIb 1. Carotid angioplasty and stenting might be considered when ischemic neurological symptoms have not responded to antithrombotic therapy after acute carotid dissection. (Level of Evidence: C)
National Stroke Foundation. Clinical Guidelines for Stroke Management 2010. Melbourne, Australia	**Carotid surgery** • Carotid endarterectomy should be undertaken in patients with non-disabling carotid artery territory ischaemic stroke or TIA with ipsilateral carotid stenosis measured at 70-99% (NASCET criteria) only if it can be performed by a specialist surgeon with low rates (<65) of peri-operative mortality/morbidity. (Grade A) • Carotid endarterectomy can be undertaken in highly selected ischaemic stroke or TIA patients (considering age, gender and co-morbidities) with symptomatic carotid stenosis of 50-69% (NASCEt criteria) or asymptomatic carotid stenosis >60% (NASCET criteria) only if it can be perfroed by a specialist surgeon with very low rates (<350 of peri-operative mortality/morbidity. (Grade A) • Eligible stable patients should undergo carotid endarterectomy as soon as possible after the stroke vent (ideally within two weeks).(Grade A) • Carotid endarterectomy should only be performed by a specialist surgeon in centres where outcomes of carotid surgery are routinely audited (Grade B) • Carotid endarterectomy is NOT recommended for those with symptomatic stenosis <50% (NASCET criteria) or asymptomatic stenosis <60% (NASCET criteria). (Grade A) • Carotid stenting should NOT routinely be undertaken for patients with carotid stenosis. (Grade A)
New Zealand Clinical Guidelines for Stroke Management 2010, Stroke Foundation of New Zealand, Auckland.	**Carotid Surgery** • Carotid endarterectomy should be undertaken in patients with non-disabling carotid artery territory ischaemic stroke or TIA with ipsilateral carotid stenosis measured at 70–99% (NASCET criteria) only if it can be performed by a specialist surgeon with low rates (<6%) of peri-operative mortality/morbidity (Cina et al, 1999; Rothwell et al, 2003; Ederle et al, 2007). (Grade A) • Carotid endarterectomy can be undertaken in highly selected ischaemic stroke or TIA patients (considering age, gender and comorbidities) with symptomatic carotid stenosis of 50–69% (NASCET criteria) or asymptomatic carotid stenosis >60% (NASCET criteria) only if it can be performed by a specialist surgeon with very low rates (<3%) of peri-operative mortality/morbidity (Chambers & Donnan, 2005; Cina et al, 1999; Ederle et al; 2007). (Grade A) • Eligible stable patients should undergo carotid endarterectomy as soon as possible after stroke event (ideally within two weeks) (Rothwell et al, 2004). (Grade A) • Carotid endarterectomy should only be performed by a specialist surgeon in centres where outcomes of carotid surgery are routinely audited (Rothwell et al, 1996; Cina et al, 1999). (Grade B) • Carotid endarterectomy is NOT recommended for those with symptomatic stenosis <50% (NASCET criteria) or asymptomatic stenosis < 60% (NASCET criteria) (Cina et al, 1999; Chambers & Donnan, 2005). (Grade A) • Carotid stenting should NOT routinely be considered for patients with carotid stenosis (Ederle et al, 2007; Eckstein et al, 2008). (Grade A)
Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. A	**Carotid Endarterectomy** • All patients with carotid artery territory stroke (without severe disability, mRS≤2) or transient ischaemic attack should be considered for carotid endarterectomy as soon as possible after the index event. (Grade A)

Guideline	Recommendations
national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN 108); 2008. 103 p.	carotid endarterectomy (on the internal carotid artery ipsilateral to the cerebrovascular event) should be considered in all: ○ male patients with a carotid artery stenosis of 50-99% (by NASCET method) ○ female patients with a carotid artery stenosis of 70-99%. (Grade A) ○ for all patients, carotid endarterectomy should be performed as soon as the patient is stable and fit for surgery, ideally within two weeks of event. (Grade B) ○ There is no justification for withholding carotid endarterectomy from older patients who are considered fit for surgery. (Grade B) ○ All patients undergoing carotid endarterectomy should receive optimal medical therapy in addition to surgery. (Grade A) **Asymptomatic Carotid Artery Disease** • CEA should be considered for asymptomatic patients with high grade carotid stenosis and no ipsilateral event for at least six months. (Grade A) • CEA should only be performed by operators with a low (<3%) perioperative stroke or death rate. (Grade B) **Carotid Surgery Technique** • patch angioplasty should be used as the closure method in all carotid endarterectomies performed by conventional methods. (Grade A) changing surgical technique from conventional carotid endarterectomy to eversion method is not recommended. (Grade A) **Carotid Angioplasty and Stenting** • carotid angioplasty and stenting is not recommended without ongoing randomised controlled trials. (Grade A) **Periprocedural antiplatelet or antithrombotic therapy** • standard antiplatelet treatment should be given after CEA (Grade A)
The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee **Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008** **Cerebrovasc Dis 2008;25:457–507**	**Surgery and Angioplasty** • CEA is recommended for patients with 70–99% stenosis (Class I, Level A). CEA should only be performed in centres with a perioperative complication rate (all strokes and death) of less than 6% (Class I, Level A) • It is recommended that CEA be performed as soon as possible after the last ischaemic event, ideally within 2 weeks (Class II, Level B) • It is recommended that CEA may be indicated for certain patients with stenosis of 50–69%; males with very recent hemispheric symptoms are most likely to benefit (Class III, Level C). CEA for stenosis of 50–69% should only be performed in centres with a perioperative complication rate (all stroke and death) of less than 3% (Class I, Level A) • CEA is not recommended for patients with stenosis of less than 50% (Class I, Level A) • It is recommended that patients remain on antiplatelet therapy both before and after surgery (Class I, Level A) • Carotid percutaneous transluminal angioplasty and/or stenting (CAS) is only recommended in selected patients (Class I, Level A). It should be restricted to the following subgroups of patients with severe symptomatic carotid artery stenosis: those with contra-indications to CEA, stenosis at a surgically inaccessible site, re-stenosis after earlier CEA, and post-radiation stenosis (Class IV, GCP). Patients should receive a combination of clopidogrel and aspirin immediately before and for at least 1 month after stenting (Class IV, GCP) • It is recommended that endovascular treatment may be considered in patients with symptomatic intracranial stenosis (Class IV, GPC)

Evidence Tables

Medical Management for Asymptomatic Patients

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
King et al. 2013 **UK** ***Asymptomatic Carotid Emboli Study (ACES)*** **Observational study**	NA	477 patients from 26 centres worldwide with ≥ 70% carotid stenosis, with no symptoms in the carotid artery territory for at least 2 years. Mean age was 71.5 years, 74% men. 37% had previous ischemia	Details of all medications (antiplatelets, anticoagulants, antihypertensive agents, lipid-lowering agents) and stroke risk factors (smoking status, HTN, diabetes, peripheral vascular disease, atrial fibrillation) were recorded/confirmed every 6 months for 2 years. Regression equations were developed to identify independent predictors of outcome	**Primary outcome:** Ipsilateral stroke or TIA during 2 years of follow-up **Secondary outcomes:** Any stroke or cardiovascular death	During follow-up, there were 32 ipsilateral stroke/TIA, 10 ipsilateral stroke, 18 any stroke, 37 any stroke/CVD death 37. 34 patients had CEA: 16 after ipsilateral TIA, one after ipsilateral stroke, and 17 for asymptomatic stenosis. Antiplatelet use was an independent predictor of reduced risk of ipsilateral stroke or TIA (adj HR=0.45, 95% CI 0.31-0.66). The use of antiplatelet and antihypertensive agents were independent predictors of lower stroke risk or CVD death (adj HR=0.13, 95% CI 0.06-0.27 and adj HR=0.26, 95% CI 0.13-0.54).

Intracranial Angioplasty

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Marks et al. 2006 **USA** **Single-group intervention study**	NA	120 patients who underwent intracranial angioplasty for symptomatic stenosis (≥50%) between 2003-2004, at 3 institutions. Mean age was 62.3 years, 70% men. Mean pre-treatment stenosis was 82.2%	Degree of stenosis was measured before and after the procedure.	**Primary outcome:** Post procedure stenosis **Secondary outcome:** Stroke during follow-up	Mean post-treatment stenosis was 36.0% (range 0-90%) Stents were placed in 12.9% of patients (range 0-90%. There were 3 strokes and 4 deaths that occurred within 30 days of the procedure (6 events in the first day after the procedure). After a mean follow-up duration of 42.3 months, there were 10 deaths, none of which

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					were attributable to stroke. There were 11 strokes and 6 TIAs that occurred during follow-up. 5-year stroke-free survival was 88.6% in the territory of the angioplasty, including periprocedural events. The 5-year stroke-free survival for all strokes including the periprocedural complications was 83.1%. During the follow-up period, 14 patients (12.1%) had a repeat angioplasty, and 8 patients (6.9%) had a stent placed. 67 patients (57.8%) had a follow-up angiogram, performed an average of 20.5 months post procedure. Of these, 18 (26.9%) showed improvement in the stenosis compared with postangioplasty angiogram, 33 (49.3%) were unchanged, and 16 (23.9%) displayed worsening stenosis at the time of last follow-up

Carotid Endarterectomy (vs. best medical management) for Carotid Stenosis

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
i) Symptomatic					
Rerkasem & Rothwel 2011 **Thailand** **Cochrane review**	NA	3 RCTs (*European Carotid Surgery Trial, North American Symptomatic Carotid Endarterectomy Trial* and *Veterans Affairs Co-operative Studies Program* including the results from 6,092 patients.	Treatment contrasts were carotid endarterectomy (CEA) as soon as possible vs. avoid surgery + best medical management.	**Primary outcome:** Any stroke recurrence or death, stratified by degree of stenosis (using groups that were used in the NASCET Trial: <30%, 30% to 49%, 50% to 69%, 70% to 99%. Near occlusions were analyzed separately). The absolute treatment effect at five-year	The risk of any stroke or operative death at 5-years among stenosis subgroups (RR, 95% CI): Near occlusion: RR= 0.95, 0.59-1.53, p= 0.84 <30%: RR=1.25, 0.99-1.56, p=0.057 30-49%: RR=0.97, 0.79-1.19, p=0.75 50-69%: RR=0.77, 0.63- 0.94, p=0.001. (favours CEA) 70-99%: RR=0.53, 0.42-0.67, p<0.0001. (favours CEA). The associated absolute risk reduction was 16.0%.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		Participants in all studies had experienced a recent minor stroke or TIA within the previous 4-6 months. The degree of stenosis varied from 0-99% (n=1) to 50%-99% (n=2) using the NACET criteria and from 40-99% (n=1) to 70%-99% (n=2) using ECST criteria. The mean age of patients was 63 and 66 years at baseline. Males represented 72% and 100% of the sample. The qualifying events were stroke (approx. 25%) and TIA (approx. 75%).		follow-up was estimated. **Secondary outcomes:** Recurrent ipsilateral ischemic stroke and any stroke or death which occurred within 30 days of trial surgery, or ipsilateral disabling or fatal ischemic stroke occurring within 30 days. (Individual patient level data from the 3 trials was used in pooled analyses).	The risk of ipsilateral ischemic stroke and any operative stroke or operative death (RR, 95% CI). Near occlusion: RR= 1.04, 0.58-1.86, p= 0.89 <30%: RR= 1.72, 0.99-2.96, p=0.053 30-49%: RR= 0.96, 0.60-1.54, p=0.88 50-69%: RR= 0.73, 0.46-1.15, p=0.17 70-99%: RR= 0.40, 0.26-0.64, p<0.0001. (favours CEA) The risk of disabling or fatal ipsilateral ischaemic or operative stroke and operative death (RR, 95% CI) Near occlusion: RR= 1.29, 0.51-3.27, p= 0.59 <30%: RR= 1.33, 0.99-1.79, p=0.058 30-49%: RR= 0.89, 0.69-1.16, p=0.39 50-69%: RR= 0.82, 0.64-1.05, p=0.11 70-99%: RR= 0.40, 0.30-0.54, p<0.0001. (favours CEA). Benefit from CEA was greatest for men, patients aged 75 years or over, and patients randomised within two weeks of stroke.
European Carotid Surgery Trialists' Collaborative Group *(ECAS)* 1998 **Europe** **RCT**	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☒	3,024 patients from 97centres who had suffered a TIA or non-disabling stroke within the previous 6 months with any degree of stenosis in one or more carotid arteries. The mean age of patients was 63 years at baseline, 72% were male. Previous neurological events included stroke (50%) and TIA (78%).	Patients were randomized to undergo CEA n=1,811) or to avoid surgery (n=1,213). Patients in both groups received best medical management, as appropriate.	**Primary outcome:** Major stroke or surgical death within 30 days **Secondary outcomes:** Any major stroke, death from any cause, any major stroke or death, disabling/fatal stroke or surgical death, fatal stroke or surgical death	The mean duration of follow-up was 6.1 years. Major stroke or death occurred in 37% of CEA patients and 36.5% in control patients. The risk of major ischaemic stroke ipsilateral to the symptomatic carotid artery over the first 2-3 years was significantly decreased in patients with stenosis ≥80% (equivalent of 70% using NASCET criteria) who received CEA (p<0.001). NNT to avoid a major disabling stroke or death from any cause within 3 years was 9.
North American Carotid	CA: ☑	659 patients from 50 centres, <80 years, with	Patients were randomized to undergo	**Primary outcome:** Failure rates during 2-year follow-	The trial was stopped prematurely due to the superiority of CEA. The trial continued for

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Endarterectomy Trial Collaborators *(NASCET)* 1991 **USA & Canada** **RCT**	Blinding: Patient: ☒ Assessor ☑ ITT: ☒	internal carotid stenosis of 70%-99%, who had experienced a TIA or non-disabling stroke in the previous 120 days. Median age was 65 years, 69% were male	CEA or best medical management (including aspirin up to 1,300 mg + antihypertensive agents, antilipid agents, etc, as required),	up.	patients with moderate stenosis (30%-69%). The occurrence of any ipsilateral stroke was significantly lower in the CEA group (9.0% vs. 26%, RRR=65%). The occurrences of any stroke or stroke or death were significantly lower in the CEA group (12.6% vs. 27.6%, RRR=54% and 15.8% vs. 32.3%, RRR=515, respectively). The occurrences of major or fatal ipsilateral stroke, any major or fatal stroke and any major stroke or death were significantly lower in the CEA groups.
ii) Asymptomatic					
Chambers & Donnan 2005 **Australia** **Cochrane review**	NA	3 RCTs, (*Asymptomatic Carotid Artery Study, MRC-Asymptomatic Carotid Surgery Trial, Veterans Affairs Cooperative Study)* including 5,223 patients with asymptomatic carotid stenosis. Mean age at baseline was 66 years. Participants were all male in 1 trial and comprised 66% of the sample in 2 studies. Degree of stenosis was ≥60% (n=2) trials and 50%-99% (n=1)	Treatment contrasts were carotid endarterectomy (CEA) + best medical management vs. best medical management.	i) Perioperative stroke or death, ii) perioperative stroke or death or subsequent ipsilateral stroke, iii), perioperative stroke or death or any subsequent stroke and, iv) any stroke or death	Median duration of follow-up ranged from 2.7-4.0 years. The risk of peri-operative stroke death was higher in the CEA group (3.0% vs. 0.46%, RR= 6.49, 95% CI 2.53-16.61, p<0.0001. CEA was associated with significant reductions in the risk of perioperative stroke or death or subsequent ipsilateral stroke, (RR=0.71, 95% CI 0.55-0.90, p= 0.0051) and stroke or death or any subsequent stroke (RR= 0.69, 95% CI 0.57-0.83, p<0.0001). CEA was associated with non-significant reduction in the risk of any stroke or death (RR= 0.92, 95% CI 0.83-1.02, p=0.095). The relative risk reduction for the outcome of perioperative stroke or death or subsequent carotid stroke was larger for men (51% vs. 4%) and for younger patients (<68 years, 50% vs. 9%).
Halliday et al. 2004, 2010	CA: ☑ Blinding:	3,120 patients with severe unilateral or bilateral carotid artery	Patients were randomized to receive immediate CEA (median	**Primary outcome:** Death, MI or peri-surgical stroke	Median duration of follow-up was 9 years. Of the immediate CEA group, 88% of patients

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
MRC-Asymptomatic Carotid Surgery Trial (ACST) **UK** **RCT**	Patient ☒ Assessor ☑ ITT: ☑	stenosis, which had not caused stroke or TIA in the previous 6 months. Mean age at baseline was 68 years. 66% of patients were males.	delay 1 month, n=1,560) or to indefinite deferral until a more definite indication had arisen (n=1,560).		had undergone the procedure by one year following randomization and 91%, by 5 years. In the deferred group, 4%/year underwent CEA. Immediate CEA was associated with a reduced risk of stroke at 5 and 10 years (6.4% vs. 11.8%, p<0.0001 and 10.8% vs. 16.9%, p<0·0001, respectively).

CA: concealed allocation; ITT: intention-to-treat

Carotid Artery Angioplasty +/- Stenting (CAS)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Systematic reviews					
Zhang et al. 2015 **China** **Systematic review**	NA	35 studies (n=27,525 patients) including 12 RCTs and 23 non RCTs	Studies compared CEA vs. CAS, with results stratified by 5-year increments, and by design (RCT vs. non RCT) and country	**Primary outcome:** Stroke or death within 30 days of procedure **Secondary outcomes:** Restenosis at 1 and 2 years, TIA within 30 days and 1 year and combined stroke/death up to 10 years	Overall, the risk of the primary outcome was significantly higher with CAS (RR=1.51, 95% CI 1.32-1.74, p<0.001). In trials published from 2001-2006, there was no significant difference in outcome, but among trials published from 2007 onward, the risk of the primary outcome was significantly higher with CAS. The risk of the primary outcome was significantly increased with CAS in both RCTs (RR=1.63, 95% CI 1.31-2.02, p<0.0001)) and non RCTs (RR=1.44, 95% CI 1.20-1.73, p<0.0001). Using the results from 3 trials, the risk of restenosis at 30 days was significantly higher with CAS (RR=1.97, 95% CI 1.28-3.05, p=0.02), but not at 2 years (RR= 1.45, 95% CI 0.82-3.41). The 30-day risk of TIA was significantly increased with CAS (RR=2.07, 95% CI 1.90-2.85, p<0.01). The risk of any stroke or death was significantly decreased at 1 year among CAS groups (RR=0.74,

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					95% CI 0.55-0.99, p=0.04). The risk of any stroke or death did not differ significantly between groups at 2 or 3-year follow-up; however, the risk was significantly increased at 4 and 10 years' follow-up for CAS-treated patients (RR=1.24, 95% CI 1.04-1.46, p=0.01 and RR=2.27, 95% CI 1.39-3.71, p=0.001, respectively).
Calvet et al. 2014 **France** ***Pooled analysis Carotid Stenting Trialists' Collaboration (CSTC)***	NA	1,546 patients included in the stenting arm of 3 major trials (EVA-3S, SPACE and ICSS).	The association between surgeon experience and the risk of the primary outcome was examined using pooled patient-level data from the 3 trials	**Primary outcome:** Stroke or death within 30 days of carotid artery stenting (CAS)	The median surgeon lifetime experience was 27 CAS procedures (100 excluding the carotid). The median in-trial volume was 4.3 procedures. Cerebral protection devices were used in 57.9% of procedures. 7.8% of patients (120) experienced the primary outcome. The crude risk of the primary outcome was significantly higher for surgeons with lower CAS volumes. Annual in-trial surgeon CAS volume High >5.6: 5.1% events; RR=1.0 (reference) Intermediate 3.2-5.6: 8.4% events: RR=1.66, 95% CI 1.04-2.64 Low ≤3.2: 10.1% events RR-1.99, 95% CI 1.27-3.10 After adjustment for prognostic factors, the risk of the primary outcome was higher for surgeons with lower in-trial CAS volumes (low; RR=2.30, 95% CI 1.36-3.87 and intermediate: RR= 1.93, 95% CI 1.14-3.27). The risk of the primary outcome did not differ by lifetime surgeon experience at the time of the procedure >37 CAS: 9.1% events, crude RR=1.00 (reference) 17-37 CAS: 7.4% events, crude RR=0.82, 95% CI 0.47-1.43) 0-16 CAS: 7.9%, crude RR=0.87, 95% CI 0.51-1.50
Bonati et al. 2012	NA	16 RCTs (n=7,572) that	Treatment contrasts	**Primary outcome:**	**Endovascular therapy was associated with a**

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UK **Cochrane review**		included patients with symptomatic stenosis, who had experienced a minor stroke, retinal stroke or TIA (n=13), asymptomatic stenosis (n=1) or both asymptomatic and symptomatic carotid stenosis (n=2). 6 of the included studies were terminated prematurely due to issues of safety or futility. Mean age of patients ranged from 63-70 years. 64%-83% of patients were male. The mean the degree of carotid stenosis was ≥70%-<80% (n=2) and ≥80% (n=8). In the remaining trials, the degree of stenosis was noted to be ≥70% in the majority of patients, or was not reported.	included any CEA procedure (e.g. use of patching or shunt) vs. any endovascular technique (e.g. simple balloon angioplasty, use of a stent or not, any type of cerebral protection device+ peri-procedural antiplatelet therapy). In one trial, endovascular therapy was compared with best medical treatment. Protection devices were used in 9 trials.	Death or any stroke occurring between randomization and 30 days of treatment, death, or stroke within 30 or ipsilateral stroke occurring until the end of follow-up. **Secondary outcomes:** Death or disabling stroke, death from any cause, any stroke, MI, all within 30 days of procedure. 3 trials stated a non-inferiority hypothesis where stenting was considered as non-inferior to CEA.	**higher risk of:** Death or any stroke within 30 days of treatment (OR=1.72, 95% CI 1.29- 2.31, p<0.0003). The risk was higher in patients aged ≥70 years (OR=2.20, 95% CI 1.47- 3.29, p<0.0001). Death or any stroke between randomization and 30 days after treatment or ipsilateral stroke until the end of follow-up (OR=1.39, 95% CI 1.10- 1.75, p<0.0005). The risk was highest in the group of studies with follow-up of 2.4 years, or longer (OR= 1.59, 95% CI 1.16-2.16, p=0.0037). Death or any stroke between randomization and end of follow-up (OR=1.41, 95% CI 1.07- 1.84, p=0.014). Severe restenosis during follow-up (OR=2.41, 95% CI 1.28-4.53, p=0.0066). **There was no difference between treatment groups for the outcomes of**: Death or major or disabling stroke between randomization and 30 days after treatment, (OR=1.28, 95% CI 0.93-1.77, p=0.13). Any stroke between randomization and 30 days after treatment (OR=1.21, 95% CI 0.36- 4.04, 9=0.76), although the risk was increased among the subgroup of patients at standard surgical risk, who received endovascular treatment (OR=1.81, 95% CI 1.40-2.34, p<0.0001). **Endovascular therapy was associated with a reduced risk of:** Cranial nerve palsy within 30 days of surgery (OR=0.08, 95% CI 0.05- 0.14, p< 0.00001). Access site hematoma (OR=0.37, 95% CI 0.18-0.77, p= 0.0082).
Murad et al. 2011	NA	13 RCTs (n=7484)	Treatment contrasts	**Primary outcome:**	Compared with CEA, stenting was associated with

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USA **Systematic review**		patients with symptomatic (8 studies) or asymptomatic carotid artery disease. In 4 studies, 3%, 47%, 71% and 100% of patients were asymptomatic). The proportion of symptomatic/asymptomatic patients was not stated in one of the included studies. The mean age of patients ranged from 63-73 years. The qualifying degree of stenosis was 60-70% in studies that recruited asymptomatic patients (50% in one trial), and 70-80% in patients who were symptomatic.	included CEA vs. endovascular treatment (stenting). Protection devices were used on a proportion of patients in 4 studies. It was not stated if such devices were used in 2 studies.	Death, stroke and MI reported at longest follow-up	a significant increased risk of stroke: RR=1.45, 95% CI 1.06-1.99. Results from 10 trials included. Compared with CEA, stenting was associated with a non-significant increase in the risk of death: RR=1.40, 95% CI. Results from 8 trials included Compared with CEA, stenting was associated with a significant decrease in the risk of periprocedural MI: RR=0.43, 95% 0.26-0.71. Results from 7 trials included. Stenting was associated with an increase of 19 strokes and 10 fewer MIs for every 1000 patients treated (compared with CEA).
i) CAS vs. best medical management					
Zaidat et al. 2015 ***Vitesse Stent Ischemic Therapy* (VISSIT)** **USA** **RCT**	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	112 patients (250 planned) 18-85 years, with symptomatic intracranial stenosis (70-99%) of the internal carotid, middle cerebral, intracranial vertebral, or basilar arteries who had experienced a stroke or TIA attributable to the territory of the target lesion within the previous 30 days. Patients were recruited from 27 sites, primarily in the US. Patents with a potential source of cardiac embolism, mRS score	Patients were randomized to receive balloon-expandable stent plus medical therapy (n=59) or medical therapy alone (n=53). Patients in both groups were treated with 75 mg clopidogrel daily, for 3 months, then aspirin (81-325 mg/day) for the study duration. Statins and antihypertensive agents were used, as required. Patients in the stenting group underwent the procedure within 48 hours of randomization.	**Primary outcome:** Composite of 2 outcomes: (1) any stroke in the same territory as the presenting event (distal to the target lesion) within 1 year of randomization; and (2) TIA in the same territory as the presenting event (distal to the target lesion) between 2 days and 1 year of randomization **Safety Outcomes:** Composite of stroke in any territory within 30 days of randomization, TIA in any territory between 2-30 days, all-cause mortality at 30 days and intracranial hemorrhage (ICH) within 30 days.	The trial was halted after the recruitment of 112 patients, when the negative results from the SAMMPRIS trial became available. The 1-year primary outcome occurred significantly more frequently in patients in the stenting group (36.2% vs. 15.1%, mean difference=21.1%, 95% CI 5.4-36.8%, p=0.02). Stroke recurrence (but not TIA) within one year was significantly higher in the stenting group (34.5 vs. 9.4%, mean difference 25.1%, 95% CI 10.5-39.6%, p=0.003). Stroke or TIA within 30 days (primary safety outcome) was more common in the stenting group (24.1% vs. 9.4%, mean difference=14.7%, 95% CI 1.2-28.2%, p=0.05)

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		≥3, unstable neurological status and concurrent intracranial pathology, were excluded. Mean age was 61.8 years, 65% were male. Median baseline NIHSS score was 1.			ICH occurred in 8.6% of patients in the stenting group vs. 0% in the medical group (mean difference=8.6%, 95% CI 1.4-15.8%, p=0.06). 30-day mortality was 5.2% in the stenting group vs. 5.5% in the medical group (mean difference=5.2%, 95% CI -0.05-10.9, p=0.25).
Chimowitz et al. 2011 (30-day outcomes) **Derdeyn et al. 2014 (final results)** ***Stenting and Aggressive Medical Management for Preventing Stroke in Intracranial Stenosis (SAMMPRIS)*** **USA** **RCT**	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	451 patients aged 30-80 years who had experienced a minor stroke or TIA (mRS ≤3) within the previous 30 days, which was attributed to stenosis (70-99%) + one additional vascular risk factor (e.g. BP >140/90 or on antihypertensive therapy). The mean age at baseline was 60 years. 60% of patients were male. 45% had 70-79% stenosis	Patients were randomized to receive best medical management (325 mg aspirin + 75 mg clopidogrel, n=227) for 90 days + management of primary risk factors, or percutaneous transluminal angioplasty and stenting (PTAS) using the Gateway balloon and Wingspan self-expanding nitinol stent, within 3 days (n=224) of randomization. Follow-up was planned for 3 years.	**Primary outcome:** Stroke or death within 30 days or a revascularization procedure during the follow-up period. **Secondary outcomes:** Disabling or fatal stroke, any major hemorrhage	The trial was stopped prematurely due to increased risk of stroke associated with PTAS. The median duration of follow-up was 32 months. A significantly higher percentage of patients in the PTAS group were lost to follow-up (11% vs. 5%, p=0.02). Within 30 days, significantly more patients in the PTAS had experienced the primary outcome (20.5% vs. 11.5%, p=0.009). The probability of the primary endpoint occurring within 30 days was significantly higher in the PTAS group (14.7% vs. 5.8%). There was an increased number of patients in the PTAS group who experienced any stroke during the study period (22.3% vs. 14.1%, p=0.03). An increased number of patients in the PTAS group experienced a major bleeding event (9.8% vs. 2.2%, p<0.001). **Final outcome:** Significantly more patients in the PTAS had experienced the primary outcome (23% vs. 15%, p=0.025). The probability of the primary outcome remained higher in the PTAS group at 1 year (19.7% vs. 12.6%, p=0.04) and 3 years (23.9% vs. 14.p%, p=0.02), but not at 2 years (20.6% vs. 14.1%, p=0.07). There were significantly more strokes and major hemorrhages over the study period among patients in the PTAS groups (26% vs. 19%, p=0.043 and

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					13% vs. 4%, p=0.0009, respectively).
ii) CAS (without protection) vs. CEA					
Brooks et al. 2014 **USA** **RCT**	CA: ☒ Blinding: Patient: ☒ Assessor ☒ ITT: ☒	189 symptomatic (n=104) and asymptomatic (n=85) patients admitted to a single institution with internal carotid stenosis of ≥ 70%, as determined by the North American Symptomatic Carotid Endarterectomy Trial and an anticipated life expectancy of 5 years.	Between 1998-2002, patients were randomized to undergo CEA (n=94) or CAS (n=95).	**Primary outcome:** Incidence of MI, stroke at 10 years **Secondary outcome:** restenosis	173 patients remained in the study at 10 years. 87 (50.2%) had died over the study period. Deaths related to all stroke occurred in 5.7% (CEA) and 1.1% (CAS). The risk of fatal and nonfatal ischemic heart disease was increased with CEA (HR=2.27, 95% CI1.35 to 3.815; p<0.002. The risk of all myocardial events (fatal and non-fatal MI) was significantly lower for patients with symptomatic and asymptomatic disease in the CAS group (p=0.001). Restenosis occurred in 3.3% of patients in the CAS group and was asymptomatic). The combined risk of incident stroke (ipsilateral to the treated artery) and MI was significantly increased in asymptomatic patients treated with CEA (HR=2.27, 95% CI 1.36-3.813, p=0.002), but was similar for symptomatic patients treated with CEA and CAS (CEA: HR=5.7, 95% CI 2.29-14.2; CAS: HR=4.0, 95% CI 1.6-10.1)
Brown et al. 2001 **Ederle et al. 2009** **UK** **RCT** ***Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	504 patients, with symptomatic or asymptomatic carotid artery stenosis of ≥30%, considered to require revascularization and suitable for surgery or endovascular treatment. 90% of patients had experienced symptoms within 6 months of enrollment, 7% had experience	Patients were randomized to endovascular treatment (n=251) with balloon angioplasty with or without stent insertion or CEA (n=253) Surgical expertise in carotid endarterectomy was requested but not defined by a minimum number of procedures.	**Primary outcome:** Disabling stroke or death within 30 days of treatment **Secondary outcome:** Death, disabling stroke, any stroke, MI, cranial nerve palsy, hematoma requiring surgery or extending hospital stay	The median delay from randomization to surgery was 20 days (endovascular treatment) and 27 days (CEA). Mean length of follow-up was 1.95 years in the endovascular group and 1.98 years in the surgical group. There were no differences between groups (endovascular treatment vs. CEA) including death (3% vs. 2%), disabling stroke (4% vs. 4%), non-disabling stroke (4% vs. 4%), death or disabling stroke (6% vs. 6%) or death or any stroke (10% vs. 10%) within 30 days.

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		symptoms more than 6 months prior to enrollment and only 3% of patients included for randomization had experienced no symptoms. Mean age at baseline was 67 years. 70% of patients were men.	Stents were used in 55 patients. No protection devices were available at the time the trial was conducted.		Cranial neuropathy was more common following surgery (8.7%) than endovascular treatment (0%; p<0.0001) as was major groin or neck hematoma following surgery (6.7% vs. 1.2%; p<0.0015). At one year following treatment, severe carotid stenosis (70%-99%) was more common in 357 in patients who had received endovascular treatment (14% vs. 4%; p<0.001). **Long-term follow-up**: (Ederle 2009) The 8-year cumulative incidence of disabling stroke or death was non-significantly higher in the endovascular treatment group: 45.2% vs. 50.4%, HR=1.02, 95% CI 0.79-1.32) as was the combined outcome of non-perioperative stroke or TIA (HR=1.37, 95% CI 0.95-1.97)
Ringleb et al. 2006 (30-day outcomes) **Eckstein et al. 2008 (final 30-day and 2-year results)** ***Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE)*** **International** **Non-inferiority RCT**	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,200 patients, > 50 years with symptomatic carotid artery stenosis, (TIA or moderate stroke [mRS≤ 3] within 180 days) with severe carotid artery stenosis (≥ 50% according to NASCET criteria or ≥ 70% according to ECST criteria) Mean age at baseline was 69 years.72% of patients were male. 62% of patients had ≥ 70% degree of stenosis.	Patients were randomized to receive carotid artery stenting (CAS) (n=599) + antiplatelet therapy 3 days prior and 30 days following the procedure or CEA (n=584) + at least 100 mg aspirin before, during, and after surgery. Embolic protection devices were used in 27% of patients in the CAS group. Non-inferiority limit for the difference in event rates between groups was <2.5%. Planned enrollment was 2,500 patients.	**Primary outcome:** 30-day ipsilateral stroke or death. **Secondary outcomes:** Disabling stroke (mRS>2) or death from any cause within 30 days, disabling stroke, procedural failures.	The trial was stopped prematurely due to concerns regarding futility and funding. Median delay from randomization to treatment was 4 days (endovascular treatment) and 5 days (CEA). There were no differences between groups on any of the outcomes (CAS vs. CEA). Primary outcome: 6.84% vs. 6.34%, OR=1.09, 95% CI 0.69-1.72. Ischemic stroke: 6.51% vs. 5.14%, OR=1.26, 95% CI 0.77-2.18. Death: 0.17% vs. 0.86%, OR=0.78, 95% CI 0.15-3.64. Disabling stroke: 4.01% vs. 2.91%, OR=1.39, 95% CI 0.74-2.62. Procedural failure: 3.17% vs. 2.05%, OR=1.56, 95% CI 0.71-3.56. The risk of Intracerebral bleeding was non-significantly lower in the CAS group (0.17% vs. 0.86%, OR=0.78, 95% CI 0.15-3.64). **Final results:**

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					89% of patients in both groups were available for follow-up at 2 years. The risk of any ipsilateral stroke, or periprocedural deaths was not significantly increased with CAS (9.5% CAS vs. 8.8% CEA, HR=1.10, 95% CI 0.75-1.61). The risks of: ipsilateral ischemic stroke or vascular death over 2 years, any death, and stroke and ipsilateral stroke within 31 days and 2 years, was not significantly increased with CAS treatment. Restenosis of ≥70% was more common in the CAS group. In sub group analysis, age <68 years was associated with a significantly decreased risk of the primary outcome for those in the CAS group (HR=0.54, 95% CI 0.28-1.03).
iii) CAS (with protection) vs. CEA					
Rosenfield et al. 2016 **USA** **Non-inferiority RCT** ***Asymptomatic Carotid Trial (ACT 1)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,453 patients <80 years with severe carotid stenosis (70-99%) who were asymptomatic with no history of stroke or TIA within the previous 180 days and were not considered to be at high risk for surgical complications. Mean age was 68 years, 71% were male. Mean stenosis was 73%. 7% of patients had suffered a previous stroke	Patients were randomized to undergo stenting, using closed-cell, nitinol stents with a tapering diameter with distal embolic protection (n=1,089) or carotid endarterectomy (CEA, n=364). All patients received 325 mg aspirin daily starting 3 days before the procedure and indefinitely thereafter. Patients who underwent stenting also received clopidogrel 3 days before, and for 30 days after the procedure.	**Primary outcome:** Composite of death, stroke (ipsilateral or contralateral, major or minor), or MI within 30 days of the procedure or ipsilateral stroke within 1 year of the procedure **Secondary outcomes:** Complications	Trial was stopped early (panned for 1,658), due to slow enrolment. 328 patients were available for follow-up assessment at 5 years. At one year, the event rate for the primary outcome was 3.8%±0.59% for stenting group vs. 3.4%±0.98% for CEA group. The threshold of a 3%-point difference for inferiority was not exceeded (upper 95% CI for difference was 2.27%). At 30 days, the event rate for stroke or death was 2.9% (stenting group) vs 1.7% (CEA group), p=0.33. The frequency of major or minor stroke within 30 days was similar between groups. The incidence of cranial nerve injury was significantly higher among the CEA (1.1% vs. 0.1%,

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					p=0.02). The incidence of other complications including peripheral nerve injury, vascular injury, noncerebral bleeding and CEA incision or puncture site bleeding was <2% and not significantly different between groups. Survival rate from 30 days to 5 years was 87.1% (stenting group) vs. 89.4% (CEA group), p=0.21. Cumulative rate of stroke-free survival was 93.1% (stenting group) vs. 94.7% (CEA group), p=0.44.
Ederle et al. 2010 **Bonati et al. 2015** **International** **RCT** ***International Carotid Stenting Study (ICSS)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	1,713 patients, aged > 40 years, recruited from 50 centres with symptomatic carotid artery stenosis ≥50% using the NASCET criteria who were deemed suitable for both surgery and stenting. Mean age at baseline was 70 years. 70% of the patients were male. In 90% of patients, the degree of stenosis was 70%-99%.	Patients were randomized to receive carotid stenting (with the recommendation that a protective device be used) + periprocedural antiplatelet therapy (n=853) or CEA (n=857). Protection devices were used in 72% of patients who received stents.	**Primary outcome:** Long-term (i.e. 3 year) rate of fatal or disabling stroke (not yet reported). **Secondary outcomes:** Stroke, death or MI within 30-day of procedure.	The results represent interim data up to 120 days post randomization. Stenting was associated with an increased risk of stroke, death or procedural MI, (8.5% vs. 5.2%, HR=1.69, 95% CI 1.16-2.45, p=0.006) any stroke (7.7% vs. 4.1%, HR=1.92, 95% CI 1.27-2.89, p=0.002), any stroke or death (8.5% vs. 4.7%, HR=1.86, 95% CI 1.26-2.74, p=0.001) and all-cause mortality (2.3% vs. 0.8%, HR=2.76, 95% CI 1.16-6.56, p=0.017). Stenting was not associated with an increased risk of disabling stroke or death (4.0% vs. 3.2%, HR=1.28, 95% CI 0.77-2.11, p=0.34). **Long-term outcomes (ITT analysis)** Median duration of follow-up was 4.2 years. **Fatal or disabling stroke:** The risk was not significantly increased for patients in the stenting group (HR=1.06, 95% CI 0.72-1.57, p=0.77). Cumulative 1-year risk was 3.9% (stenting) vs. 3.2% (CES). Absolute risk difference =0.7% (95% CI -1.0% to 2.5%). Cumulative 5-year risk was 6.4% (stenting) vs. 6.5% (CES). Absolute risk difference = -0.2% (95% CI -2.8% to 2.5%).

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					Any stroke: The risk was significantly increased in the stenting group (HR=1.71, 95% CI 1.28 -2.3, p=0.0003). Cumulative 1-year risk was 9.5% (stenting) vs. 5.1% (CES). Absolute risk difference = 4.4% (95% CI 1.9% to 6.9%). Cumulative 5-year risk was 15.2% (stenting) vs. 9.4% (CES). Absolute risk difference =5.8% (95% CI 2.4% to 9.3%). **Periprocedural stroke/procedural death or ipsilateral stroke during follow-up:** The risk was significantly increased in the stenting group (HR=1.72, 95% CI 1.24-2.39, p=0.001). **All-cause mortality:** The risk was not significantly increased in the stenting group (HR=1.17, 95% CI 0.92-1.48, p=0.19)
Brott et al. 2010, 2016 (10-year results) **USA & Canada** **RCT** ***Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	2,502 patients with asymptomatic or symptomatic carotid artery stenosis who had experienced a minor stroke or TIA within the previous 180 days. To be eligible, patients had carotid stenosis ≥50 by angiography or ≥70% by ultrasound or ≥ 70% by CTA or MRA. Mean age at baseline was 69 years. 65% of patients were male. 86% of patients had ≥70% stenosis	Patients were randomized to receive CEA (n=1,251) or carotid artery stenting + protection device with perioperative antiplatelet therapy (n=1,271) within 2 weeks of the randomization. Of patients randomized to the stenting procedure, 1,144 patients underwent the assigned surgery. Of the patients randomized to CEA, 1,194 received the assigned surgery.	**Primary outcome:** Stroke, death or MI within the perioperative period (30 days) or ipsilateral stroke within 4 years. **Secondary outcome:** Components of the primary outcome.	The median follow-up was 2.5 years. There was no difference between groups in the estimated 4-year rates of the primary endpoint (7.2% vs. 6.8%, HR = 1.11, 95% CI 0.81-1.51, p=0.51). The 4-year rate of stroke or death was higher in the stenting group (6.4% vs. 4.7%, HR=1.50, 95% CI 1.05-2.15, p=0.03). During the periprocedural period, there was an increased risk of stroke or death associated with stenting (4.4% vs. 2.3%, HR=1.90, 95% CI 1.21-2.98, p=0.005), but no difference in risk for stroke, death or MI between treatment conditions from 31 days to end of follow-up (4.4% stenting vs. 2.3%, HR=1.18, 95% CI 0.82-1.68, p=0.38). Stenting was associated with a significantly greater risk for periprocedural stroke (4.1% vs. 2.3%,

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					HR=1.79, 95% CI 1.14-2.82, p=0.01) and a significantly reduced risk for periprocedural MI (1.1% vs. 2.3%, (HR=0.50, 95% CI 0.26-0.94, p=0.03). After the 30-day, periprocedural period, incidence of ipsilateral stroke was similarly low in both groups (2.0 vs. 2.4% in CAS & CEA, p=0.85). Cranial nerve palsies were more frequent in the CEA group (4.7% vs. 0.3%). **Long-term Follow-up** At 10 years, there was no significant difference between groups in the risk of the primary outcome (11.8% [stenting] vs. 9.9% [CEA]; HR=1.10, 95% CI 0.83-1.44, p=0.51). There were no significant interactions (age, sex, asymptomatic vs. symptomatic status or severe vs. moderate stenosis.) The risk of stroke over 10 years was not significantly different between groups (6.9% [stenting] vs. 5.6% [CEA]; HR=0.99, 95% CI 0.64-1.52). The risk of stroke or death in the periprocedural period was significantly higher for patients in the stenting group (11.0% vs. 7.9%; HR=1.37, 95% CI 1.01-1.86, p=0.04).
Yadav et al. 2004, Gurm et al. 2008 (3-year follow-up) **USA** **RCT** ***Stenting and Angioplasty with Protection in Patients at High Risk for***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	334 patients, ≥18 years, with symptomatic coronary artery stenosis of at least 50% or asymptomatic stenosis of 80% with at least 1 coexisting condition that would increase risk associated with CEA. Mean age at baseline	Patients were randomized to receive either CEA (n=167) or stenting (with protection device) + peri-operative antiplatelet therapy (n=167). (Of the 167 patients randomized to the stenting group, 159 received the assigned	**Primary outcome:** Stroke, death or MI within 30 days of treatment, or stroke within 1 year. **Secondary outcome:** Complications **Long-term outcome:** The composite of death or ipsilateral stroke between 31 days and 1080 days.	The primary end point occurred in more patients in the CEA group (20.1% vs.12.2%, absolute difference =7.9%, p=0.004 for non-inferiority, p=0.053 for superiority). There was no difference in the number of patients who had experienced a stroke at 1 year (6.2% stent vs.7.9% CEA, p=0.08) The 30-day incidence of stroke, myocardial infarction or death was 4.8% in the stenting group vs. 9.8% among the CEA patients

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Endarterectomy Investigators (SAPPHIRE)		was 73 years. 67% of patients were male. 27% of patients (in both groups) had received a previous CEA.	treatment. Of the 167 patients randomized to the CEA group, 151 received the assigned treatment).		(p=0.09). Cranial nerve palsy was associated with CEA (0% vs. 4.9%, p=0.04. **3-year outcomes:** There was no difference between groups in the incidence of stroke or death (24.6% stenting vs. 26.9% CEA; absolute difference = -2.3%, 95% CI -11.8%-7.0%, p=0.71). For stroke alone, the absolute difference was 0%, 95% CI -6.1% -6.1%, p=0.99).
Mas et al. 2006, Mas et al. 2008 (4-year follow-up) **France** **RCT** ***Endarterectomy vs. Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA-3S)***	CA: ☑ Blinding: Patient: ☒ Assessor ☑ ITT: ☑	527 patients, ≥18 years who had experienced a carotid TIA or non-disabling stroke within the previous 4 months, with stenosis of ≥60% using the NASCET criteria and who were deemed suitable for both carotid endarterectomy and endovascular treatment. Mean age was 70 years. 75% of patients were male. The qualifying events were approx. 50% each stroke and TIA.	Patients were randomized to carotid angioplasty and stenting with cerebral protection (n=265) +periprocedural antiplatelet therapy or CEA (n=262). Protection devices were used in 92% of patients who received stents.	**Primary outcome:** Any stroke or death within 30 days of the procedure. **Secondary outcomes:** Nonfatal stroke, any disabling stroke or death, TIA or MI within 30 days	The trial was stopped prematurely due to issues of futility and safety. Stenting was associated with an increased risk of any stroke or death (9.6% vs. 3.9%, RR=2.5, 95% CI 1.2-5.1, p<0.01) and nonfatal stroke (8.8% vs. 2.75, RR=3.3, 95% CI, p=0.004). There was a non-significant increase in the risk of any disabling stroke or death associated with stenting (3.4% vs. 1.5%, RR=2.2, 95% CI 0.7-2.6, p=0.72) and TIA (2.35 vs. 0.8%, RR=3.0, 95% CI 0.6-14.6, p=0.28). At 6 months following the procedure, there was a significant increase in occurrence of stroke or death associated with the stenting group (11.7% vs. 6.1%, p=0.02) Stenting was associated with a non-significant increase in the number of local complications (3.1% vs. 1.2%, p=0.22). CEA was associated with a non-significant increase in systemic complications (3.1% vs. 1.95, p=0.42) and a significant increase in cranial-nerve injury (7.7% vs. 1.1%, p<0.001). Stenting failed in 13 patients randomized to receive a stent. These patients were treated with CEA.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					4-year outcomes: At 4 years, the occurrence of stroke or death was still significantly higher among patients in the stenting group (11.1% vs. 6.2%, HR=1.97, 95% CI 1.06-3.67, p=0.03). Most strokes occurred within the first 30 days of the procedure and accounted for the increased risk associated with stenting. The 4-year rate for a "nonprocedural" stroke was similar between groups (4.49% in the stenting group vs.4.94% in the CEA group (HR= 1.02 95% CI 0.42-2.44).

CA: concealed allocation; ITT: intention-to-treat

Risk of Recurrent Stroke in Patients with Symptomatic Carotid Stenosis

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ratner et al. 2017 (Carotid Stenosis Trialists' Collaboration) **Austria** **Pooled analysis**	NA	Data from 4 RCTs (EVA-36, SPACE, ICSS and CREST), representing 4,138 patients who had been randomly assigned to received treatment for symptomatic carotid stenosis using CAS (n=2,096) or CEA (n=2,045). Mean age of all patients was 69.5 years, 60% were men, 18% of patients had a prior history of stroke.	The association between timing of procedure (0-7 days following initial stroke vs. >7 days) and recurrent stroke (based on per-protocol analysis of primary trials)	**Primary outcome:** Stroke or death occurring within 30 days of treatment **Secondary outcomes:** Any stroke, fatal or disabling stroke occurring within 30 days	The median delay between qualifying event and treatment was 26 days for CAS and 29 days for CEA. 14% of CAS patients and 11% of CEA patients received their procedure within the first week of stroke. The risk of any stroke or death within 30 days was significantly higher among patients treated by CAS (7.3% vs. 3.3%; adj RR=1.92, 95% CI 1.50-2.47) **Treatment within 7 days** CAS was associated with a significantly higher risk of periprocedural stroke and death compared with CEA (8.4% vs. 1.3%, adj HR=6.74, 95% CI 2.07-21.92). CAS was associated with significantly higher risks of any stroke and fatal or disabling stroke within 30 days (RR=6.27, 95% CI 1.92-20.44 and RR=8.29, 95% CI 1.07-64.28, respectively) **Treatment >7 days**

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					CAS was associated with a significantly higher risk of stroke and death compared with CEA (7.1% vs. 3.6%, adj RR=2.0, 95% CI 1.5-2.68) CAS was associated with significantly higher risks of any stroke and fatal or disabling stroke within 30 days (RR=1.98, 95% CI 1.47-2.67 and RR=1.77, 95% CI 1.10-2.85, respectively). Tests of interaction between timing of treatment and treatment (CEA vs. CAS) were p= 0.06 (adjusted) for outcome of any stroke or death, and p=0.07 for any stroke at 30 days
Johansson et al. 2016 **Sweden** **Pooled analysis**	NA	377 patients with symptomatic carotid stenosis (50-99%), deemed eligible for CEA or CAS, who had sustained a cerebral or retinal ischemic event who were admitted to one of 3 European centers in Dublin, Spain and Sweden (2005-2013). Median age was 71 years, 69% were men.	Patients were followed for early recurrence of stoke by telephone or in-person interviews. Individual patient-level data were pooled to determine estimates of stroke risk	**Primary outcome:** Ipsilateral ischemic stroke or retinal artery occlusion (RAO) **Secondary outcomes:** Disabling or fatal ipsilateral stroke, any ischemic stroke or RAO	51 patients had a recurrent ipsilateral stroke or RAO within 90 days of the presenting event. 245 (65%) of patients had a revascularization procedure >14 days of symptom onset, 29 patients (7.7%) never underwent the procedure. Within 48 hours of symptom onset, 91% of patients were treated with antiplatelet therapy. Pooled risk of stroke or RAO Day 1: 2.7% (95% CI 1.1- 4.3%) 3 days: 6.6% (95% CI 4.1- 9.1%) 14 days: 11.5% (95% CI 8.2- 14.8%) 30 days: 13.7% (95% CI 10.0- 17.4%) 90 days: 18.8% (95% CI 13.1- 24.5%) Pooled risk of disabling or fatal stroke Day 1: 0.8% (95% CI 0.0- 1.8) 3 days: 1.6% (95% CI 0.4- 2.8%) 14 days: 3.1% (95% CI 1.3- 4.9%) 30 days: 4.0% (95% CI 1.8- 6.2%) 90 days: 7.1% (95% CI 3.0- 11.2%) Age (10-year increments) was associated with an increased risk of 90-day RAO/stroke recurrence (HR= 1.5, 95% CI 1.1-2.2) after adjusting for study center, age and sex.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Degree of ipsilateral stenosis (50-69% and 70-99%), contralateral stenosis, smoking vascular risk factors and medication use (antiplatelets, anticoagulants, blood-pressure medications and statins) were not independent predictors of RAO/stroke recurrence.
Johansson et al. 2013 ANSYSCAP study **Sweden** **Prospective study**	NA	230 patients with recent minor stroke or TIA (within previous 6 months) who were candidates for CEA (carotid stenosis 50%-99%). Mean age was 71 years, 64% were men.	Follow-up was conducted by in-person interview or by telephone.	**Primary outcome:** 90-day recurrence of neurological events before CEA **Secondary outcome:** Surgical complications	183 patients underwent CEA. Median delay to procedure was 29 days. The overall frequency of ipsilateral ischemic stroke recurrence before CEA was 18.6%. The frequency of ipsilateral ischemic stroke recurrence was 5.2% within two-days, 7.9% within 7days, and 11.2% within 14 days of the presenting event. 7.7% of patients suffered a stroke or TIA within 30 days of CEA
Mono et al. 2013 **Switzerland** **Retrospective study**	NA	94 patients admitted to hospital within 48 hours of non-disabling stroke or TIA, with carotid stenosis of ≥50% who were considered suitable candidates for carotid artery intervention within 14 days of the onset of symptoms. Mean age was 70 years, 74% were men. 60% of qualifying events were stroke.	Chart review	**Primary outcome:** Recurrent events occurring within 72 hours of admission, 72 hours to 7 days, and >7 days. **Secondary outcome:** Procedure-related complications	The median time from symptom onset to intervention was 5 days. 21 patients underwent carotid intervention within 5 days (CEA n=85 and CAS n=9) There were 15 recurrent events in 12 patients (11 TIA, 3 stroke), of which 9 occurred within 72 hours of symptom onset, 1 occurred from 72 hours to 7 days and 5 occurred from day 7-day 14. The CAS group had a significantly higher rate of recurrence of cerebrovascular events compared with the CEA group (44% vs. 10.4%, p= 0.003). The incidence of procedure-related events was 4.3% (3 strokes and 1 TIA).

Cervical Artery Dissection

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Incidence and Risk of Recurrent Events					
Béjot et al. 2014 **France** **Retrospective study**	NA	1,368 patients with first-ever cerebrovascular events (stroke and TIA) occurring in Dijon, France, from 2006 to 2011. Mean age was 75 years, 44% were men.	Patients with cervical artery dissections (CAD) were identified, excluding those with major trauma. Clinical characteristics and outcome at hospital discharge were recorded.	**Primary outcome:** Crude incidence rate of CAD **Secondary outcomes:** Functional outcome at hospital discharge and 3 months	27 patients (2% of all strokes) were identified with CAD. Of these, 11 occurred in the internal carotid artery and 17, in the vertebral artery. European standardized rate of CAD was 2.89/100,000/year (95% CI 0–6·23) Mean age of patients with CAD was 49 years, 52% were men. 70% of events were strokes, 30%, TIA. 96% of patients presented with headache or neck pain. At hospital discharge, 78% of patients had a good outcome (mRS 0-2). There were no deaths. At 3 months, 89% of patients had a good outcome. There was one death, at 38 days.
Weimar et al. 2010 **Germany** **Prospective study**	NA	250 patients admitted to one of 30 neurology units from 2002-2006 with confirmed cervical artery dissection (CAD). Mean age was 48 years, 40% were women.	Long-term follow-up was conducted biannually by telephone or mailed questionnaire. Recurrent stroke and stroke free-survival rates were calculated	**Primary outcome:** Recurrent stroke, recurrent CAD and death	Among all patients consecutively admitted with stroke, CAD represented 1.1% of all stroke admissions, but 8.2% of persons <45 years. Distribution of vessels with dissection was: 49.2%, internal carotid artery, 46.8%, vertebral artery, 2.8%, common carotid artery and 1.2%, multiple vessels. Five patients (2.0%) died in the documenting hospital, and 13 patients (5.2%) suffered a recurrent stroke during hospital stay. 151 (61.6%) were discharged on oral anticoagulation, 36 patients (14.7%) were discharged on high-dose heparin, 9

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(3.6%) were discharged on body-weight-adjusted low-molecular weight heparin, 32 (13.1%) were discharged on antiplatelet agents only, and 17 patients (6.9%) received only low-dose heparin or no antithrombotic medication. Mean duration of follow-up was 30.9 months. Long-term follow-up data were available for 198 patients (80.8%). During follow-up, 14 patients suffered a recurrent stroke (11 ischaemic, one ICH, 2 of unknown cause). 5 patients died. The cumulative recurrent stroke rate during the first year was 10.7% (95% CI 6.5% to 14.9%) and 14.0% (95% CI 8.9% to 19.1%) over 3 years. The cumulative recurrent rate of CAD was 1.7% (95% CI 0.3% to 3.6%) for the first year. The frequency of recurrent stroke up to 6 months was significantly lower in patients treated with anticoagulants vs. antiplatelets (2% vs.16.7%, HR=0.11; 95% CI 0.02 to 0.69, p<0.02).
Lee et al. 2006 **USA** **Retrospective study**	NA	48 patients with a diagnosis of spontaneous internal carotid dissection (ICAD) or vertebral artery dissection (VAD) included in the Rochester Epidemiology Project, between 1987 and 2003. Mean age was 46 years, 50% were men.	Case ascertainment through ICD-9 codes for dissection. Patients with dissection due to major trauma were excluded.	**Primary outcome:** Incidence of CAD	There were 32 patients with ICAD and 18 with VAD. The average annual incidence rate for ICAD was 1.89 per 100,000 population (95% CI, 1.13 to 2.65) and for VAD was 1.12 per 100,000 population (95% CI, 0.5 to 1.71). The overall average annual incidence rate for CAD was 3.01 per 100,000 population (95% CI, 1.86 to 3.33). The most commonly reported clinical

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					symptoms were head or neck pain (80%), cerebral ischemia (TIA or infarct) (56%), and Horner syndrome (25%).
Rubinstein et al. 2005 **USA** **Systematic review**	NA	31 studies including patients who experienced cerebral artery dissection (CAD)	Risk factors for CAD were abstracted from each study and grouped into 4 categories including: genetic or inborn predisposition/disorders with a familial association, environmental exposures, trauma and risk factors for atherosclerosis	**Primary outcome:** Strength of association between CAD and individual risk factors	Strong associations were reported for aortic root diameter >34 mm (OR=14.2, 95% CI 3.2-63.6, n=1 study), migraine (adj OR=3.6, 95% CI, 1.5-8.6, n=1 study), relative diameter change (>11.8%) during the cardiac cycle of the common carotid artery (adj OR=10.0, 95% CI 1.8- 54.2, n=1 study), and trivial trauma as manipulative therapy of the neck (adj OR=3.8, 95% CI 1.3-11, n=1 study). Weak associations were found for homocysteine (OR= not reported, 95% CI, 1.05-1.52; and OR=1.3, 95% CI 1.0-1.7), and recent infection (adj OR=1.60, 95% CI 0.67-3.80, n=1 study).
Beletsky et al. 2003 **Canada** **Prospective study**	NA	116 patients >18 years, admitted to multiple centres over 36 months with confirmed cervical dissection.	Data collection included clinical and radiological details, recurrence of ischemic cerebral events, and medical or surgical treatment.	**Primary outcome:** TIA, stroke or death at one-year follow-up **Secondary outcome:** Proportion of patients with a good outcome at one year, defined as Barthel Index score >90 and Rankin score 0-2	**Carotid dissections** 49 patients (42%) had carotid dissections. Of those, 24 were traumatic and 25 were nontraumatic 42 patients presented with stroke/TIA, 1 with SAH, 5 with headache and 1 patient was asymptomatic. **Vertebral dissections** 67 patients (58%) had vertebral dissections. (Of those, 44 were traumatic and 23 were nontraumatic 60 patients presented with stroke/TIA, 3 with SAH, 4 with headache and no patients were asymptomatic. All patients received some form of medical therapy. Most received anticoagulants (67%), followed by antiplatelet agents (20%). 4% of patients received both drugs.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Headache or neck pain occurred more commonly in patients with vertebral dissections (74% vs. 59%, p<0.001). The timing of onset of neurological events occurring after acute dissection, based on presence of headache or neck pain was: 70% within 24 hours, 18% within one week and 12% within 2 months. Mean duration of follow-up was 10.0 months. During one-year follow-up, data were available for 105 patients. There was a total of 17 patients (15%) with recurrent events, including stroke/TIA and death. 89% of patients had a good outcome using Rankin criteria and 86% had a good outcome using BI criteria.
Touzé et al. 2003 **France** **Retrospective study**	NA	459 patients admitted to one of 24 neurology departments over a one-year period, with a confirmed diagnosis of cervical artery dissection (CAD)(traumatic and nontraumatic), who were still alive after one month. Mean age was 44 years, 53% were men.	Patients were follow-up by phone or clinic visits.	**Primary outcome:** Recurrent stroke or CAD	Initial clinical presentation included: ischemic stroke (63.8%), isolated local signs (23.3%), TIA (11.8%), and SAH (1.1%). There were 384 carotid artery and 170 vertebral artery dissections. Initial treatments included heparin (88.8%), oral anticoagulants (2.4%), aspirin (5.3%), and rt-PA (0.4%). 3.15 of patients did not received any antithrombotic treatment. Mean duration of follow-up was 31 months. Two patients died prior to interview. During follow-up, 2 patients had stroke not due to recurrent CAD, 2 had stroke due to recurrent CAD, 2 had recurrent

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					CAD without stroke, and 8 had TIA not due to recurrent CAD. The incidence of recurrent dissection was 0.3%/year. The incidence of ischemic stroke was also 0.3%/year. Timing of recurrent stroke was <6 months after initial event (n=2) and 34.2 and 38.8 months, in 2 patients with recurrent CAD
Schievink et al. 1994 **USA** **Retrospective study** **USA**	NA	200 patients admitted consecutively to a single centre from 1970-1990 with spontaneous cervical artery dissection (CAD). Patients with traumatic CAD were excluded. Mean age was 45 years, 48% were men.	Patients were followed by telephone or correspondence. The association between CAD and risk factors was examined.	**Primary outcome:** Recurrent CAD	Internal carotid dissections were found in 15 patients, vertebral arteries were found in 37 patients and in 13 patients, both carotid and vertebral arteries were affected. Mean follow-up was 7.4 years, representing 1,472 person years. 16 patients (8%) had recurrent dissection. Mean time to recurrence was 4.8 years. The cumulative rate of dissection was 2.0% at 1 month, 3.7% over first 2 years, 5.0% over 5 years and 11.9% at 10 years. Increasing age was the only variable associated with CAD recurrence, with younger patients at higher risk.
Giroud et al. 1994 **France** **Retrospective study**	NA	36 patients included in the stroke Registry of Dijon from 1985-1993 with spontaneous internal carotid artery dissection (ICAD). Mean age was 39 years for women (n=21) and 44 years for men (n=15). Number of persons at risk was 150,000	Review of cases of ICAD	**Primary outcome:** Annual average incidence rate of ICAD	The average annual incidence for all age groups was 2.9 per 100 000 population (95% CI 1.9-3 9). CAD represented 2% of all strokes in the region and 10.1% of the 356 stroke patients under 50 years. The mean age was 39 9 years for the 21 women, 43.7 years for the 15 men. All patients presented with headache or

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					neck pain; 19 patients presented with cerebral ischaemic symptoms, 4 with retinal ischaemic symptoms; one patient had had a subarachnoid haemorrhage. Oculosympathetic palsy was noted in 12 patients. There were no recurrent arterial dissections found at follow up, which ranged from 3 months to 9 years.
Treatment					
Lin et al. 2016 **China** **Systematic review & meta-analysis**	NA	10 studies including 846 patients with stroke due to cervical artery dissection	Treatment contrasts included thrombolysis (148 intravenous thrombolysis and 26 another form of thrombolytic treatment) vs. no thrombolytic treatment (n=672)	**Primary outcome:** Favorable outcome (mRS 0-2) **Secondary outcomes:** Excellent outcome (mRS 0-1), symptomatic ICH, death, recurrent stroke	Mean duration of follow-up ranged from 3-15 months. The proportions of patients with favorable functional outcome in thrombolysis and non-thrombolysis groups were 53.7% and 58.2%, respectively. The difference between groups at 3 months follow-up was not statistically significant (OR=0.78, 95% CI 0.49–1.33). The proportions of patients with excellent functional outcome in thrombolysis and non-thrombolysis groups were 34.4% and 52.4%, respectively. The difference between groups at 3 months follow-up was statistically significant OR=0.49, 95% CI 0.31-0.77). There was no significant difference in the frequency of sICH, mortality or recurrent stroke rates between the 2 group.
Markus et al. 2015 **UK** **RCT** ***Cervical Artery Dissection in Stroke (CADISS)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor☑ Intention-to-	250 patients with extracranial carotid (n=118) or vertebral artery dissection (n=132) recruited from one of 46 centres with specialized stroke services (2006-2013) within 7 days of an acute event. Mean age was 49 years, 69%	Patients were randomized (1:1) to receive antiplatelet agents (dipyridamole, aspirin or clopidogrel, alone or in combination) or anticoagulant therapy (UFH, LMWH, followed by warfarin. Target INR was 2-3) for the study duration.	**Primary outcome:** Ipsilateral stroke or death within 3 months **Secondary outcomes:** Ipsilateral TIA, stroke or death, any stroke or death, any stroke, death or major bleed, any stroke, any stroke or TIA, major	Mean time to randomization was 3.65 days. Dissection was confirmed through central review in 198 patients **Intention-to-treat analysis** Primary outcome: There were 4 recurrent strokes (3 antiplatelet vs. 1

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Study	treat: ☑	were male. Mean baseline mRS was 2.1		bleeding, and death	anticoagulant). There were no deaths in either group. (OR=0.34, 95% CI 0.0006-4.23, p=0.63) Any stroke, death or major bleed: 3 antiplatelet group vs. 2 anticoagulant group (OR=0.67, 95% CI 0.055-5.98, p=1.00) Ipsilateral stroke, TIA or death: 4 antiplatelet group vs. 5 anticoagulant group (OR=1.28, 95% CI 0.27-6.16, p=0.98) Any stroke or TIA: 5 in each group (OR=1.02, 95% CI 0.23-4.54, p=1.00)
Caprio et al. 2014 **USA** **Retrospective study**	NA	149 patients admitted to a single institution from 2010-2013, with cervical artery dissection. Mean age was 43.4 years, 63.1% were women, 70.5% of cases were vertebral artery dissections.	The use of antithrombotic medications prescribed at discharge was retrieved and outcomes among treatment groups compared. Antithrombotic medications included NOAC (dabigatran, rivaroxaban, or apixaban), traditional anticoagulation (warfarin or LMWH), or antiplatelet (aspirin, clopidogrel, or aspirin/extended-release dypyridamole).	**Primary outcome:** Recurrent stroke **Secondary outcomes:** Major bleeding events	Antithrombotic medications prescribed included NOAC (n=39), anticoagulants (AC n=70) and antiplatelets (AP n=40). Median duration of follow-up was 7.5 months There were 2 recurrent strokes in the NOAC group and 1 in each of the AC and AP groups. There were significantly more major hemorrhagic events in the AC group (11.4%) compared to the NOAC (0.0%) and AP (2.5%) groups (p=0.034).
Menon et al. 2008 **UK** **Systematic review & meta-analysis**	NA	34 non-randomised studies included 762 patients who had suffered a cervical artery dissection.	Treatments evaluated included: anticoagulation vs. antiplatelet therapy during the first month of symptom onset, thrombolysis and stenting	**Primary outcomes:** Stroke, TIA or stroke, and stroke or death	Meta-analyses were possible only for the treatment contrast of anticoagulant vs. antiplatelet. There were 15 strokes, 5/268 (1.9%) in the antiplatelet group and 10/494 (2.0%) in the anticoagulant group. The risk difference was not significant (-1%, 95% CI (-6% to 4%, p = 0.66). There were 13/185 (7.0%) in the antiplatelet group and 17/447 (3.8%) in

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					the anticoagulant group who suffered a TIA or stroke. The risk difference was not significant (5%, 95% CI -1% to 11%, p = 0.11). There were 9/268 (3.4%) patients in the antiplatelet group and 19/ 494 (3.8%) in the anticoagulant group suffered stroke or death. The risk difference was not significant (-2%, 95% CI -7% to 3%, p=0.43).

Reference List

Béjot Y, Daubail B, Debette S, Durier J, Giroud M. Incidence and outcome of cerebrovascular events related to cervical artery dissection: the Dijon Stroke Registry. *Int J Stroke* 2014;9(7):879-82.

Beletsky V, Nadareishvili Z, Lynch J, Shuaib A, Woolfenden A, Norris JW. Cervical arterial dissection. *Stroke* 2003;34(12):2856-60.

Bonati LH, Dobson J, Featherstone RL et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet* 2015;385(9967):529-538.

Bonati LH, Lyrer P, Ederle J et al. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev 2012*;9:CD000515.

Brooks WH, Jones MR, Gisler P et al. Carotid angioplasty with stenting versus endarterectomy: 10-year randomized trial in a community hospital. *JACC Cardiovasc Interv* 2014;7(2):163-168.

Brott TG, Hobson RW, Howard G et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med 2010*;363:11-23.

Brott TG, Howard G, Roubin GS et al. Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. *N Engl J Med* 2016; 374 (11):1021-31.

Calvet D, Mas JL, Algra A, et al. Carotid stenting: is there an operator effect? A pooled analysis from the carotid stenting trialists' collaboration. *Stroke* 2014;45(2):527-532.

Caprio FZ, Bernstein RA, Alberts MJ, Curran Y, Bergman D, Korutz AW, et al. Efficacy and safety of novel oral anticoagulants in patients with cervical artery dissections. *Cerebrovasc Dis* 2014;38(4):247-53.

Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database Syst Rev 2005*;CD001923.

Chimowitz MI, Lynn MJ, Derdeyn CP et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med 2011*;365:993-1003.

Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, Montgomery J, Nizam A, Lane BF, Lutsep HL, Barnwell SL, Waters MF, Hoh BL, Hourihane JM, Levy EI, Alexandrov AV, Harrigan MR, Chiu D, Klucznik RP, Clark JM, McDougall CG, Johnson MD, Pride GL, Jr., Lynch JR, Zaidat OO, Rumboldt Z, Cloft HJ: Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet 2014;*383:333-341.

Eckstein HH, Ringleb P, Allenberg JR et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;7(10):893-902**.**

Ederle J, Bonati LH, Dobson J et al. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol 2009*;8:898-907.

Ederle J, Dobson J, Featherstone RL et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet 2010*;375:985-997.

Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729-1737.

European Carotid Surgery Trialists' Collaborative Group Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351(9113):1379-1387.

Giroud M, Fayolle H, Andre N, Dumas R, Becker F, Martin D, Baudoin N, Krause D. Incidence of internal carotid artery dissection in the community of Dijon. *J Neurol Neurosurg Psychiatry* 1994;57:1443.

Gurm HS, Yadav JS, Fayad P et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med 2008*;358:1572-1579.

Halliday A, Harrison M, Hayter E et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010;376:1074-1084.

Halliday A, Mansfield A, Marro J et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet 2004*;363:1491-1502.

Johansson E, Cuadrado-Godia E, Hayden D, Bjellerup J, Ois A, Roquer J, et al. Recurrent stroke in symptomatic carotid stenosis awaiting revascularization: A pooled analysis. *Neurol 2016*;86(6):498-504.

Johansson EP, Arnerlöv C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. *Int J Stroke* 2013;8(4):220-7.

King A, Shipley M, Markus H: The effect of medical treatments on stroke risk in asymptomatic carotid stenosis. *Stroke 2013;*44:542-546.

Lee VH, Brown RD, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection A population-based study. *Neurology* 2006;67(10):1809-12.

Lin J, Sun Y, Zhao S, Xu J, Zhao C. Safety and Efficacy of Thrombolysis in Cervical Artery Dissection-Related Ischemic Stroke: A Meta-Analysis of Observational Studies. *Cerebrovasc Dis* 2016;42(3-4):272-9.

Marks MP, Wojak JC, Al-Ali F, et al. Angioplasty for symptomatic intracranial stenosis: clinical outcome. *Stroke 2006*;37(4):1016-1020.

Markus HS, Hayter E, Levi C, Feldman A, Venables G, Norris J. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. *Lancet Neurol* 2015;14(4):361-367.

Mas JL, Chatellier G, Beyssen B et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med 2006*;355:1660-1671.

Mas JL, Trinquart L, Leys D et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol 2008*;7:885-892.

Menon R, Kerry S, Norris JW, Markus HS. Treatment of cervical artery dissection: a systematic review and meta-analysis. *J Neurol, Neurosurg Psychiatry* 2008;79(10):1122-7.

Mono ML, Steiger I, Findling O, Jung S, Reinert M, Galimanis A, Kuhlen D, Beck J, El-Koussy M, Brekenfeld C, Schroth G. Risk of very early recurrent cerebrovascular events in symptomatic carotid artery stenosis. *J Neurosurg* 2013;119(6):1620-6.

Murad MH, Shahrour A, Shah ND, Montori VM, Ricotta JJ: A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting. *J Vasc Surg* 2011;53:792-797.

North American symptomatic carotid endarterectomy trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325(7):445-453.

Rantner B, Kollerits B, Roubin GS, et al. Early Endarterectomy Carries a Lower Procedural Risk Than Early Stenting in Patients With Symptomatic Stenosis of the Internal Carotid Artery: Results From 4 Randomized Controlled Trials. *Stroke* 2017;48(6):1580-1587.

Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database Syst Rev 2011*;CD001081.

Ringleb PA, Allenberg J, Bruckmann H et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet 2006*;368:1239-1247.

Rosenfield K, Matsumura JS, Chaturvedi S et al. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. *N Engl J Med* 2016; 374 (11):1011-1020.

Rubinstein SM, Peerdeman SM, Van Tulder MW, Riphagen I, Haldeman S. A systematic review of the risk factors for cervical artery dissection. *Stroke* 2005;36(7):1575-80.

Schievink WI, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. *N Engl J Med* 1994; 330: 393–97.

Touze E, Gauvrit JY, Moulin T, Meder JF, Bracard S, Mas JL, Multicenter Survey on Natural History of Cervical Artery Dissection. Risk of stroke and recurrent dissection after a cervical artery dissection A multicenter study. *Neurol* 2003;61(10):1347-51.

Weimar C, Kraywinkel K, Hagemeister C, et al. Recurrent stroke after cervical artery dissection. *J Neurol Neurosurg Psychiatry* 2010;81:869 – 873.

Yadav JS, Wholey MH, Kuntz RE et al. Protected carotid-artery stenting versus endarterectomy in high-Risk patients. *N Engl J Med 2004*;351(15):1493-501.

Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA.* 2015;313(12):1240-1248.

Zhang L, Zhao Z, Ouyang Y et al. Systematic Review and Meta-Analysis of Carotid Artery Stenting Versus Endarterectomy for Carotid Stenosis: A Chronological and Worldwide Study. *Medicine (Baltimore)* 2015;94(26):e1060.