Eur J Vasc Endovasc Surg (2018) 55, 3–81

Editor's Choice – Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

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Keywords: Carotid, Vertebral, Stroke, Transient ischaemic attack, Endarterectomy, Stenting, Medical therapy, Screening, Dementia, Asymptomatic, Symptomatic, Thrombolysis, Imaging, Bypass, Surgical techniques, Complications, Patch infection, Restenosis

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http://dx.doi.org/10.1016/j.ejvs.2017.06.021

ABBREVIATIONS AND ACRONYMS

AAA	abdominal aortic aneurysm
ACAS	Asymptomatic Carotid Atherosclerosis Study
ACE	angiotensin converting enzyme
ACES	Asymptomatic Carotid Emboli Study
ACS	asymptomatic carotid stenosis
ACSRS	Asymptomatic Carotid Stenosis and Risk of Stroke
ACST-1	Asymptomatic Carotid Surgery Trial (first trial)
ACST-2	Asymptomatic Carotid Surgery Trial (second trial)
ACT-1	Asymptomatic Carotid Trial (first trial)
ACTRIS	Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher than average Risk of Ipsilateral Stroke
AF	atrial fibrillation
AHA	American Heart Association
AMBDAP	AMBulatory Dual Anti-Platelet
ARR	absolute risk reduction
ARWMC	age-related white-matter change
bd	bis die (twice daily)
BMS	bare metal stent
BMT	best medical therapy
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CAPTURE	Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events
CARE	Carotid Artery Revascularization and Endarterectomy
CAS	carotid artery stenting
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CCA	common carotid artery
CCB	calcium channel blocker
CCF	congestive cardiac failure
CEA	carotid endarterectomy
CEMRA	contrast enhanced magnetic resonance angiography
CETC	Carotid Endarterectomy Trialists Collaboration
CFA	common femoral artery
CHANCE	Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CI	confidence interval
CMS	Centre for Medicare and Medicaid Services
CNI	cranial nerve injury
COPD	chronic obstructive pulmonary disease
CPD	cerebral protection device
CREST	Carotid Revascularization versus Stenting Trial
CSN	carotid sinus nerve
CSTS	Carotid Stent Trialists Collaboration
CT	computed tomography
CTA	computed tomography angiography
CVR	cerebral vascular reserve
DAPT	dual antiplatelet therapy
DES	drug eluting stent
DSA	digital subtraction angiography
DUS	Duplex ultrasound
DWI	diffusion weighted imaging
ECA	external carotid artery

EC IC	extracranial intracranial
ECST	European Carotid Surgery Trial
EDV	end-diastolic velocity
EEG	electroencephalography
EJVES	European Journal of Vascular and Endovascular Surgery
ENT	Ear, Nose, and Throat surgeon
ESC	European Society of Cardiology
ESPRIT	European-Australasian Stroke Prevention in Reversible Ischaemia Trial
ESPS-2	European Stroke Prevention Study-2
ESVS	European Society for Vascular Surgery
EVA-3S	Endarterectomy versus Stenting in patients with Symptomatic Severe carotid Stenosis
FLAIR	fluid-attenuated inversion recovery
GA	general anaesthesia
GALA	General Anaesthesia versus Local Anaesthesia
GC	Guidelines Committee
HDU	high dependency unit
HR	hazard ratio
HS	hyperperfusion syndrome
HTA	Health Technology Assessment
HRQoL	Health Related Quality of Life
ICA	internal carotid artery
ICH	intracerebral haemorrhage
ICSS	International Carotid Stenting Study
IMT	intima media thickness
ISR	in-stent restenosis
IVT	intravenous thrombolysis
LDL	low-density lipoprotein
LMWH	low molecular weight heparin
LRA	locoregional anaesthesia
MCA	middle cerebral artery
MDT	multidisciplinary team
MES	microembolic signals
MI	myocardial infarction
MMSE	Mini Mental State Examination
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NICE	National Institute for Health and Care Excellence
NSQIP	National Surgical Quality Improvement Program
NSTEMI	non ST elevation myocardial infarction
OR	odds ratio
PAD	peripheral arterial disease
PCA	posterior cerebral artery
PPI	proton pump inhibitor
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PSV	peak systolic velocity
PTA	percutaneous transluminal angioplasty
PTFE	polytetrafluoroethylene
RASP	rapid access stroke prevention
RCT	randomised controlled trial
rTPA	recombinant tissue plasminogen activator
RR	relative risk
RRI	relative risk increase
RRR	relative risk reduction
SAPPHIRE	Stenting & Angioplasty with Protection in Patients at High Risk for Endarterectomy
SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis
SVS	Society of Vascular Surgery
SPACE	Stent Protected Angioplasty versus Carotid Endarterectomy
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SSYLVIA	Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries
SVACS	Symptomatic Veterans Affairs Carotid Study
TIA	transient ischaemic attack
TCD	transcranial Doppler
USPSTF	US Preventive Services Taskforce
VACS	Veteran's Affairs Co-operative Study
VA	vertebral artery
VAST	Vertebral Artery Stenting Trial
VIST	Vertebral Artery Ischaemia Stenting Trial
VSGNE	The Vascular Surgery Group of New England
WG	Writing Group

WHAT HAVE THE 2017 GUIDELINES ADDED TO THE 2009 GUIDELINES?

- Updated analysis of evidence supporting the prevention of stroke in patients with asymptomatic and symptomatic carotid disease.
- New section incorporating evidence supporting the prevention of stroke in patients with atherosclerotic vertebral artery disease.
- New sections on screening for asymptomatic carotid disease and the potential role of carotid interventions in preventing dementia.
- New section on the evidence supporting rapid interventions in recently symptomatic patients and the timing of interventions after thrombolysis.
- New section on the evidence supporting patching, shunting, endarterectomy method, protamine reversal, treatment of coils and kinks, antegrade versus retrojugular exposure, sinus nerve blockade, and the role of monitoring.
- New section on the evidence supporting various carotid artery stenting techniques including adjuvant medical therapy, wires, catheters, and stents, and cerebral protection devices.
- New section on the evidence for managing complications following carotid interventions including

stroke, hypotension, hypertension, haematoma, patch infection, and restenosis.
- ❖ New section on the management of concurrent carotid and cardiac disease.
- ❖ New section on the management of patients with asymptomatic carotid stenoses undergoing major non-cardiac surgical procedures.
- ❖ New section on managing patients with occlusive disease of the proximal common carotid artery and innominate artery.

1. METHODOLOGY AND GRADING OF RECOMMENDATIONS

1.1. Purpose of the guidelines

The European Society for Vascular Surgery (ESVS) has prepared guidelines for treating patients with atherosclerotic carotid and vertebral artery (VA) disease. This does not include non-atherosclerotic conditions such as fibromuscular dysplasia, dissection, arteritis, or trauma. Potential users include vascular surgeons, neurologists, stroke physicians, angiologists, primary care physicians, cardiologists, and interventional radiologists. Guidelines promote standards of care, based on evidence; however, they should not be viewed as the legal standard of care. This document is a "guiding principle" and care given depends on the individual patient (presentation, comorbidities, age) and treatment setting (techniques available, local expertise).

1.2. The Writing Group

Writing Group (WG) members were selected by the ESVS to represent clinicians involved in the treatment of carotid and VA disease. WG members provided disclosure statements regarding relationships that might be perceived as real or potential conflicts of interest, which are available at ESVS headquarters. WG members received no financial support from any pharmaceutical device, or surgical industry.

1.3. Evidence collection

The WG held an introductory meeting in Copenhagen in November 2014, at which the list of topics and author tasks were allocated. The WG agreed a literature search strategy using Medline, Embase, Cardiosource Clinical Trials Database, and the Cochrane Library databases up to December 31, 2016. Reference checking and journal hand searching added other literature. Only peer-reviewed, published literature and studies presenting predefined outcomes were considered. The selection process followed the "pyramid of evidence," with systematic reviews and meta-analyses at the top, then randomised controlled trials (RCTs), then observational studies. Case reports and abstracts were excluded, leaving expert opinion at the bottom.

1.4. Recommendations

The European Society of Cardiology (ESC) system was used for grading levels of evidence and class of recommendation. The letter A, B, or C reflects the level of evidence (Fig. 1) and each recommendation was graded class I, IIa, IIb, or III (Fig. 2). WG members reviewed each chapter of the evolving guideline on several occasions. Following preparation of the first draft, WG members participated in a teleconference at which the wording/grading of each recommendation was reviewed. If there was no unanimous agreement, discussions were held to decide how a consensus might be achieved. If this failed, then the wording, grade, and level of evidence was secured via a majority vote of the WG members.

Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomised clinical trial or large non-randomised studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

Figure 1. Level of evidence.

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful

Figure 2. Class of recommendation.

1.5. The review process and update of guidelines

The guidelines underwent external review by Guideline Committee (GC) members and other independent experts in the field of cerebrovascular disease. Each draft was revised according to reviewer suggestions and the final document submitted to the *European Journal of Vascular and Endovascular Surgery* (EJVES) on June 12, 2017. The GC proposes that these guidelines should be updated in 2021.

1.6. Definition of primary, secondary, and tertiary prevention

The WG adopted the prevention classification proposed by the Institute of Work and Health.[1] *Primary prevention* aims to prevent carotid and VA disease from ever developing (outside the scope of these guidelines). *Secondary prevention* aims at reducing the clinical impact of asymptomatic carotid and VA stenoses (i.e. stenoses are present and the aim is to prevent

them from causing a transient ischaemic attack [TIA] or stroke). The goal of *tertiary prevention* is to reduce the risk of recurrent TIA or stroke in patients who present with a TIA or stroke secondary to carotid or VA stenoses.

2. MANAGEMENT OF CAROTID ARTERY DISEASE

2.1. Introduction

2.1.1. Burden of stroke. In a European population of 715 million, about 1.4 million strokes occur each year.[2] Stroke causes 1.1 million deaths annually in Europe, making it the second commonest cause of death.[3] Over half of stroke survivors remain dependent on others for some aspect of everyday activities.[4] Stroke imposes an enormous financial burden on health systems and caregivers. In Europe, annual stroke costs exceed 38 billion Euros.[3]

2.1.2. Definition of stroke and transient ischaemic attack. For three decades, a stroke diagnosis has been based on the World Health Organization (WHO) definition of a focal, occasionally global, loss of neurological function lasting >24 hours (or leading to death) and which has a vascular aetiology. A TIA was defined in a similar manner, but the duration was <24 hours.[5]

Brain imaging with magnetic resonance imaging (MRI) has shown that many TIA patients have evidence of acute infarction (particularly when symptoms lasted several hours) and this led to proposals that the classical definitions of stroke/TIA should be revised. One revised definition of TIA proposed by the American Heart Association (AHA) is "a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischaemia, which is not associated with acute cerebral infarction." Ischaemic stroke is defined as "an episode of neurologic dysfunction caused by focal cerebral or retinal infarction, where infarction is defined as brain or retinal cell death, attributable to ischaemia, based on neuropathologic, neuroimaging, and/or clinical evidence of permanent injury." Silent infarction is defined as "imaging or neuropathological evidence of cerebral/retinal infarction without a history of acute neurological dysfunction attributable to the lesion."[6] This "tissue-based" definition of TIA is not applied in all healthcare settings, especially outside the USA, because the definition is dependent on the type of neuroimaging performed (computed tomography [CT], MRI) and the availability and timing of such imaging. Accordingly, the clinical (WHO) definition has been used throughout these guidelines.[5]

2.1.3. Aetiology of carotid territory ischaemic stroke. The principal causes of ischaemic, carotid territory stroke are thromboembolism from the internal carotid artery (ICA) or middle cerebral artery (MCA) (25%), small vessel intracranial disease (25%), cardiac embolism (20%), other specified rarer causes (5%), and unknown causes despite investigation (25%).[7] Overall, about 10–15% of all strokes follow thromboembolism from a previously asymptomatic ICA stenosis >50%.[8]

2.1.4. Methods for measuring carotid artery stenosis severity. The European Carotid Surgery Trial (ECST)[9] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[10] used different methods for measuring stenosis severity (Fig. 3). Both used minimum residual luminal diameter as the numerator. In ECST, the denominator was the estimated vessel diameter where the residual luminal diameter was measured (usually the carotid bulb). In NASCET, the denominator was the diameter of a disease-free ICA segment above the stenosis, where the vessel walls were approximately parallel. Each method provides different measures of stenosis severity and this has been a source of confusion as to whether interventions should be based on "50%" or "70%" thresholds.

A 50% NASCET stenosis is equivalent to a 75% ECST stenosis. A 70% NASCET stenosis equates to an 85% ECST stenosis.[11] Some units remain uncertain about which measurement method is being used, and this could lead to inappropriate patient selection (or exclusion) from interventions.[12] The NASCET measurement method has been adopted by the WG throughout these guidelines, unless stipulated otherwise.

There is one situation in which the ECST measurement method has important advantages over NASCET. The NASCET method does not permit reliable measurement of stenosis severity in patients with large volume plaques within dilated carotid bulbs. Here, the residual luminal diameter may be only slightly less than that of the distal ICA. In this situation, the NASCET measurement method will record a <50% stenosis, whereas the ECST method will measure this as being >70%. In this rare situation, recently symptomatic

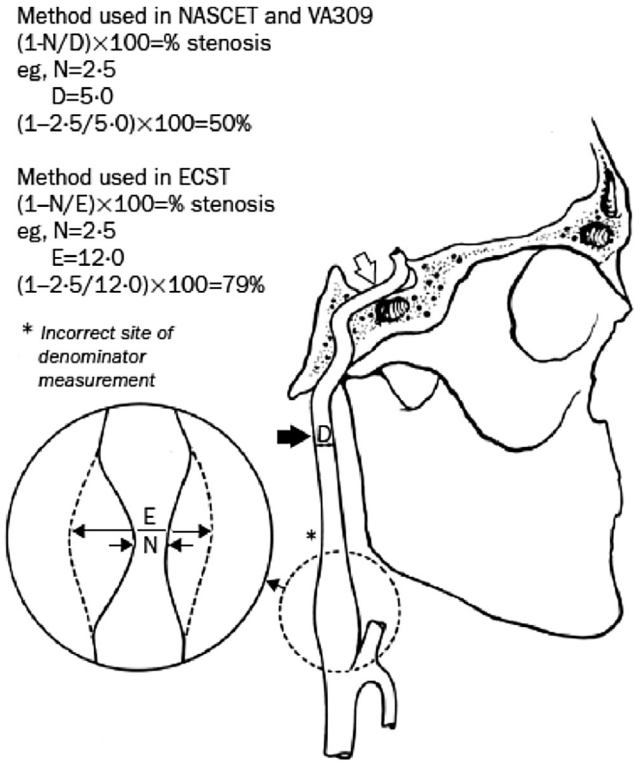

Figure 3. ECST and NASCET methods for measuring stenosis severity. Reproduced with permission from Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107–16.

patients with large volume plaques consistent with an ECST >70% stenosis should be considered for revascularisation.

2.1.5. Imaging strategies in carotid artery disease. When ECST/NASCET were randomising patients, everyone underwent intra-arterial angiography. This has now been abandoned because of angiography-related stroke. In the Asymptomatic Carotid Atherosclerosis Study (ACAS), the 30-day death/stroke rate was 2.3% after CEA, but about half of these strokes (1.2%) were angiographic related.[13]

Duplex ultrasound (DUS) is usually the first-line imaging modality because of its low cost and accessibility. B-mode imaging is combined with colour flow, as well as the ability to undertake Doppler flow velocity measurements. Table 1 details DUS criteria for defining stenosis thresholds using peak systolic velocity (PSV), end-diastolic velocity (EDV) and their ratios in the ICA and common carotid artery (CCA), based on the NASCET measurement method.[14]

The advantage of computed tomographic angiography (CTA) and MR angiography (MRA) is the ability to simultaneously image the aortic arch, supra-aortic trunks, carotid bifurcation, distal ICA, and the intracranial circulation, which is mandatory if a patient is being considered for carotid artery stenting (CAS). Contrast-enhanced MRA (CEMRA) has a higher accuracy than non-contrast MRA techniques (time of flight), but requires administration of a paramagnetic contrast agent such as gadolinium. In a Health Technology Assessment (HTA) meta-analysis, DUS, MRA, and CTA were equivalent for detecting significant ICA stenoses.[18] Catheter angiography is now rarely required, unless there are discrepancies on non-invasive imaging. The HTA advise that where centres rely on DUS alone prior to CEA, the patient should undergo a second corroborative DUS scan, preferably by a second operator.

Table 1. Diagnostic velocity criteria for NASCET-based carotid stenosis measurement.

% stenosis NASCET	PSV ICA cm/s	PSV_{ICA}/PSV_{CCA} ratio	St Mary's ratio[15] PSV_{ICA}/EDV_{CCA}
<50%	<125[16]	<2[16]	<8
50–69%	≥125[16]	2.0–4[16]	8–10
60–69%			11–13
70–79%	≥230[16]	≥4[16]	14–21
80–89%			22–29
>90% but not near occlusion	≥400[16]	≥5[17]	≥30
Near-occlusion	High, low – string flow	Variable	Variable
Occlusion	No flow	Not applicable	Not applicable

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Recommendation 1	Class	Level	References
Duplex ultrasound (as first-line), computed tomographic angiography and/or magnetic resonance angiography are recommended for evaluating the extent and severity of extracranial carotid stenoses	I	A	18
Recommendation 2			
When carotid endarterectomy is being considered, it is recommended that Duplex ultrasound stenosis estimation be corroborated by computed tomographic angiography or magnetic resonance angiography, or by a repeat Duplex ultrasound performed by a second operator	I	A	18
Recommendation 3			
When carotid stenting is being considered, it is recommended that any Duplex ultrasound study be followed by computed tomographic angiography or magnetic resonance angiography which will provide additional information on the aortic arch, as well as the extra- and intracranial circulation	I	A	18
Recommendation 4			
Units who base management decisions on Duplex ultrasound stenosis measurement should state which measurement method is being used	I	C	12,14
Recommendation 5			
Intra-arterial digital subtraction angiography should not be performed in patients being considered for revascularisation, unless there are significant discrepancies on non-invasive imaging	III	A	18

2.1.6. Role of the multidisciplinary team. Where possible, decisions regarding carotid interventions should involve a multidisciplinary team (MDT) including neurologists/stroke physicians, vascular surgeons, and interventional radiologists. Evidence suggests that MDTs increase the proportion of patients undergoing urgent CEA (4% vs. 22%, $p < .0001$),[19] but it is important that urgent decisions can be made by at least two MDT members if meetings only occur weekly. Outcomes after CEA/CAS vary according to who performs the assessment. Rothwell observed that perioperative stroke rates after CEA were 7.7% when patients were assessed by a

neurologist, vs. 2.3% where the operating surgeon adjudicated outcomes.[20] A German Carotid Stenting Registry also observed that neurologist assessment resulted in higher rates of transient (8.2% vs. 5.1%) and permanent (3.3% vs. 0.9%) neurological deficits following CAS, compared with when assessments were undertaken by the interventionist.[21]

Recommendation 6	Class	Level	References
Multidisciplinary assessment is recommended to achieve consensus regarding the indication and optimal treatment of patients by carotid endarterectomy or carotid stenting	I	C	19
Recommendation 7			
Independent assessment after carotid interventions is recommended to audit procedural risks	I	C	20,21

2.2. Secondary prevention in asymptomatic patients

2.2.1. Optimal medical therapy

2.2.1.1. Risk factor control. In a pooled analysis of four population-based screening cohorts, smoking was associated with a significant increase in the prevalence of a >50% ICA stenosis (OR 2.3, 95% CI 1.8—2.8) and of a >70% stenosis (OR 3.0, 95% CI 2.1—4.4).[22] About 5% of males aged >65 years who are current smokers have a >50% ICA stenosis on DUS screening[23] and smoking has been shown to increase plaque progression.[24] In a meta-analysis of 32 studies, smoking was associated with a significant increase in late ischaemic stroke (relative risk increase [RRI] 1.9, 95% CI 1.7—2.2).[25] In a meta-analysis, moderate or high levels of physical activity were associated with a 25% relative risk reduction (RRR) in ischaemic stroke,[26] possibly via reductions in blood pressure (BP), body weight, and effects on other risk factors. Finally, in a meta-analysis of 25 studies involving 2 million people, obesity was associated with a significant increase in stroke prevalence (RRI 1.64, 95% CI 1.36—1.99).[27]

Recommendation 8	Class	Level	References
A healthy diet, smoking cessation, and physical activity are recommended for all patients with asymptomatic carotid disease	I	B	24—27

2.2.1.2. Antiplatelet therapy. There is conflicting opinion regarding antiplatelet therapy in asymptomatic patients because of concerns that inappropriate therapy might increase the risk of major bleeding events without reducing stroke risk. In the Asymptomatic Cervical Bruit study, patients with >50% asymptomatic ICA stenoses were randomised to 325 mg aspirin versus placebo (Table 2). After a median 2.3 years' follow-up, there was no difference in "any ischaemic events" or "any death."[28] By contrast, the Asymptomatic Carotid Emboli Study (ACES) reported that antiplatelet therapy was an independent predictor of lower rates of "ipsilateral stroke/TIA" and "any stroke/cardiovascular death" in patients with asymptomatic 70—99% stenoses.[29]

However, up to two-thirds of asymptomatic patients have subclinical coronary artery disease (CAD).[30] In a systematic review of 17 natural history studies reporting 5-year all-cause mortality in 11,391 patients with >50% asymptomatic ICA stenoses, 63% of late deaths were cardiac, representing an average cardiac-related mortality of 2.9% per year.[31] In addition, a multicentre review of stroke severity and outcomes, stratified for whether patients were taking aspirin prior to stroke onset or not, observed that pre-existing aspirin users had reduced stroke severity at presentation and improved functional outcomes at discharge, even though aspirin had failed to prevent their stroke. This beneficial effect was only seen in patients with large artery atherosclerotic strokes, as opposed to cardioembolic or lacunar strokes.[32] Park's data were not included in Table 2 because a small proportion had experienced a remote TIA/stroke in the past and were not, therefore, truly asymptomatic.[32]

In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study, where 7% had an asymptomatic 50—99% ICA stenosis, there was no evidence that dual antiplatelet therapy (DAPT) conferred any benefit over single antiplatelet therapy.[33] In a meta-analysis of the primary prevention trials, aspirin allocation yielded a 12% RRR in serious vascular events, mainly because of a reduction of about a fifth in non-fatal myocardial infarction (MI) (0.18% vs. 0.23% per year, $p < .0001$). The net effect on stroke was not significant (0.20% vs. 0.21% per year, $p = .4$: haemorrhagic stroke 0.04% vs. 0.03%, $p = .05$; other stroke 0.16% vs. 0.18% per year, $p = .08$).[34] Accordingly, monotherapy with aspirin remains the first-line antiplatelet agent in asymptomatic patients, with clopidogrel reserved for patients who are aspirin intolerant.

Recommendation 9	Class	Level	References
Low-dose aspirin (75—325 mg) is recommended in patients with asymptomatic carotid stenoses for prevention of late myocardial infarction and other cardiovascular events	I	A	29,34
Recommendation 10			
Clopidogrel 75 mg daily should be considered in asymptomatic carotid stenosis patients if aspirin intolerant	IIa	C	

Table 2. Effect of antiplatelet therapy on stroke prevention in patients with asymptomatic carotid stenoses.

Study	ICA stenosis, n = Antiplatelet strategy	Endpoint	Outcomes Antiplatelet vs. no antiplatelet
Asymptomatic Carotid Bruit study[28]	50—99%, $n = 372$	Annual rate of TIA, stroke, unstable angina, MI, or death from any cause at a mean of 2.3 years	11% vs. 12.3% $p = .61$
	Randomised to 325 mg enteric-coated aspirin vs. placebo	Annual rate of TIA, stroke, unstable angina, or MI at a mean of 2.3 years	10.7% vs. 11% $p = .71$
Asymptomatic Carotid Emboli Study[29]	70—99%, $n = 477$	2-year risk of ipsilateral stroke or TIA	HR 0.45 (95% CI 0.31—0.66) $p < .001$
	Observational study: antiplatelet vs. no antiplatelet therapy[a]	2-year risk of stroke or any cardiovascular death	HR 0.13 (95% CI 0.06—0.27) $p < .001$

[a] 95% of patients took antiplatelet therapy during sequential follow-up.

2.2.1.3. Lipid-lowering therapy. In a *post-hoc* analysis of patients randomised within the Asymptomatic Carotid Surgery Trial (ACST-1) who were on lipid-lowering therapy, the 10-year risk of stroke/death was 13.4% in best medical therapy (BMT) patients and 7.6% after CEA. However, in patients not taking statins, the 10-year stroke risk was 24.1% in BMT patients, versus 17.9% after CEA, suggesting that statins reduced long-term stroke in patients with asymptomatic stenoses.[35] With regard to dosage and/or intensity of statin therapy, there are insufficient data from carotid stenosis studies in asymptomatic patients. However, evidence-based treatment goals from studies involving patients with symptomatic and asymptomatic cardiovascular disease advise high-intensity statin treatment goals, including a low-density lipoprotein (LDL) level of <1.8 mmol/L (70 mg/dL) or a 50% reduction of LDL by either 40—80 mg atorvastatin or 20—40 mg rosuvastatin.[36—38] A 2013 Cochrane review of 18 RCTs (56,934 patients) on the role of statins in the primary prevention of cardiovascular disease, observed significant reductions in all-cause mortality, fatal/non-fatal stroke, and revascularisation procedures in patients randomised to statins.[39]

Because of the increased risk of cardiovascular complications and the generally low rate of serious adverse-effects associated with statins, it seems reasonable to apply the same recommendation to patients with symptomatic carotid disease (Section 2.3.2.3.). The role of statin therapy in reducing the perioperative risk of stroke/death following CEA and CAS is discussed in Sections 2.3.2.3.2 and 2.3.2.3.3.

2.2.1.4. Management of hypertension. Hypertension is associated with an increased risk of carotid disease.[40] Treatment in older adults with ICA stenoses (compared with placebo) reduces stenosis progression (14% vs. 31%) and promotes regression (32% vs. 0%).[41] Regression of carotid intima-media thickness (IMT) has been attributed to reductions in carotid pulse pressure.[42] The European Lacidipine Study on Atherosclerosis, which compared lacidipine (calcium channel blocker [CCB]) with atenolol, observed that lacidipine was associated with greater reductions in carotid IMT progression and fewer atherosclerotic plaques, despite smaller falls in BP, suggesting an independent, anti-atherosclerotic action.[43] Similar results have been obtained for angiotensin converting enzyme (ACE) inhibitors; however, CCBs reduce IMT progression more than diuretics, beta-blockers, or ACE inhibitors.[44]

No RCT has evaluated the effect of antihypertensive therapy on stroke prevention in patients with asymptomatic carotid stenoses (ACS). However, a meta-analysis of 25 BP RCTs in patients with no history of vascular disease reported significant reductions in late stroke (RRR 45%, 95% CI 35—55),[45] with stroke reduction being proportional to reductions in systolic BP.[45] In a RCT of Chinese hypertensive patients without a history of stroke/MI, enalapril and folic acid (versus enalapril alone) reduced the risk of first stroke.[46] In practice, BP should be maintained <140/90 mmHg in patients with ACS.[47] The European Society of Cardiology (ESC)/European Society for Hypertension advise that the target for end-diastolic BP should be 85 mmHg in patients with diabetes.[48]

Recommendation 11	Class	Level	References
Statin therapy is recommended for long-term prevention of stroke, myocardial infarction and other cardiovascular events in patients with asymptomatic carotid disease	I	A	36—39

Recommendation 12	Class	Level	References
Antihypertensive treatment is recommended for patients with hypertension and asymptomatic extracranial internal carotid artery stenoses to maintain long-term blood pressure <140/90 mmHg	I	A	45,47

2.2.1.5. Treatment in diabetic patients. Diabetes is associated with an increased risk of ACS,[22] as well as hypertension and abnormal lipid profiles. However, neither plaque burden nor plaque instability are increased in diabetic patients.[49] Diabetes doubles the risk of stroke.[50] In meta-analyses, however, there is no evidence that tight glycaemic control reduces stroke risk,[51] but it will reduce other diabetes-related complications, for example microangiopathy. In a study of type II diabetic patients who received risk factor advice and took statin, antiplatelet, and antihypertensive therapy (as appropriate), there was a 60% reduction in cardiovascular events (hazard ratio [HR] 0.41, 95% CI 0.25—0.69, $p < .001$) and cardiovascular deaths (HR 0.43, 95% CI 0.19—0.94, $p = .04$).[52] The UK Prospective Diabetes Study observed that tight BP control (mean BP 144/82 mmHg) was associated with a 44% RRR in stroke (95% CI 11—65, $p = .013$), compared with patients who had less tight BP control (mean BP 154/87 mmHg).[53] Accordingly, the ESC/European Society for Hypertension advise that the target for end-diastolic BP should be 85 mmHg in patients with diabetes.[48]

Recommendation 13	Class	Level	References
In diabetic patients with asymptomatic carotid stenoses, strict glycaemic control is recommended	I	C	
Recommendation 14			
In diabetic patients with asymptomatic carotid stenoses, the target blood pressure should be <140/85 mmHg	I	B	48

2.2.1.6. Adherence to optimal medical therapy. In patients with carotid disease, there is a paucity of data relating to the potentially adverse effect of non-adherence with antiplatelet/antithrombotic therapy and medications for hypertension, diabetes mellitus, and dyslipidaemia. This was never evaluated in the landmark RCTs.[9,10,13,35,54] In a single-centre study, 114 patients with TIA or ischaemic stroke were recruited via a rapid access stroke prevention (RASP) or inpatient vascular neurology service between 2006 and 2009 and followed-up for a median of 630 days.[55] The proportion continuing medications prescribed at the initial RASP clinic assessment or hospital admission and who were also taking these medications at their last follow-up was 94% for aspirin, 73% for dipyridamole MR, 81% for clopidogrel, 88% for statins, and 90% for antihypertensives. Overall, 99% reported that they were fully adherent to prescribed medications the preceding day, while 11% reported they had missed at least one medication over the preceding 14 days. Half of the patients in this study (54%) reported that they never forgot to take their medications.[55]

Studies in CAD or heart failure patients report better clinical outcomes in those who adhered to their prescribed medications, compared with those who did not.[56] It has been suggested that adherence to antihypertensive medications has important implications for primary stroke prevention in the general population,[57] where "real world" compliance may be worse than in RCTs.[58] Statins have the widest variation in treatment compliance, possibly because of side-effects.[59] This may contribute to many patients not achieving pre-defined LDL-cholesterol reduction targets, thereby predisposing them to recurrent or new cardiovascular events. The same may also be true for aspirin plus dipyridamole (because of dipyridamole-induced headache), but this can be reduced by dose escalation during treatment initiation.

In patients with ACS, adherence to medications may be significantly reduced in the presence of undiagnosed cognitive impairment, which also has implications for monitoring medication usage.[60] Other predictors of poor compliance include psychological problems (particularly depression), asymptomatic disease, inadequate follow-up or discharge planning, medication side-effects, a patient's lack of belief in the benefits of medical treatment, a patient's lack of insight into the illness, poor provider—patient relationships, presence of barriers to care or medications, missed appointments, complexity of treatment, and cost of medication, co-payment, or both.[61] In a simulation model in patients with ACS, survival was significantly better for patients who remained adherent to BMT, compared with non-adherent patients.[62]

2.2.2. Screening for asymptomatic carotid stenoses. According to Wilson and Jungner, the rationale for screening requires that: (i) the condition being prevented is important, has a latent phase, and its natural history is fully understood; (ii) there is a reliable screening test that is acceptable to the population in question; (iii) there is an accepted treatment for screen-positive patients and an agreed policy for whom to treat; and (iv) the intervention for screen-positive patients should be cost-effective.[63]

2.2.2.1. Is stroke important to prevent? In Europe, stroke causes 1.1 million deaths annually.[3] It is the commonest cause of acquired disability in adults, with more than half of stroke survivors being dependent on others for everyday activities.[4] Stroke costs health providers in Europe 38 billion Euros per year,[3] and successful prevention strategies could have enormous clinical, social, and financial benefits. It is, therefore, a very important condition to prevent.

2.2.2.2. Unheralded stroke and asymptomatic carotid stenoses. About 10—15% of all first-ever stroke patients will experience an unheralded ischaemic, carotid territory stroke following thromboembolism from a previously untreated, asymptomatic significant carotid stenosis.[8]

2.2.2.3. Is Duplex ultrasound reliable for diagnosing stenosis severity? The US Preventive Services Taskforce (USPSTF) concluded that DUS was accessible and non-invasive, with a sensitivity of 94% and a specificity of 92% for diagnosing 60—99% carotid stenoses.[64] However, USPSTF observed that the accuracy of DUS varied considerably (especially in inexperienced hands) and that its indiscriminate use in low prevalence populations could result in a low positive predictive value because of a large number of false

positives. USPSTF cited an example where screening 100,000 adults with a 60–99% stenosis prevalence of 1% would yield 893 true positives and 7920 false positives. Even if all false positive tests underwent MRA corroboration, 792 patients with false positive scans might still be considered for CEA/CAS (i.e. almost as many as the 893 true positives).[64] USPSTF concluded that if reliable risk stratification tools were available to distinguish persons who were more likely to have ACS, thereby allowing identification of a population subset with a higher prevalence, then the ratio of true positives to false positives for DUS screening (with/without confirmatory testing) would improve.[64]

2.2.2.4. Prevalence of asymptomatic carotid disease. Using DUS, the prevalence of asymptomatic moderate (>50%) and severe (>70%) stenoses in a population of 23,706 people (mean age 61 years, 46% male) recruited from four population-based cohort studies (Malmö Diet and Cancer Study, Tromsø Study, Carotid Atherosclerosis Progression Study, and the Cardiovascular Health Study) was 2.0% and 0.5%, respectively.[22] Table 3 details the prevalence of >50% and >70% ACS, stratified for age and gender.[22] Assuming that patients aged >80 years with asymptomatic stenoses do not benefit from CEA (Section 2.2.3.1.3.1), the yield for finding patients with >70% stenoses through unselected screening of patients aged <80 years would be <2%,[22] which is not enough to be cost-effective or clinically effective.

2.2.2.5. Can a "high risk for stenosis" cohort be identified? A predictive model was developed by Greco, based on a self-selected cohort of 2,885,257 patients who paid to have a carotid DUS via the Lifeline Screening company, where 66% were female and 20% were <55 years.[65] Overall, 71,004 (2.4%) had a >50% ACS. Half the cohort were used to develop the scoring system, which identified increasing age, smoking history, history of PAD, CAD, high BP, diabetes, abdominal aortic aneurysm (AAA), and high cholesterol as independent predictors of a >50% ACS. African Americans, Asians, and Hispanic participants had a low prevalence of ACS and this was factored into the model, which was tested on the second half of the cohort. With a score of 11–15, <2% of screened participants had a >50% ACS, increasing to 4% in those with a score of 21, and 6% for those whose score was 25. Screening those with the lowest "useful score" of 11 identified 100% of subjects with an ACS >50% at a cost of 41 screenings per >50% ACS detected. This study provided no data on their ability to identify a cohort with an increased likelihood of having a >70% stenosis, which is the more clinically important stenosis threshold.[65]

Table 3. Prevalence of asymptomatic >50% and >70% stenoses in the general population, stratified for gender and age.[a]

Age	Stenosis	Males	Females
<50 years	>50%	0.2%	0.0%
	>70%	0.1%	0.0%
50–59 years	>50%	0.7%	0.5%
	>70%	0.2%	0.1%
60–69 years	>50%	2.3%	2.0%
	>70%	0.8%	0.2%
70–79 years	>50%	6.0%	3.6%
	>70%	2.1%	1.0%
≥80 years	>50%	7.5%	5.0%
	>70%	3.1%	0.9%

[a] Based on analyses from de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 2010;41:1294–7.

2.2.2.6. Potential benefits of selective screening. Screening for ACS could enable risk factor modification and BMT for all screened patients (irrespective of stenosis severity or whether they undergo CEA/CAS) and this could contribute towards preventing MI and cardiac deaths, which are more common than late stroke.[66] In ACST-1, 40% of patients aged <75 years at trial entry died within 10 years, with 55% of deaths being cardiac.[35] In a recent systematic review and meta-analysis, 17 studies reported late mortality in 11,391 patients with an ACS >50%.[31] Overall, 5-year mortality was 24% (95% CI 20.5–26.8). Two-thirds of late deaths were the result of heart disease. Accordingly, risk factor modification and implementation of BMT in patients with screen-detected ACS could significantly reduce cardiac morbidity and mortality.

2.2.2.7. Harm associated with screening. Patients might undergo an unnecessary intervention following a false positive screen and suffer a stroke after CEA or CAS. This was the main concern of USPSTF.[64]

2.2.2.8. Harm associated with carotid interventions. All RCTs involving CEA or CAS in asymptomatic patients reported 30-day death/stroke rates <3% (Section 2.2.3.1.2). However, most surgeons/interventionists were credentialed before randomising patients and 40% of surgeon applicants in ACAS were rejected following review of their track record.[67] Several audits and registries of "real world" practice suggest that many surgeons/interventionists do not achieve death/stroke rates ≤3% in asymptomatic patients.[68–70]

2.2.2.9. Does screening prevent fatal or nonfatal ipsilateral stroke? There is no evidence that population screening reduces stroke and there have been no RCTs of the benefits of screening versus no screening for ACS.

2.2.2.10. Who advocates population or selective screening? The AHA recommends against screening low-risk populations, but did not define who they meant.[71] The Society for Vascular Surgery (SVS) advise that screening for ACS should be considered in selected patients with multiple risk factors, provided that "patients are fit for and willing to consider a carotid intervention if a significant stenosis is discovered." Such patients might include those with PAD (regardless of age), and patients aged >65 years with a history of one or more of CAD, smoking, or hypercholesterolemia.[72] The "14 Society" guidelines advise against routine screening of low-risk patients, but advise that screening might be considered in people without clinical evidence of atherosclerosis who had at least two risk factors, including hypertension, hyperlipidaemia, tobacco smoking, a family history of stroke and "early onset" atherosclerosis.[73] Using the SVS screening criteria described above, Thapar determined that

screening all 60-year-old UK claudicants with a "one off" DUS would cost £17 million (€20 million). If all patients with a 70–99% stenosis then underwent CEA, this would prevent about 230 strokes annually in the UK, which represents only 0.2% of the annual UK stroke burden.[74] In practice, 143 claudicants would need to be screened to identify 20 with a 70–99% stenosis for CEA, to prevent one stroke at 10 years. This would cost £76,000 (€88,300) per stroke prevented.[74]

USPSTF recommends against screening for ACS[64] on the basis that RCTs may have overestimated benefits and used highly selected surgeons, while DUS screening (even with MRA corroboration) might lead to a large number of false positive patients being diagnosed as having a significant ACS. They also noted that medical therapy in the RCTs was outdated (Section 2.2.3.1.4), stroke rates have probably declined over recent decades and 'real world' stroke risks may have been under-reported.[64]

Recommendation 15	Class	Level	References
Routine population screening for asymptomatic carotid stenosis is not recommended	III	C	64
Recommendation 16			
Selective screening for asymptomatic carotid stenoses may be considered in patients with multiple vascular risk factors to optimise risk factor control and medical therapy to reduce late cardiovascular morbidity and mortality, rather than for identifying candidates for invasive carotid interventions	IIb	C	72,73

2.2.3. Interventions in asymptomatic patients

2.2.3.1. Randomised trials: endarterectomy versus best medical therapy. The Veteran's Affairs Co-operative Study (VACS), ACAS and ACST-1 compared CEA plus contemporary BMT, versus BMT alone in 5526 patients who were recruited from Europe and North America. VACS randomised males with 50–99% stenoses ($n = 444$) between 1983 and 1987, with follow-up to 1991.[75] All underwent intra-arterial angiography prior to randomisation. ACAS randomised 1662 patients aged <80 years with 60–99% stenoses between 1987 and 1993, with follow-up to 1997.[13] ACAS patients had to have reported no previous ipsilateral cerebral events at any time. All were screened by DUS (with an inclusion cut-off corresponding to a ≥60% stenosis) and those randomised to CEA then underwent intra-arterial angiography. Patients randomised to BMT did not undergo angiography. Any angiographic related stroke in patients randomised to CEA were included within the "intention to treat" analysis of surgical morbidity and mortality. Patients with bilateral ACS had the side with the tightest stenosis treated in the trial. If there were bilateral equal stenoses, the left ICA was designated the "trial" artery. About 40% of surgeons who applied to join ACAS were excluded following a review of their track record.[67] ACST-1 randomised 3120 patients with 70–99% stenoses between 1993 and 2003, with follow-up extending to 2008. ACST-1 had no age limit and 20% were aged >75 years at trial entry. Pre-randomisation angiography was not required for either trial arm.[54]

2.2.3.1.1. Medical therapy in the randomised trials. In VACS, 650 mg of aspirin (daily) was taken by 55% of patients, while 27% took lower doses. Antihypertensive therapy was less commonly used in VACS and no patient received statins. During ACAS/ACST-1, the use of BP and antithrombotic treatments increased. ACST-1 and ACAS included patients who took fibrates and statins, although ACST-1 had longer follow-up and more robust evidence about statin use (13% ACAS patients were on lipid-lowering therapy at entry vs. 32% in ACST-1).

2.2.3.1.2. Outcomes of randomised trials. Table 4 summarises the 30-day risks of death/stroke after CEA in the RCTs. Approximately half of the perioperative strokes in CEA patients randomised within VACS and ACAS followed angiography.[13,75] Table 4 also details late "ipsilateral" and "any" stroke rates (including the perioperative risk). Overall, VACS observed no difference in "ipsilateral" or "any" stroke (including the perioperative risk) at 4 years.[75] By contrast, ACAS and ACST observed that CEA conferred significant reductions in "any" stroke (including the perioperative risk), while ACAS reported that CEA significantly reduced the 5-year rate of "ipsilateral" stroke.[13,35] The ACAS and ACST trials were pivotal in developing international practice guidelines, most of which advise that CEA should be performed with a 30-day death/stroke rate <3% and that the patient should have a predicted survival >5 years.[13,35]

2.2.3.1.3. Important subgroup analyses

2.2.3.1.3.1. Age. ACST-1 published outcomes stratified for age (<65 years [$n = 912$]; 65–74 years ($n = 1558$); and >75 years [$n = 650$]), but long-term analyses excluded perioperative deaths/strokes. CEA patients aged <65 years had a 5-year risk of "any" stroke of 1.8% vs. 9.6% after BMT (absolute risk reduction [ARR] 7.8%, 95% CI 4.3–11.3). CEA patients aged 65–74 years had a 5-year risk of "any" stroke of 2.2% vs. 9.7% after BMT (ARR 7.5%, 95% CI 4.7–10.3), while

Table 4. Perioperative and late outcomes following CEA and BMT in VACS, ACAS, and ACST.

RCT	30-day death/stroke after CEA[a]	Ipsilateral stroke plus perioperative death/stroke		Any stroke plus perioperative death/stroke	
		CEA + BMT	BMT alone	CEA + BMT	BMT alone
VACS[75]	4.6%[a]	7.0% at 4 years	9.4% at 4 years	10.4% at 4 years	12.0% at 4 years
ACAS[13]	2.3%[a]	5.1% at 5 years	11% at 5 years	12.4% at 5 years	17.8% at 5 years
ACST-1[35]	2.8%	Not available	Not available	6.4% at 5 years	11.8% at 5 years

[a] Includes strokes occurring after diagnostic angiography as well.

CEA patients aged >75 years had a 5.5% risk of "any" stroke at 5 years vs. 8.8% after BMT (ARR 3.3%, 95% CI 1.9–8.4).[35] Half of all patients aged >75 who were randomised to CEA were dead within 5 years and once the perioperative risks (3.7% in patients aged >75 years) were included, there was no evidence that CEA conferred any benefit in patients aged >75.[35] However, if it were possible to develop imaging algorithms for identifying patients at higher risk of experiencing a stroke on BMT (Section 2.2.3.1.5), it is possible that a higher risk subgroup of patients aged >75 years with a predicted life expectancy >5 years might benefit from intervention.

2.2.3.1.3.2. Gender. An early meta-analysis of pooled data from ACAS and ACST-1 reported that males randomised to BMT were twice as likely to suffer a stroke at 5 years (OR 2.04, 95% CI 1.5–2.8).[69] However, at 5 years, CEA conferred no benefit in females (OR 0.96, 95% CI 0.63–1.45). After 10 years of follow-up, ACST-1 reported that females now gained a similar benefit to men (ARR 5.8%, 95% CI 1.1–11.4, $p = .05$).[35] Reasons for the lack of benefit in women at 5 years were that while their hazard from CEA was similar to men, the "background" stroke risk (without surgery) was lower, so benefit took longer to accrue.

2.2.3.1.3.3. Stenosis severity. Unlike symptomatic patients in ECST/NASCET (Section 2.3.3), ACST-1 and ACAS reported that increasing stenosis severity (including bilateral stenoses and contralateral occlusion) were not associated with increased rates of late stroke in patients randomised to BMT.[13,35] A meta-analysis involving 41 studies (6 RCTS, 35 observational studies) reported that ipsilateral stroke risk was 1.9/100 person years in patients with 50–70% stenoses at baseline, compared with 2.1/100 person years in those with 70–99% stenoses ($p = .427$).[76]

2.2.3.1.4. Controversy over modern medical therapy. ACAS, ACST-1, and VACS are the only RCTs to compare CEA with BMT, but they recruited patients from 1983–2003 when, for most of the time, the concept of "BMT" did not include statins and a greater proportion of patients smoked. Some now question whether their data remain relevant in the modern era.[77] Several studies suggest that the annual risk of stroke may be less than when ACAS and ACST-1 were recruiting. In a meta-analysis of 41 studies, the rate of ipsilateral stroke was 2.3/100 person years in studies completing recruitment before 2000, compared with 1.0/100 person years in studies completing between 2000 and 2010 ($p < .001$).[76] The 39% decline in ipsilateral stroke per decade was attributed to improvements in BMT and smoking cessation. In studies where >25% of participants took statins, ipsilateral stroke was 1.2/100 person years, compared with 2.3/100 person years where <25% of participants took statins ($p = .009$).[76] Another review has reported that the temporal trend towards declining annual stroke rates in medically treated patients was consistent across all grades of stenosis at baseline (50–99%, 60–99%, and 70–99%) and was also apparent in ACAS and ACST.[78]

In 1995, ACAS reported a 17.5% 5-year risk of "any" stroke in patients with a 60–99% stenosis who were treated

Table 5. Clinical/imaging features associated with an increased risk of late stroke in patients with asymptomatic 50–99% stenoses treated medically.

Imaging/clinical parameter and stenosis severity Type of study	Annual rate of ipsilateral stroke	OR/HR (95% CI) $p =$
Silent infarction on CT[84] 60–99% stenoses Multicentre, observational	Yes = 3.6% No = 1.0%	3.0 (1.46–6.29) $p = .002$
Stenosis progression[85] 50–99% stenoses Multicentre, observational	Regression = 0.0% Unchanged = 1.1% Progression = 2.0%	1.92 (1.14–3.25) $p = .05$
Stenosis progression[86] 70–99% stenoses Multicentre, RCT	Regression No change Progression 1 stenosis grade Progression 2 stenosis grades	0.7 (0.4–1.3) Comparator 1.6 (1.1–2.4) 4.7 (2.3–9.6)
Plaque area on computerised plaque analysis[87] 70–99% Multicentre, observational	<40 mm^2 = 1.0% 40–80 mm^2 = 1.4% >80 mm^2 = 4.6%	HR 1.0 2.08 (95% CI 1.05–4.12) 5.81 (95% CI 2.67–12.67)
JBA on computerised plaque analysis[88] 50–99% stenoses Multicentre, observational	<4 mm^2 = 0.4% 4–8 mm^2 = 1.4% 8–10 mm^2 = 3.2% >10 mm^2 = 5.0%	Trend $p < .001$
Intra-plaque haemorrhage on MRI[89] 50–99% stenoses Meta-analysis	Yes vs. no	OR 3.66 (2.77–4.95) $p < .01$
Impaired CVR[90] 70–99% stenoses Meta-analysis	Yes vs. no	OR 6.14 (95% CI 1.27–29.5) $p = .02$
Plaque lucency on Duplex US[91] 50–99% stenoses Meta-analysis	Predominantly echolucent 4.2% Predominantly echogenic 1.6%	OR 2.61 (95% CI 1.47–4.63) $p = .001$
Spontaneous embolisation on TCD[92] 50–99% stenoses Meta-analysis	Yes vs. no	OR 7.46 (95% CI 2.24–24.89) $p = .001$
Spontaneous embolisation plus uniformly or predominantly echolucent plaque[93] 70–99% stenoses Multicentre, observational	Yes = 8.9% No = 0.8%	OR 10.61 (95% CI 2.98–37.82) $p = .0003$
Contralateral TIA/stroke[94] 50–99% stenoses Multicentre, observational	Yes = 3.4% No = 1.2%	OR 3.0 (95% CI 1.9–4.73) $p = .0001$

medically (3.5% per year). The 5-year risk of "any stroke" in patients randomised to medical therapy then decreased to 11.8%, when ACST reported its first 5-year data in 2004 (2.4% per year). When ACST reported its second 5-year data (i.e. years 5—10), the five-year risk of any stroke on medical therapy had declined to 7.2% (1.4% per year), part of which may be attributable a proportion of patients randomised to BMT undergoing deferred CEA.[13,35,54,79] The same phenomenon was evident in the 5-year incidence of ipsilateral stroke in medically treated patients. ACAS reported a 5-year rate of ipsilateral stroke of 11.0% in medically treated patients in 1995 (2.2% per year). By 2004, when ACST reported its first 5-year data, the 5-year risk of ipsilateral stroke had fallen to 5.3% (1.1% per year). When ACST reported its 10-year data, the rate of ipsilateral stroke for the second 5-year period had decreased even further to 3.6% (0.7% per year).[13,35,54,79] Overall, this represents a 60% decline in annual stroke rates between 1995 and 2010. It could be argued that patients at "high risk for stroke" in ACST might already have had outcome events in the first 5 years and were thus censored from further trial follow-up, potentially leaving "lower risk" patients in the 5—10 year cohort. However, the decline at 5 and 10 years in ACST exactly parallels the decline in the 5-year rates of "any" stroke in two entirely independent cohorts observed by ACAS in 1995 and ACST-1 in 2004.

Awareness that the risk of stroke in asymptomatic patients treated medically may be less than previously thought, has led to calls for contemporary RCTs evaluating management strategies in asymptomatic patients to include an additional limb for BMT. The second Stent Protected Angioplasty versus Carotid Endarterectomy trial (SPACE)-2) planned to randomise patients to CEA, CAS, and BMT, but was abandoned after randomising only 513 patients because of slow recruitment.[80] The second Carotid Revascularization versus Stenting Trial (CREST-2) has started randomising asymptomatic patients to CEA vs. BMT and CAS vs. BMT, while the second ECST trial (ECST-2) includes a medical limb for asymptomatic patients. The French randomised trial (Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher than average Risk of Ipsilateral Stroke [ACTRIS]) has not yet started but will compare BMT and CEA/CAS in asymptomatic patients who exhibit one or more features suggestive of them being at higher risk of suffering a late ipsilateral stroke[81] (Section 2.2.3.1.5). The second ACST trial (ACST-2) has been randomising asymptomatic patients to CEA or CAS and should complete recruitment in 2019. It is hoped that all surgeons and interventionists will support these RCTs.

2.2.3.1.5. Who is at higher risk for stroke on medical therapy? The AHA has repeatedly advised that only "highly selected" asymptomatic patients should undergo CEA,[71,82] but never defined what "highly selected" means. An alternative interpretation of ACST-1 is that (at 10 years) only 46 strokes will be prevented at 5 years per 1000 CEAs (i.e. 95% of all CEAs were ultimately unnecessary). This, along with evidence that the annual risk of stroke on BMT may be declining, suggests that there is a need to develop clinical/imaging algorithms for identifying a smaller, but higher-risk for stroke cohort in whom CEA/CAS might be targeted. This is important as multi-state audits have suggested that CEA was being performed in asymptomatic patients with 30-day death/stroke rates that often exceeded the 3% threshold,[83] while a recent systematic review observed that 9/21 (43%) registries reported 30-day death/stroke rates that exceeded 3% after CAS.[70]

Accordingly, an uncritical recommendation to revascularise "highly selected" patients without defining who these patients might be, cannot be justified. It is inevitable that a smaller subgroup with clinical and/or imaging features that make them "higher risk for stroke" on BMT will benefit from carotid revascularisation. While awaiting data from CREST-2, ECST-2, ACST-2, and ACTRIS and the development of validated algorithms for patient selection, the presence of one or more clinical and/or imaging features such as silent infarction on CT/MRI, stenosis progression, large plaque area, large juxta-luminal black area (JBA) on computerised plaque analysis, plaque echolucency, intra-plaque haemorrhage on MRI, impaired cerebral vascular reserve (CVR), and spontaneous embolisation on transcranial Doppler (TCD) monitoring, might be useful for selecting "higher-risk for stroke" patients for revascularisation (Table 5).

2.2.3.2. Randomised trials: endarterectomy versus stenting

2.2.3.2.1. 'Average' risk for surgery patients. Five RCTs have published outcomes comparing CEA with CAS in "average-risk for CEA" patients.[80,95—98] Lexington, Mannheim, SPACE-2, and the Asymptomatic Carotid Trial (ACT-1) randomised asymptomatic patients from the outset. CREST-1 was originally a symptomatic RCT, but a protocol change enabled them to randomise asymptomatic patients because of sluggish recruitment. Table 6 details 30-day death/stroke rates from the five RCTs. A meta-analysis of data from four of the five RCTs shown in Table 6 (Lexington was excluded as there were no early or late strokes) observed a 30-day death/stroke rate of 1.6% after CEA (95% CI 1.02—2.45) versus 2.7% (95% CI 2.1—3.6%) after CAS (OR 1.71, 95% CI 0.99—2.94; $p = .0553$). Fig. 4 provides a forest plot of a meta-analysis of all five RCTs.

In the Lexington RCT, no strokes or recurrent stenoses were reported at 4 years. In CREST-1, the 4-year rate of ipsilateral stroke (including the perioperative risk) was 8% following CAS, versus 6.7% after CEA. Restenosis (>70%) was 6.7% at 4 years after CAS and 6.2% after CEA.[96,99] In ACT-1, including perioperative stroke/death/MI, the 1-year

Table 6. 30-day death/stroke in randomised trials comparing CEA and CAS in asymptomatic patients.

30-day outcomes	Lexington[95]		CREST-1[96]		ACT-1[97]		SPACE-2[80]			Mannheim[98]	
	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	BMT	CEA	CAS
	42	43	587	364	364	1089	203	197	113	68	68
Death/stroke	0%	0%	1.4%	2.5%	1.7%	2.9%	2.0%	2.5%	0.0%	1.5%	2.9%
Death/disabling stroke	0%	0%	0.3%	0.5%	0.6%	0.6%					
Death/stroke/MI	0%	0%	3.6%	3.5%	2.6%	3.3%				1.5%	2.9%

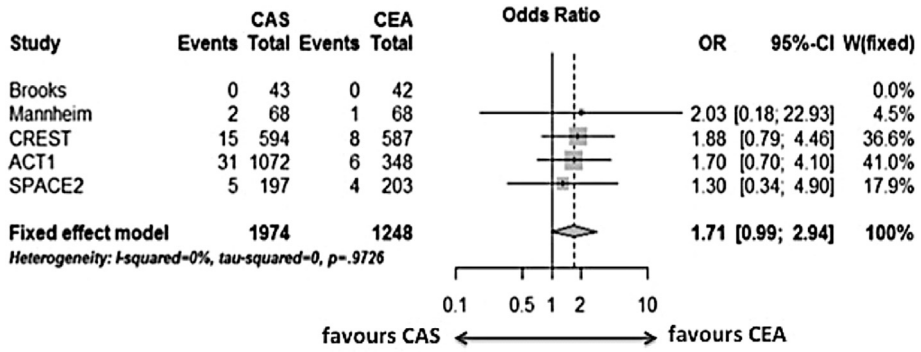

Figure 4. Forest Plot comparing 30-day death/stroke in four randomised trials comparing carotid endarterectomy and carotid artery stenting in asymptomatic patients.

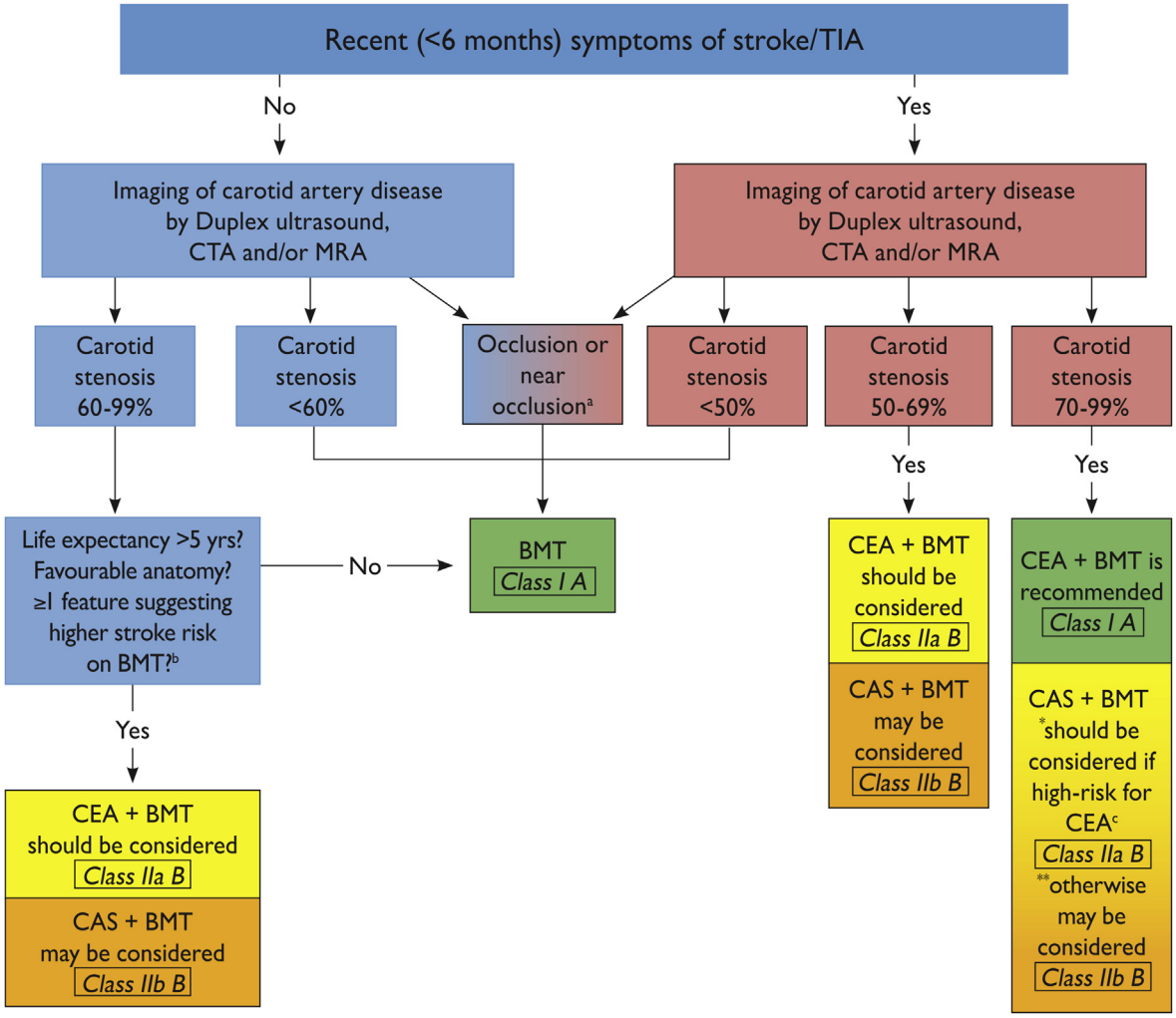

Figure 5. Algorithm detailing management strategies in patients with symptomatic and asymptomatic atherosclerotic extracranial carotid artery stenoses. Green boxes denote Level I recommendations, yellow boxes denote level IIa and IIb recommendations.
BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.
a = post-stenotic internal carotid artery narrowed to the point of near occlusion.
b = clinical/imaging features that might be associated with an increased risk of late stroke on BMT in asymptomatic patients (see Table 5).
c = clinical/imaging features that might make a patient 'high risk for CEA' (see Section 2.3.9).
* denotes recommendation for CAS in symptomatic patients with 70—99% stenoses deemed 'high-risk for CEA'.
** denotes recommendation for CAS in symptomatic patients with 70—99% stenoses deemed 'average risk for CEA'.
Fig. 5 reproduced with permission from; Aboyans V, Ricco JB, Bartelink ML EL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, developed in collaboration with the European Society for Vascular Surgery (ESVS). European Heart Journal Aug 2017 ehx095. doi: 10.1093/eurheartj/ehx095 (IN PRESS). Reproduced with permission of Oxford University Press on behalf of the European Society of Cardiology (www.escardio.org).

rate of ipsilateral stroke was 3.8% after CAS versus 3.4% after CEA. The 5-year rate of ipsilateral stroke (excluding perioperative events) was 2.2% after CAS and 2.7% after CEA ($p = .51$). The 5-year rate of "any" stroke (excluding perioperative events) was 6.9% after CAS, versus 5.3% after CEA. At 1 year, freedom from "target-lesion" revascularization was 99.4% after CAS and 97.4% after CEA.[97]

Despite protocol amendments, SPACE-2 stopped in 2015 after recruiting 513 patients.[80] The 30-day stroke/death rate was 1.97% in 203 patients randomised to CEA vs. 2.54% in 197 patients randomised to CAS. No strokes occurred <30 days of randomisation in the 113 BMT patients. Follow-up will continue to 5 years, with data being available for future meta-analyses. In Mannheim's RCT, there were no late strokes at a mean follow-up of 26 months; 3/68 CEA patients (4.4%) developed a 70—99% restenosis, versus 1/68 (1.5%) after CAS.[98]

Only experienced and credentialed CAS interventionists participated in CREST and ACT-1. In ACT-1 (the largest completed RCT), the 2.9% rate of death/stroke after CAS only just fell within the accepted 3% risk threshold, which many now believe to be too high, given the apparent reductions in stroke on BMT (Section 2.2.3.1.4). In addition, because of the learning curve associated with CAS, as well as it being performed in low numbers by multiple specialties with different patient selection criteria,[100] there are concerns as to whether death/stroke rates in RCTs can be replicated in "real world" practice. While some national CAS registries have published death/stroke rates <3%,[101,102] others have reported wide variations in practice. In a review of 19,381 CAS procedures in the USA, there was a fourfold variation in in-hospital death/stroke, despite adjusting for case-mix.[100] A systematic review of large administrative dataset registries (>1.5 million procedures) found that 40% of registries reported death/stroke rates after CAS in excess of 3% in asymptomatic patients, while 14% reported death/stroke rates >5%.[70] In some large registries, the median annual number of CAS procedures in asymptomatic patients may only be one to two per interventionist,[103] which is known to be associated with higher rates of perioperative stroke/death (Section 2.5.7).

2.2.3.2.2. 'High-risk' for surgery patients. The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study randomised 334 patients deemed "high-risk for CEA" to either CEA or CAS. The criteria for defining a "high-risk for CEA" asymptomatic patient included an asymptomatic 70—99% stenosis in the presence of one or more of: clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery); severe pulmonary disease; contralateral carotid occlusion; contralateral laryngeal-nerve palsy; previous radical neck surgery, cervical radiation therapy; recurrent stenosis after CEA and age >80 years.[104] However, the majority of SAPPHIRE patients (70%) were asymptomatic, in whom 30-day death/stroke was 5.8% after CAS and 6.1% after CEA.[104,105] At these levels of risk, none would gain benefit in terms of late stroke prevention, suggesting they should be treated medically.

An algorithm for managing asymptomatic patients with carotid disease is presented in Fig. 5.

Recommendation 17	Class	Level	References
In "average surgical risk" patients with an asymptomatic 60—99% stenosis, carotid endarterectomy should be considered in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,[a] provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years	IIa	B	13,35,54,84—94, 96,97
Recommendation 18			
In "average surgical risk" patients with an asymptomatic 60—99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,[a] carotid stenting may be an alternative to carotid endarterectomy, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years	IIb	B	80,84—98
Recommendation 19			
Carotid stenting may be considered in selected asymptomatic patients who have been deemed by the multidisciplinary team to be "high-risk for surgery" and who have an asymptomatic 60—99% stenosis in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,[a] provided documented procedural risks are <3% and the patient's life expectancy exceeds 5 years	IIb	B	84—94,104,105

[a] Imaging/clinical criteria that might confer an increased risk of stroke on BMT include silent infarction on CT, stenosis progression, large plaque area, large JBA, plaque echolucency, intra-plaque haemorrhage on MRI, impaired CVR, spontaneous embolisation on TCD, and history of contralateral TIA (Table 5).

2.2.3.3. Carotid revascularisation to prevent dementia

2.2.3.3.1. Alzheimer's, vascular, and "mixed" dementias. Worldwide, 44 million people have dementia. In 2012, the cost of treating dementia in the UK exceeded £23 billion (27 billion Euros). In 20% of dementia sufferers, the underlying cause is atherosclerosis or other occlusive diseases affecting cerebral blood vessels (vascular dementia), while 20–30% have a mixture of vascular dementia and Alzheimer's disease. Important risk factors for dementia include poor diet, mid-life hypertension, hypercholesterolaemia, diabetes, smoking, and excess alcohol intake.[106]

2.2.3.3.2. Dementia and carotid disease. Cognitive impairment is relatively common in stroke patients, attributed to the site and extent of the underlying brain injury. However, there has been interest in whether there is a causal association between ACS and cognitive impairment. In a recent systematic review, 9 out of 10 observational studies reported a significant association between ACS and cognitive impairment.[107] However, many of the risk factors for ACS are the same as for dementia. The Baltimore Longitudinal Study of Ageing observed that patients in the upper quintile of carotid IMT or who had bilateral carotid plaques (of any severity) had a doubling of dementia rates at 14 years, compared with patients in the lower quintiles.[108] In the Framingham Offspring Study, which included 1975 participants who were free of stroke and dementia at the time of study entry, ICA IMT thickness (but not CCA IMT thickness) was associated with MRI-derived indices of brain ischaemia as well as cognitive impairment.[109]

Buratti undertook serial DUS in 159 patients with bilateral, 70–99% ACS over a 3-year period. Cognitive decline was lowest in patients with no evidence of impaired CVR at baseline, becoming more apparent in patients with unilateral CVR impairment. The highest levels of cognitive impairment were in patients with bilaterally impaired CVR.[110] Similar findings were reported by Balucani in a cohort of 333 asymptomatic patients with unilateral ($n = 150$), or bilateral ($n = 127$) carotid stenoses >60% and patients with no carotid stenosis ($n = 56$) who acted as controls. Patients with unilateral or bilateral ACS were more likely to have cognitive impairment, compared with those with no stenoses.[111] Cognitive impairment was maximal in patients with impaired CVR. Interestingly, there was no difference in cognitive impairment in controls compared with patients with bilateral ACS who had no evidence of impaired CVR.

In the Cardiovascular Health Study Group, a high-grade stenosis of the left ICA (>75%) was associated with cognitive decline using the modified Mini-Mental State Examination (MMSE) test, which is more specific for testing dominant hemisphere cognitive function.[112] The Tromso study also observed that the presence of a carotid stenosis (defined as >35%) was associated with impaired neuropsychological performance.[113]

2.2.3.3.3. How might carotid stenoses cause cognitive decline? Cognitive decline may be a result of "silent embolisation," with the development of cerebral infarctions and increasing subcortical deep white matter and cortical lesions, which have been associated with cognitive impairment.[114] Chronic hypoperfusion, especially in patients with impaired CVR, may also be responsible. However, an alternative explanation may be that because patients with ACS share the same risk factors as those who develop dementia, the presence of ACS may simply be a risk marker, rather than a cause of cognitive decline.

In the Cardiovascular Health Study, the persistence of a significant association between severe left-sided ACS and impaired cognitive function, after adjustment for the presence of right-sided carotid stenoses, was interpreted as meaning that the association could not be attributed to underlying vascular risk factors or atherosclerosis in general.[112] However, interpretation of the data was limited by the small number of patients with severe stenoses ($n = 35$). Silent embolisation has long been associated with cognitive decline, but the evidence supporting this is limited. In the Tromso study, impaired cognition could not be attributed to embolisation, because there was no increase in silent ischaemic lesions on MRI.[113]

In a series of projects from Manchester UK, spontaneous embolisation on TCD was detected in 43% of patients with Alzheimer's disease and 45% with vascular dementia.[115] The presence of microemboli was associated with faster deterioration in cognitive function during 2 years of surveillance. However, only 8% of Alzheimer's patients had ACS on DUS, compared with 21% of vascular dementia patients. Microemboli were associated with elevated BP and a high prevalence of venous to arterial shunts (detected in 26% of dementia patients), which may be indicative of an underlying patent foramen ovale.[115] The investigators identified >50% ICA stenoses in only 13% of dementia patients who had microemboli on TCD, compared with 14% of patients without emboli. By contrast, a venous to arterial shunt was identified in 18% of dementia patients who were microemboli negative, compared with 35% who were microemboli positive.[116] In the Manchester series, a >70% stenosis was present in only 2% of dementia patients who were microemboli positive, compared with 0% of microemboli negative patients.[116] In addition, in a series of 96 healthy older people (median age 77 years) with no history of dementia or stroke, microemboli were detected in 12%.[116] In this cohort, cognitive decline over a 2.5-year period was not associated with microemboli after correcting for age, gender and baseline cognition.[116] These data, therefore, support Johnston's hypothesis that silent embolisation from an underlying ACS is unlikely to be an important cause of dementia.[112]

There is probably more evidence supporting the hypothesis that chronic hypoperfusion, in association with impaired CVR, is associated with a higher prevalence of cognitive impairment. As a carotid stenosis becomes more severe, patients with inadequate collateralisation via the circle of Willis compensate by progressive dilatation of arteries/arterioles in the ipsilateral hemisphere. This maintains cerebral blood flow, but a point is reached where the vessels cannot vasodilate any more; that is they are now in a state of impaired CVR with no capacity to compensate further. CVR can be measured in several ways. One method is to measure the increase in MCA velocities using TCD at baseline and

then after breath holding (which raises CO_2 levels), or after the inhalation of 5% CO_2, or by the administration of acetazolamide. Patients with exhausted CVR cannot increase their MCA velocities, because they are already maximally vasodilated. Interestingly, Fearn observed that CEA was able to improve postoperative cognitive function in patients who had evidence of impaired preoperative CVR.[117]

2.2.3.3.4. Do carotid interventions improve cognitive function? It is hypothesised that CEA/CAS have the potential to improve cognitive function by increasing brain perfusion, as well as by removing a source of embolisation. In a systematic review of 15 studies on the effect of CEA on cognitive function, there was no change in six studies, there was a deterioration in five studies and an improvement in four. Four studies reported on the effect of CAS on cognitive function, with no change in cognition post-CAS in one study, while in three, there was an improvement.[118] A subsequent systematic review compared changes in postoperative cognitive function after CEA versus CAS.[119] Six studies reported no difference, three reported that cognitive function deteriorated more significantly after CAS (than CEA), whereas in one study, cognitive function deteriorated after both CEA and CAS with the effect being more persistent after CEA.[119]

To date, there is no compelling evidence that carotid interventions either improve or prevent cognitive impairment. However, there are a number of reasons why a beneficial effect might have been missed, including a "learning effect" through repeated patient testing; the type of neuropsychological test employed; the lack of involvement of a specialised neuropsychologist; the hemisphere being tested (MMSE mainly tests dominant hemispheric function); the type of patient (symptomatic/asymptomatic); a lack of controls; short duration of follow-up (most studies focused on the early perioperative period); small sample size and underpowered studies; and the lack of standardised timing of postoperative assessments.

Further data will be available from CREST-2, which is randomising asymptomatic patients to CEA or CAS versus BMT and which plans to include serial cognitive function testing. In addition, ACST-1 (with extended follow-up to 22 years in some patients) is comparing rates of dementia between patients who underwent CEA with those who remained on medical treatment alone.

Recommendation 20	Class	Level	References
Until a causal association between severe asymptomatic carotid stenoses and cognitive decline has been established, carotid interventions are not recommended for the prevention of cognitive impairment in patients with severe asymptomatic carotid stenoses	III	B	118,119

2.3. Tertiary prevention in recently symptomatic patients

2.3.1. Symptoms attributable to carotid artery disease. For the purpose of these guidelines, the term "symptomatic" refers to any patient who has suffered a carotid territory symptom within the preceding 6 months. Carotid territory symptoms include (i) hemi-sensory impairment (numbness, paraesthesia of face/arm/leg); (ii) hemimotor deficits (weakness of face/arm/leg, or limb clumsiness), and (iii) higher cortical dysfunction (dysphasia/aphasia, visuospatial problems). Most symptoms are "negative" (i.e. loss of function), but occasionally a "limb-shaking" TIA can occur, characterised by involuntary limb movements caused by haemodynamic failure in patients with severe carotid stenoses (or occlusion). "Crescendo TIAs" involve multiple TIAs within a short time period, with full recovery in between. The exact number and/or frequency has never been defined, but at least three events in 7 days would seem reasonable. "Stroke-in-evolution" refers to a fluctuating deficit (never fully back to normal) or a progressively worsening neurological deficit.

Amaurosis Fugax (transient monocular blindness) refers to transient impairment or loss of vision in one eye. Occasionally, visual loss can be permanent because of retinal infarction (analogous to stroke). Patients with retinal infarction are still candidates for revascularisation to prevent hemispheric stroke. Ocular ischaemia syndrome is rare and involves a spectrum of clinical findings secondary to chronic ocular hypoperfusion (progressive visual loss, pain, dilated conjunctival/episcleral vessels, rubeosis iridis, narrowing of retinal arteries, retinal haemorrhages, and microaneurysms). In rare patients, entering a brightly lit room will trigger transient visual loss or "whiteout" of vision.[120] Ocular ischaemia syndrome is nearly always associated with severe extracranial ICA stenotic/occlusive disease, although if collateralisation via the circle of Willis is extremely poor, it can occur in patients with 50% stenoses.[120] Important differential diagnoses include diabetic retinopathy and central retinal vein occlusion. Treatment involves local ophthalmic measures to control anterior segment inflammation, raised intra-ocular pressures and neovascular glaucoma. Medical treatment should focus on traditional risk factor control and optimal medical therapy, while the aim of CEA is to try and prevent further deterioration in visual acuity by preventing further neovascularisation, which is prone to haemorrhage onto the retinal surface. Carotid endarterectomy is probably less likely to be successful in patients who already have neovascularisation-related glaucoma or iris neovascularisation, as this indicates more severe longer-term ocular hypoperfusion.[120]

2.3.2. Optimal medical therapy

2.3.2.1. Risk factor control. The control of modifiable risk factors including smoking, exercise, diet, and obesity are the same as for Section 2.2.1.1.

Recommendation 21	Class	Level	References
A healthy diet, smoking cessation and physical activity are recommended for all patients with symptomatic carotid disease	I	B	24–27

2.3.2.2. Antiplatelet therapy

2.3.2.2.1. Antiplatelet therapy as tertiary prevention. Table 7 summarises key RCT findings regarding roles for mono or DAPT in patients with TIA or ischaemic stroke, including the European Stroke Prevention Study-2 (ESPS-2), the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE), the European-Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT),

Table 7. RCTs of antiplatelet therapy for tertiary prevention in patients with TIA and/or minor ischaemic stroke.

Study Mean follow-up	Inclusion criteria (n =)	Antiplatelet therapy[a]	Endpoint	Outcome
ESPS-2[121] 1996 2 years	TIA or ischaemic stroke in preceding 3 months (n = 6602)	Dipyridamole 200 mg bd[b] vs. aspirin 25 mg bd vs. aspirin 25 mg bd plus dipyridamole 200 mg bd vs. placebo	2-year stroke	Relative risk reduction (all $p < .05$) dipyridamole vs. placebo: 16% aspirin vs. placebo: 18% aspirin + dipyridamole vs. placebo: 37% aspirin + dipyridamole vs. dipyridamole: 25% aspirin + dipyridamole vs. aspirin: 23%
ESPRIT[122] 2006 3.5 years	TIA or minor ischaemic stroke <6 months but not if urgent CEA planned (n = 2739)	Aspirin 30–325 mg daily vs. aspirin 30–325 mg daily and dipyridamole 200 mg bd	Non-fatal stroke or MI/non-fatal major bleeding/vascular death Non-fatal stroke or MI/vascular death	Aspirin and dipyridamole vs. aspirin (HR 0.80, 95% CI 0.66–0.98) Aspirin and dipyridamole vs. aspirin (HR 0.78, 95% CI 0.63–0.97)
CAPRIE[123] 1996 3 years	Ischaemic stroke, MI, or PAD <6 months (n = 19,185)	Clopidogrel 75 mg daily vs. aspirin 325 mg daily	Ischaemic stroke, MI, or vascular death	RRR with clopidogrel vs. aspirin for overall vascular disease population = 8.7% (p = .043) RRR with clopidogrel vs. aspirin for stroke subgroup = 7.3% (p = ns)
PRoFESS[124] 2008 2.5 years	TIA or minor ischaemic stroke <4 months and >50 years old (n = 20,332)	Aspirin 25 mg bd + dipyridamole 200 mg bd vs. clopidogrel 75 mg	Recurrent stroke Stroke/MI or vascular death	Aspirin and dipyridamole vs. clopidogrel (HR 1.01, 95% CI 0.92–1.11, p = .8) Aspirin and dipyridamole vs. clopidogrel (HR 0.99, 95% CI 0.9–1.07, p = .8)
CHANCE[125] 2013 90 days	High-risk TIA or minor ischaemic stroke <24 hours (n = 5170)	75–300 mg aspirin on day 1, then 75 mg aspirin for 21d PLUS clopidogrel 300 mg, then clopidogrel 75 mg for 90 days vs. 75–300 mg aspirin on day 1, then aspirin 75 mg for 90 days	New ischaemic stroke or tissue-defined TIA or haemorrhagic stroke at 90 days	Aspirin and clopidogrel vs. aspirin (HR 0.68, 95% CI 0.57–0.81, $p < .01$)

[a] Modified release form of dipyridamole was used in the various RCTs unless specified.
[b] bd = twice daily (12 hourly).

the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS), and the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE).[121–125] These studies did not specifically include patients with symptomatic carotid stenoses, but it is reasonable to extrapolate the data in the absence of large studies in patients with symptomatic carotid disease. NICE (National Institute for Health and Care Excellence) concluded that in patients with stroke or TIA, clopidogrel should be the first-line antiplatelet agent, followed by aspirin and dipyridamole (if clopidogrel intolerant), followed by aspirin monotherapy, followed by modified release dipyridamole monotherapy, if aspirin and clopidogrel intolerant.[126]

Most of the trials in Table 7 recruited patients some time after the index event. This is important as observational studies suggest that the risk of recurrent stroke is highest in the first few days/weeks after symptom onset (Section 2.3.5). The importance of starting antiplatelet therapy early was illustrated in a meta-analysis of 12 RCTs ($n = 15,778$) comparing aspirin started in the first few days after symptom onset, versus control. Early aspirin therapy reduced the 6-wk risk of recurrent stroke by 60% (HR 0.42, 95% CI 0.32–0.55, $p < .0001$) as well as disabling or fatal stroke by 70% (HR 0.29, 95% CI 0.2–0.42, $p < .0001$).[127]

There is also considerable interest in whether there is a role for starting DAPT in the very early time period after symptom onset. Spontaneous microembolic signals (MES), detected using TCD, are a recognised marker of an increased risk of recurrent stroke in symptomatic patients.[92] Table 8 details the findings from several RCTs and observational studies, which evaluated the role of DAPT in reducing spontaneous embolisation in symptomatic patients.

Phase-2 trials support the hypothesis that aspirin + clopidogrel might be more effective than either alone in early stroke prevention. The CHANCE trial[125] recruited 5170 patients in China within 24 hours of suffering a minor stroke

Table 8. Antiplatelet strategies for reducing recurrent stroke and spontaneous embolisation in recently symptomatic patients.

Study (year)	Inclusion criteria Trial design	Intervention	Outcome
Payne[128] (2004)	100 consecutive CEA patients with ≥50% stenosis (≥70% asymptomatic) randomised	Aspirin 150 mg daily for 4 wks preop vs. aspirin 150 mg daily for 4 wks preop plus a single 75 mg dose of clopidogrel 12 hours preop	After 3 hours of postoperative TCD monitoring, aspirin + clopidogrel was associated with a tenfold reduction in the proportion of patients with ≥20 emboli detected: (OR 0.10, 95% CI 0.01–0.77, $p = .01$)
CARESS[129] (2005)	107 patients with >50% symptomatic carotid stenosis with ≥1 micro-emboli detected on TCD randomised	Aspirin 75 mg daily + clopidogrel 300 mg on day 1, followed by 75 mg of clopidogrel daily until day 7 vs. aspirin 75 mg daily	At 7 days, aspirin + clopidogrel was associated with a significant reduction in proportion of patients with persisting embolisation: (43.8% vs. 72.7%, $p = .0046$)
CLAIR[130] (2010)	100 recently symptomatic patients with intra- or extra-cranial large artery stenosis randomised	Aspirin 75–160 mg daily for 7 days vs. aspirin 75–160 mg daily for 7 days + clopidogrel 300 mg on day 1, followed by 75 mg of clopidogrel daily for 6 days	Aspirin + clopidogrel associated with significant reductions in persistent embolisation: at day 2 (31% vs. 54%, $p = .025$) at day 7 (23% vs. 51%, $p = .006$)
AMBDAP[131] (2011)	60 recently symptomatic patients with ≥50% carotid stenosis randomised	Aspirin 300 mg, then 75 mg daily + dipyridamole 200 mg bd for 30 days vs. aspirin 300 mg, then 75 mg daily + 300 mg clopidogrel, then 75 mg daily for 30 days	At 48 hours, there was a similar reduction in the frequency of microembolisation for: aspirin + dipyridamole (75.5%) aspirin + clopidogrel (77.5%, $p = .77$)
Batchelder[132] (2015)	100 consecutive symptomatic patients undergoing CEA within 8 days of symptom onset, compared with preceding 212 CEA patients observational	Aspirin 300 mg, then 75 mg daily + 75 mg clopidogrel 12 hours preop vs. aspirin 300 mg, then 75 mg daily + 75 mg clopidogrel 48–72 hours preop	Starting aspirin and clopidogrel 48–72 hours preop (compared with 12 hours preop) was associated with significant reductions in: recurrent TIA/stroke prior to CEA (3% vs. 13%) (OR 0.20, 95% CI 0.06–0.66, $p = .01$) spontaneous embolisation (5% vs. 21%) (OR 0.24, 95% CI 0.09–0.66, $p = .0047$)

or high-risk TIA, who were randomised to clopidogrel (300 mg, then 75 mg daily for 90 days) plus aspirin (75 mg daily for first 21 days) or aspirin alone (75 mg daily for 90 days). A "high-risk TIA" patient was defined as having an ABCD[2] score $\geq$4 (based on **A**ge, **B**lood pressure, **C**linical features, **D**uration of TIA, and presence or absence of **D**iabetes).[133] There was a significant (32%) RRR in recurrent stroke in patients receiving early DAPT, versus aspirin alone (8.2% vs. 11.7%, $p < .001$), with no excess risk of moderate/severe haemorrhage (0.3% in both groups). A subgroup analysis involving >1000 subjects with imaging observed that the benefit conferred by DAPT was particularly marked in patients with extracranial ICA or MCA stenoses.[134] A meta-analysis, which included the CHANCE data, reported that in patients with acute, non-cardioembolic ischaemic stroke/TIA, DAPT conferred a 31% RRR in stroke, compared with monotherapy.[135]

Further data supporting a beneficial role for DAPT in the early time period after onset of symptoms comes from analyses of recurrent TIA/stroke rates prior to urgent CEA. In audits involving 198 symptomatic patients with ipsilateral 50—99% ICA stenoses who were admitted within 5 days of symptom onset, 13% suffered recurrent TIA/stroke in the 2—3 day period between transfer from the daily TIA clinic to undergoing CEA, despite being preloaded with 300 mg aspirin daily.[136,137] Starting 75 mg clopidogrel daily in the TIA clinic (in addition to regular aspirin) prior to transfer to the surgical unit (once parenchymal haemorrhage was excluded on CT/MRI) was associated with significant reductions in spontaneous embolisation from 21% down to 5% (OR 0.24, 95% CI 0.09—0.66) $p = .0047$) and a significant reduction in recurrent events prior to CEA, down from 13% to 3% (OR 0.20, 95% CI 0.06—0.66) $p = .01$).[132] A similar reduction in recurrent events following early introduction of DAPT prior to expedited CEA has been reported by a Danish group.[138]

2.3.2.2.2. Antiplatelet therapy during carotid endarterectomy. Boysen reported that starting antiplatelet therapy *after* CEA did not reduce late stroke, compared with patients receiving placebo.[139] In a RCT, Lindblad demonstrated that starting 75 mg aspirin *prior* to CEA reduced disabling stroke without increasing bleeding complications.[140] Kretschmer showed that long-term aspirin therapy after CEA was associated with significantly better long-term survival.[141]

In NASCET, patients were advised to take 1300 mg aspirin daily.[142] In an unplanned *post-hoc* analysis, patients taking 81—325 mg of aspirin had a 30-day stroke/death rate of 6.9% compared with 1.8% in those taking 650—1300 mg doses,[143] suggesting that higher-dose aspirin might be beneficial. The Aspirin and Carotid Endarterectomy trial[143] thereafter randomised 2849 CEA patients to 81 mg, 325 mg, 650 mg, or 1300 mg of aspirin throughout the perioperative period. Aspirin doses of 81—325 mg were termed "low dose," whereas 650—1300 mg were termed "high dose." The risk of stroke, MI, or death at 30 days was non-significantly lower in patients randomised to low-dose (5.4%) vs. high-dose aspirin (7.0%, $p = .07$). However, it was noted that the data were biased by the inclusion of patients taking >650 mg aspirin before randomisation, alongside patients who only started aspirin the day before CEA. In an efficacy analysis that excluded the latter, the risk of stroke, MI, or death at 30 days was 3.7% on low-dose vs. 8.2% on high-dose aspirin ($p = .002$).[143]

Increasing embolisation on TCD in the early post-operative period after CEA increases the risk of post-operative thrombotic stroke.[144] A small RCT ($n = 22$) reported that preoperative treatment with aspirin plus dipyridamole was associated with a significant reduction in the accumulation of indium-labelled platelets to the end-arterectomy zone in the first few hours after CEA, compared with placebo.[145] In a larger RCT, Payne demonstrated that regular administration of 150 mg aspirin daily plus a single 75 mg dose of clopidogrel the night before surgery significantly reduced embolisation rates in the first 3 hours after CEA, compared with aspirin plus placebo (OR 0.1, 95% CI 0.01—0.77, $p = .01$).[128]

2.3.2.2.3. Antiplatelet therapy during carotid artery stenting. Virtually every guideline recommends that CAS patients should receive DAPT throughout the perioperative period. However, this is largely based on the coronary literature, with no data from large RCTs in CAS patients. Intimal injury after CAS releases pro-coagulant factors and exposes sub-endothelial collagen, which acts as a nidus for platelet adhesion and secondary thrombus formation. Meta-analyses of RCTs suggested that aspirin plus clopidogrel were as effective as aspirin and ticlopidine in preventing *in-stent* thrombosis after coronary artery stenting.[146] In the only RCT in CAS patients, aspirin plus heparin was associated with significantly more perioperative neurological events (25 vs. 0%, $p = .02$), and a non-significantly higher risk of bleeding complications compared with aspirin plus clopidogrel.[147] No RCT has randomised CAS patients to aspirin and clopidogrel vs. aspirin and dipyridamole. Notwithstanding this, most investigators advise at least 4 wks of treatment with aspirin and clopidogrel after CAS.[147] Long term aspirin plus clopidogrel confers no additional benefit over antiplatelet monotherapy, unless indicated for cardiac reasons.[152,153]

2.3.2.2.4. When to prescribe gastric protection medications? There was a substantial reduction in gastrointestinal bleeding when clopidogrel was co-prescribed with a proton pump inhibitor (PPI).[148] However, studies suggest that PPIs, such as omeprazole, may reduce clopidogrel's effectiveness.[149,150] Accordingly, current advice is that in the absence of risk factors, it is reasonable to prescribe clopidogrel without a PPI. However, if the patient has one or more risk factors, they should be prescribed an agent for gastric protection along with clopidogrel. These risk factors include a prior history of gastrointestinal bleeding, older age, *Helicobacter pylori* infection, and concomitant use of aspirin or other non-steroidal anti-inflammatory agents, anticoagulants, selective serotonin re-uptake inhibitors, or

steroids.[151] In these circumstances, one could empirically consider ranitidine as an agent for gastric protection. If a PPI is preferred, then it may be preferable to use pantoprazole, which does not appear to interact with clopidogrel.[150]

Recommendation 22	Class	Level	References
Antiplatelet therapy is recommended in symptomatic patients with 50—99% stenoses not undergoing carotid endarterectomy or carotid stenting. First choice therapy is clopidogrel 75 mg daily or aspirin 75 mg daily plus modified release dipyridamole 200 mg twice daily. If intolerant of dipyridamole or clopidogrel, aspirin monotherapy (75—325 mg) should be used. If aspirin and clopidogrel intolerant, use modified release dipyridamole 200 mg twice daily	I	A	121—124,126,131
Recommendation 23			
It is recommended that all patients undergoing carotid endarterectomy should receive antiplatelet therapy throughout the perioperative period and also in the long term	I	B	140,141
Recommendation 24			
Low-dose aspirin (75—325 mg daily) is recommended rather than higher doses (>625 mg daily) in patients undergoing carotid endarterectomy	I	B	143
Recommendation 25			
Early institution of aspirin + clopidogrel (or aspirin plus modified release dipyridamole) after transient ischaemic attack or minor stroke may be considered to reduce early recurrent events in patients with a >50% carotid stenosis awaiting carotid endarterectomy	IIb	C	125,129,131,132,138
Recommendation 26			
It is recommended that patients undergoing carotid stenting should receive dual antiplatelet therapy with aspirin (75—325 mg daily) and clopidogrel (75 mg daily). Clopidogrel should be started at least 3 days prior to stenting or as a single 300 mg loading dose in urgent cases. Aspirin and clopidogrel should be continued for at least 4 wks after stenting and then optimal long-term secondary preventive antiplatelet therapy should be continued indefinitely	I	B	147
Recommendation 27			
Long-term aspirin plus clopidogrel therapy is not recommended in patients undergoing carotid endarterectomy or carotid stenting unless indicated for cardiac reasons	III	C	152,153
Recommendation 28			
Concurrent gastro-protection treatment or proton pump inhibition with pantoprazole should be considered in patients prescribed clopidogrel who have one or more risk factors that increase the patient's risk of gastrointestinal bleeding (prior history of gastrointestinal bleeding, older age, *Helicobacter pylori* infection, and concomitant use of aspirin, or other non-steroidal anti-inflammatory agents, anticoagulants, selective serotonin re-uptake inhibitors or steroids)	IIa	B	148—151

2.3.2.3. Lipid-lowering therapy. Most of the available data comes from RCTs that included carotid stenosis patients within larger cohorts of patients with vascular disease.

2.3.2.3.1. Statins as tertiary prevention. SPARCL included 4731 patients with a prior TIA/stroke 1—6 months before randomisation, of whom 966 had a median ICA stenosis of 51%.[154] Within 30 days of screening, patients were randomised to 80 mg atorvastatin or placebo. The primary endpoint was time to fatal or non-fatal stroke. Patients with carotid stenoses who were randomised to atorvastatin had a 33% RRR in fatal/non-fatal stroke, as well as a 42% RRR in cardiovascular events.[154] A subgroup analysis from the Heart Protection Study included 3280 patients with a TIA or non-disabling ischaemic stroke[155] who were

randomised to 40 mg of simvastatin daily ($n = 1055$) or placebo ($n = 1052$). The mean interval from the most recent TIA/stroke was 4.3 years and patients were excluded if they had been hospitalised for stroke within 6 months. Simvastatin conferred a 20% RRR in stroke, MI, or vascular death ($p = .001$).

reported by Reiff who observed that preoperative statin therapy was associated with significant reductions in perioperative death/stroke/MI (6.8%) versus 13.9% in those not taking statins pre-CAS (OR 0.31, 95% CI 0.3—0.71, $p = .006$).[166] Finally, Verzini observed that pre-treatment with statins was associated with a significant reduction

Recommendation 29	Class	Level	References
Statin therapy is recommended for the prevention of long-term stroke, myocardial infarction, and other cardiovascular events in patients with symptomatic carotid disease	I	A	36,154,155

2.3.2.3.2. Statins during carotid endarterectomy. Several studies have reported that statin therapy (started preoperatively) was associated with significant reductions in 30-day death/stroke.[156—158] This may be mediated via their pleiotropic effects in reducing inflammation, direct plaque

in 30-day death/stroke, compared with no statin therapy (OR 0.33, 95% CI 0.13—0.80, $p = .016$).[165] Statin usage has not been evaluated in RCTs, but the evidence would suggest that pre-treatment with statins prior to undergoing CAS is desirable.

Recommendation 30	Class	Level	References
It is recommended that patients start statin therapy prior to endarterectomy or stenting and that statins should not be stopped during the perioperative period and should be continued long term	I	B	156—159,162, 164—166

stabilisation, and a general reduction in the inflammatory response to surgery.[159] Interestingly, patients receiving statin therapy prior to CEA may have significantly lower rates of preoperative spontaneous embolisation than those not taking statins.[160] However, in a 2013 Cochrane review on the role of perioperative statin therapy for improving outcomes after "non-cardiac vascular surgery procedures" the findings were inconclusive. This was probably because of the relatively small number of patients who had not been taking statins prior to their operation.[161] In a much larger, multicentre study involving 15,478 patients undergoing a variety of vascular, general surgical, thoracic, gynaecological, and urological procedures, multivariable logistic modelling observed that patients who started statins preoperatively had significant reductions in 30-day myocardial injury, stroke, or death.[162] Patients prescribed statin therapy should not have this medication withdrawn acutely, because this may be associated with significant increases in perioperative cardiovascular morbidity and mortality.[163]

2.3.2.3.3. Statins during carotid artery stenting. As with CEA (Section 2.3.2.3.2), studies have reported that statin therapy started prior to CAS was associated with significant reductions in 30-day risk.[164—166] Groschel reported that 30-day death/stroke/MI risk was significantly lower in CAS patients who were pre-treated with statins (4%), versus 15% in patients who were not on statins (OR 0.23, 95% CI 0.05—0.99, $p = .049$).[164] A similar finding was

2.3.2.4. Treatment of hypertension

2.3.2.4.1. Tertiary prevention in patients with symptomatic carotid stenoses. No RCT has evaluated the role of antihypertensive therapy in patients with symptomatic carotid stenoses. However, a meta-analysis of 13 BP treatment trials in patients with a history of stroke reported a significant RRR in stroke with antihypertensive therapy (34%, 95% CI 15—32).[45] A recent Cochrane review concluded that there was insufficient evidence to support lowering BP during the acute phase of stroke, because there was no improvement in functional outcome.[167] In addition, in recently symptomatic patients with severe bilateral ICA stenoses, aggressive BP lowering before revascularization may not be advisable.[168] However, in patients being considered for early CEA, a balance must be struck. This is because a systolic BP >180 mmHg is an independent predictor for stroke after CEA.[169] Accordingly, it is reasonable to perform an urgent CEA in symptomatic patients whose preoperative BP is <180 mmHg. Symptomatic patients with a preoperative BP >180 mmHg should receive urgent antihypertensive treatment to reduce this to <180 mmHg before proceeding with CEA. Persisting or worsening hypertension after CEA should be actively treated postoperatively, as post-CEA hypertension is associated with an increased risk of hyperperfusion syndrome (HS), intracranial haemorrhage (ICH), bleeding complications, and cardiac events in the early postoperative period.[170] This will be discussed in Section 2.6.1.3.3.

Recommendation 31	Class	Level	References
Antihypertensive treatment is recommended for patients with hypertension and symptomatic extracranial internal carotid artery carotid stenoses to maintain long-term blood pressure <140/90 mmHg	I	A	45,47
Recommendation 32			
Caution should be exercised in significantly reducing blood pressure immediately prior to carotid endarterectomy or stenting in the early period after onset of symptoms, but uncontrolled hypertension (>180/90 mmHg) should be treated	IIa	C	168,169

2.3.2.5. Treatment in diabetic patients. The management of patients with diabetes is the same as for asymptomatic patients (see Section 2.2.1.5).

Recommendation 33	Class	Level	References
In diabetic patients with symptomatic carotid stenoses, strict glycaemic control is recommended	I	C	
Recommendation 34			
In diabetic patients with symptomatic carotid stenoses, the target blood pressure should be <140/85 mmHg	I	B	48

2.3.2.6. Compliance with medical treatment. This subject has been reviewed in Section 2.2.1.6.

2.3.3. Randomised trials comparing endarterectomy with medical therapy. The three most important RCTs comparing CEA with BMT were NASCET, ECST, and the Symptomatic Veterans Affairs Co-operative Study (SVACS) Trial.[9,10,171] The SVACS trial was discontinued following publication of NASCET/ECST in 1991.[171] NASCET randomised 2905 patients who reported symptoms within the preceding 6 months and who had 30—99% carotid stenoses to BMT or CEA (plus BMT). ECST randomised 3024 patients who reported symptoms within the preceding 6 months and who had 0—99% stenoses to BMT or CEA (plus BMT). To standardise stenosis measurement for individual patient meta-analyses, the pre-randomisation angiograms for the 6092 patients randomised within NASCET, ECST, and SVACS were remeasured using the NASCET method (Table 9). CEA (plus BMT) did not prevent stroke in recently symptomatic patients with <50% stenoses. CEA conferred significant benefit in patients with moderate (50—69%) and severe (70—99%) stenoses (Table 9). The benefit conferred by CEA increased with increasing stenosis severity, with the exclusion of "near-occlusion." Patients with chronic near occlusion (defined as a 95—99% stenosis with distal ICA collapse or a narrow calibre lumen with "trickle flow") gained no obvious benefit from CEA.[172,173]

Because of the large number of randomised patients included within ECST, NASCET, and SVACS, it was possible to perform meaningful subgroup analyses to establish who gained greater (lesser) benefit from CEA.[175] The principle findings are summarised in Table 10. Clinical predictors of an increased stroke risk on BMT include

Table 9. Individual patient meta-analysis of the 5-year risk of any stroke (including the perioperative risk) from pooled ESCT, NASCET, and SVACS Trial data.[a]

Stenosis severity (NASCET)	*n* =	5-year risk of any stroke (inc. perioperative)		ARR @5 years	RRR @5 years	NNT to prevent one stroke @5 years	No. of strokes prevented per 1000 CEAs @5 years
		CEA + BMT	BMT alone				
0—30%	1746	18.4%	15.7%	−2.7%	No benefit	No benefit	None
30—49%	1429	22.8%	25.5%	+2.7%	No benefit	No benefit	27
50—69%	1549	20.0%	27.8%	+7.8%	28%	13	78
70—99%	1095	17.1%	32.7%	+15.6%	48%	6	156
Near occlusion	262	22.4%	22.3%	−0.1%	No benefit	No benefit	None

ARR = Absolute Risk Reduction in stroke; RRR = Relative Risk Reduction in stroke;. NNT = number needed to treat to prevent one stroke at 5 years.

[a] Data derived from the Carotid Endarterectomy Trialists Collaboration.[172—174]

Table 10. Clinical and imaging features that were predictive of a significant increase in late stroke in patients with 50–99% stenoses randomised within ECST and NASCET.

Clinical features	Imaging features
Increasing age[172,173,176] 5 y ARR in ipsilateral stroke conferred by CEA <65 y = 5.6%; 65–75 y = 8.6%; >75 y = 19.2%	Irregular vs. smooth plaques[173] 5 y ARR in ipsilateral stroke conferred by CEA smooth = 8%; irregular = 17%
Recency of symptoms[173] 5 y ARR in ipsilateral stroke conferred by CEA <2 wks = 18.5%; 2–4 wks = 9.8%; 4–12 wks = 5.5%; >12 wks = 0.8%	Increasing stenosis severity[172] 5 y ARR in ipsilateral stroke conferred by CEA 50–69% = 4%; 60–69% = 5.9%; 70–79% = 15.8%; 80–99% = 17.7%; 90–99% = 32.4%; near-occlusion = 0.1%
Males vs. females[174] 5 y ARR in ipsilateral stroke conferred by CEA males = 11%; females = 2.8%	Contralateral occlusion[173] 5 y ARR in ipsilateral stroke conferred by CEA Contralateral occlusion = 24%; no occlusion = 13%
Hemispheric vs. ocular symptoms[173] 5 y ARR in ipsilateral stroke conferred by CEA ocular = 5%; TIA = 15%; stroke = 18%	Tandem intracranial disease[178] 3 y risk of ipsilateral stroke in medically treated patients with tandem intracranial disease increased with extracranial ICA stenosis severity 50–69% = 19%; 70–84% = 29%; 85–99% = 45%
Cortical vs. lacunar stroke[177] 3 y ARR in ipsilateral stroke conferred by CEA non-lacunar stroke = 15%; lacunar stroke = 9%	No recruitment of collaterals[179] 2 y ARR in ipsilateral stroke conferred by CEA collaterals recruited = 5%; no recruitment = 19%
Increasing medical comorbidities[10] 2 y risk of ipsilateral stroke on BMT 0–5 comorbidities = 17%; 6 = 23%; 7+ = 39% 2 y risk of ipsilateral stroke with CEA 0–5 comorbidities = 11%; 6 = 6%; 7+ = 8%	

y = year(s).

increasing age, male gender, recent symptoms, a hemispheric TIA/stroke, a cortical stroke, and increasing medical comorbidities. Imaging predictors of an increased risk of stroke on BMT include irregular stenoses, increasing stenosis severity (but not subocclusion), contralateral occlusion, tandem intracranial stenoses, and a failure to recruit intracranial collaterals.

2.3.4. Randomised trials comparing endarterectomy with stenting. Eighteen RCTs (9492 patients) have published outcomes comparing CEA with CAS or carotid angioplasty since 1998. Nine included symptomatic patients only,[180–188] while four randomised asymptomatic patients only.[80,95,97,98] Five RCTs included both symptomatic and asymptomatic patients,[104,189–192] but did not always stratify outcomes for symptom status. Meta-analyses have combined data from all RCTs,[193] or focused on RCTs with >50 patients.[194] Outcomes from the four largest symptomatic RCTs comprise the main evidence base in these guidelines; including the Endarterectomy versus Stenting in patients with Symptomatic Severe carotid Stenosis (EVA-3S), the SPACE trial, the International Carotid Stenting Study (ICSS), and CREST.[184,185,187,189] The RCTs involving symptomatic patients used a 6-month threshold for inclusion.

2.3.4.1. 30-day procedural risks

2.3.4.1.1. Principle outcomes. Table 11 details 30-day risks following CEA and CAS in RCTs that randomised >500 symptomatic patients,[184,185,187,189] while Table 12 summarises

Table 11. 30-day risks following CEA and CAS in trials that randomised >500 recently symptomatic patients into EVA-3S, SPACE, ICSS, and CREST.[184,185,187,189]

30-day risks	EVA-3S[184]		SPACE[185]		ICSS[187]		CREST[189]	
	CEA *n* = 262	CAS *n* = 261	CEA *n* = 589	CAS *n* = 607	CEA *n* = 857	CAS *n* = 853	CEA *n* = 653	CAS *n* = 668
Death	1.2%	0.8%	0.9%	1.0%	0.8%	2.3%		
Any stroke	3.5%	9.2%	6.2%	7.2%	4.1%	7.7%	3.2%	5.5%
Ipsilateral stroke			5.1%	6.4%	3.5%	6.8%		
Disabling stroke	0.4%	2.7%	2.9%	4.1%	2.3%	2.0%	0.9%	1.2%
Death/any stroke	3.9%	9.6%	6.5%	7.4%	4.7%	8.5%	3.2%	6.0%
Disabling stroke/death	1.5%	3.4%	3.8%	5.1%	3.2%	4%		
Clinical MI	0.8%	0.4%			0.5%	0.4%		
Death/stroke/MI					5.2%	8.5%	5.4%	6.7%
Cranial nerve injury	7.7%	1.1%			5.3%	0.1%	5.1%	0.5%

Table 12. Summary of statistically significant findings in the perioperative period from meta-analyses of RCTs comparing CEA with CAS.[a]

30-day outcomes	Symptomatic patients hazard ratio (95% CI)
Any stroke	1.81 (1.40–2.34) favouring CEA[195]
Death/stroke	1.72 (1.29–2.31) favouring CEA[195]
Death/stroke (males)	1.86 (1.19–2.91) favouring CEA[195]
Death/stroke (females)	1.53 (1.02–2.29) favouring CEA[195]
Death/stroke/MI	1.44 (1.15–1.80) favouring CEA[195]
Cranial nerve palsy	0.08 (0.04–0.14) favouring CAS[195]
Myocardial infarction	0.44 (0.23–0.87) favouring CAS[195]
Severe haematoma	0.37 (0.18–0.77) favouring CAS[195]

[a] HR and 95% CIs less than 1.0 favour CAS. HR and 95% CIs greater than 1.0 favour CEA.

statistically significant differences between CEA and CAS in symptomatic patients.

The higher rates of perioperative stroke after CAS were largely a result of higher rates of non-disabling stroke. There was no difference in 30-day death/disabling stroke in symptomatic patients (HR 1.28, 95% CI 0.93–1.77).[195]

2.3.4.1.2. Outcomes stratified for age. A meta-analysis of ICSS, CREST, EVA-3S, and SPACE data in symptomatic patients showed a strong association between increasing age and higher rates of death/stroke after CAS, but not after CEA (Table 13). In CAS patients, the risk increased with age (compared with patients aged <60 years), CAS patients aged >80 years were four times more likely to suffer a procedural stroke/death (OR 4.15, 95% CI 2.20–7.84). In CEA patients, increasing age was not associated with an increased risk of perioperative stroke/death. When CAS was compared with CEA, the age effect started to become apparent in patients aged 60–65, while CEA was clinically superior to CAS in patients aged >70 years (HR 2.09, 95% CI 1.32–2.32).[196] Interestingly, the same finding (no association between age and procedural risk after CEA) was reported by NASCET in 2001.[176]

Table 13. Relationship between age and 30-day rates of death/stroke after CEA and CAS in symptomatic patients randomised within ICSS, CREST, EVA-3S, and SPACE.[196]

	CAS HR (95% CI)[a]	CEA HR (95% CI)[a]	CAS vs. CEA HR (95% CI)[b]
<60 years	1.0[c]	1.0[c]	0.62 (0.31–1.23)
60–64 years	1.79 (0.89–3.60)	1.01 (0.34–1.9)	1.07 (0.56–2.01)
65–69 years	2.16 (1.13–4.13)	0.81 (0.43–1.52)	1.61 (0.90–2.88)
70–74 years	4.01 (2.19–7.32)	1.20 (0.68–2.13)	2.09 (1.32–2.32)
75–79 years	3.94 (2.14–7.28)	1.29 (0.74–2.25)	1.91 (1.21–3.01)
≥80 years	4.15 (2.20–7.84)	1.09 (0.57–2.10)	2.43 (1.35–4.38)

[a] Hazard ratio (95% CI).

[b] Age-based HR calculation for CAS compared with CEA. If HR is <1.0, CAS is associated with lower perioperative death/stroke. If HR is >1.0, CAS is associated with higher rates of perioperative stroke/death.

[c] All HR age-based calculations compared against age <60 years.

2.3.4.2. Long-term outcomes in the randomised trials

2.3.4.2.1. Late ipsilateral stroke. A 2015 meta-analysis reported that CAS was associated with a significantly increased risk of late ipsilateral stroke and/or peri-procedural stroke/death (OR 1.45, 95% CI 1.20–1.75).[194] However, most strokes after CAS occurred in the perioperative period. CREST, ICSS, SPACE, and EVA-3S have now shown that once the 30-day perioperative period has elapsed, late ipsilateral stroke rates are no different between CEA and CAS, that is CAS appears durable after 30 days has elapsed.[185,197–199] Accordingly, the key consideration in deciding whether to recommend CEA or CAS in individual patients will be to identify features which increase or lessen the procedural risk (e.g. recency of symptoms, surgeon/interventionist experience, patient age, plaque length, sequential plaque, heavily calcified plaques, tortuous arteries, overall burden of cardiovascular risk, nature of presenting event, crescendo symptoms, contralateral occlusion, likelihood of overlying thrombus, type III arch, bovine arch, arch atheroma, and (of course) patient preference). For a more detailed review of factors associated with higher procedural risks after CEA and CAS, see Sections 2.6.1.1.3 and 2.6.1.2.2.

2.3.4.2.2. Quality of life. Health Related Quality of life (HRQoL) was assessed among 2502 CREST patients.[200] CAS was associated with better HRQoL in the postoperative period (compared with CEA), especially for physical limitation and pain ($p = .01$). These differences were significant at 4 wks, but not at 1 year. Using disease-specific scales, CAS patients reported fewer problems with driving, eating/swallowing, neck pain, and headaches, but greater difficulty with walking and leg pain ($p < .05$). However, by 1 year, there was no difference in any HRQoL measure. Peri-procedural stroke was associated with poorer 1-year HRQoL scores across all SF-36 domains, while periprocedural MI and CNI were not.

2.3.4.2.3. Survival following perioperative stroke or myocardial infarction. A meta-analysis of seven observational studies and two RCTs (5959 patients) observed that CAS was associated with a significant reduction in ECG diagnosed MI or non-ST elevation MI (NSTEMI) with troponin elevation (OR 0.37, 95% CI 0.22–0.61, $p = .0001$).[201] The significance of perioperative MI (especially NSTEMI with biomarker elevation) has been a source of controversy since its inclusion within the primary endpoint in SAPPHIRE and CREST.[104,189] The rationale for including perioperative MI was because historical studies had suggested that it was associated with poorer long-term survival.[202]

In a CREST subgroup analysis, patients suffering a perioperative MI faced a threefold increase in late mortality (HR 3.4, 95% CI 1.7–6.0, $p = .001$), while patients with biomarker elevation alone faced a near fourfold increase in late death (HR 3.6, 95% CI 1.5–8.7, $p = .023$).[203] However, poorer survival after suffering a perioperative MI must be balanced against the findings of a further subgroup analysis from CREST,[204] which showed that the adjusted risk of

death at 4 years was significantly higher (by a factor of almost three) in patients suffering a perioperative stroke (HR 2.78, 95% CI 1.63—4.76).[204] Meta-analyses confirm the increased risk of peri-operative MI after CEA.[205] However, in a further meta-analysis, Vincent calculated that CAS was associated with a 0.3% absolute reduction in perioperative MI, which was offset by a 1.8% increase in perioperative stroke.[194] Accordingly, long-term survival appears to be similarly reduced in CEA or CAS patients suffering either a perioperative MI or stroke.

An algorithm for managing recently symptomatic patients with carotid disease is presented in Fig. 5.

thought. Contemporary natural history studies report that the incidence of recurrent stroke after the index TIA ranges from 5% to 8% at 48 hours, 4% to 17% at 72 hours, 8% to 22% at 7 days, and 11% to 25% at 14 days (Table 14). Note that recurrent stroke rates at 14 days are similar to those observed at 5 years in patients who were randomised to BMT in ECST, NASCET, and VA, suggesting that many patients destined to suffer an early stroke after onset of symptoms were never randomised within these landmark RCTs.

Few studies have reported risks after CEA, stratified for delay. In a single-centre series involving 475 patients from Leicester, UK, 30-day death/stroke rate was 2.4% when CEA

Recommendation 35	Class	Level	References
Carotid endarterectomy is recommended in patients reporting carotid territory symptoms within the preceding 6 months and who have a 70—99% carotid stenosis, provided the documented procedural death/stroke rate is <6%	I	A	172—174,205
Recommendation 36			
Carotid endarterectomy should be considered in patients reporting carotid territory symptoms within the preceding 6 months and who have a 50—69% carotid stenosis, provided the documented procedural death/stroke rate is <6%	IIa	A	172—174,205
Recommendation 37			
It is recommended that most patients who have suffered carotid territory symptoms within the preceding 6 months and who are aged >70 years and who have 50—99% stenoses should be treated by carotid endarterectomy, rather than carotid stenting	I	A	196
Recommendation 38			
When revascularisation is indicated in patients who have suffered carotid territory symptoms within the preceding 6 months and who are aged <70 years, carotid stenting may be considered an alternative to endarterectomy, provided the documented procedural death/stroke rate is <6%	IIb	A	196
Recommendation 39			
Carotid endarterectomy or carotid stenting are not recommended in symptomatic patients with a chronic internal carotid near-occlusion, unless associated with recurrent ipsilateral symptoms (despite optimal medical therapy) and following multidisciplinary team review	III	C	172

2.3.5. Timing of interventions after onset of symptoms.

There is confusion over the definition of "first event," "index event," and "most recent event".[206] The "first event" is the first symptom to affect the patient. The "index event" is the symptom that led the patient to seek medical advice. The "most recent event" is the symptom that occurred most recently. These terms have been misused in the past[206] and must be interpreted carefully when analysing the literature on the risks/benefits of intervening early.

2.3.5.1. Carotid endarterectomy. CEA has often been delayed because of a perception that this reduces procedural risk.[207] However, there is increasing evidence that CEA confers maximum benefit if performed <14 days,[173,174] and there is compelling evidence that the risk of early, recurrent stroke after TIA onset may be much higher than previously

Table 14. Risk of stroke in the early time period after the index TIA in patients with 50—99% carotid stenoses compared with pooled data from the randomised trials.

	48 hours	72 hours	7 days	14 days	5 years
ECST + NASCET + VA, BMT patients[173]					21%
Fairhead[208]				20%	
Purroy[209]			10%		
Ois[210]		17%	22%	25%	
Bonifati[211]	8%				
Johansson[212]	5%		8%	11%	
Mono[213]		4%			
Merwick[214]			8%		
Marnane[215]	5%	9%	16%		

was performed <48 hours of symptom onset, 1.8% when CEA was performed at 3–7 days, 0.8% where CEA was performed between 8 and 14 days, and 0.7% when CEA was performed after 14 days.[216] An Austrian audit, involving 761 patients, corroborated the Leicester findings, observing that CEA was associated with a 4.4% risk of death/stroke when performed <48 hours of the index symptom, 1.8% when CEA was performed within 3–7 days, 4.4% for operations between 8 and 14 days, and 2.5% when >14 days had elapsed.[217] Only three countries (worldwide) have published national audit data on the effect of delay to CEA on 30-day death/stroke rates after CEA. The principle findings are detailed in Tables 15 and 16.

Only a minority underwent CEA <48 hours (6% Sweden, 3% UK, and 9% Germany). However, a higher proportion underwent CEA <7 days of symptom onset (37% Sweden, 25% UK, and 43% Germany), while 63% underwent CEA within 14 days in Sweden, compared with 52% in the UK and 72% in Germany. The median delay from symptom to undergoing CEA was 12 days in the UK, 9 days in Germany, and 8 days in Sweden.[218–220] Table 16 details 30-day rates of death/stroke in national audits, stratified for delay to surgery.

The paper associated with the most controversy was the 2012 Swedvasc Report, which observed that when CEA was performed <48 hours of the first symptom, 30-day death/stroke was 11.5%.[218] However, only 148 patients underwent CEA during this time period. Thereafter, procedural risks were 3.6% at 3–7 days, 4.0% at 8–14 days, and 5.4% after 14 days had elapsed.[218] By contrast, 30-day death/strokes rates were 3% (Germany) and 3.7% (UK) when CEA was performed <48 hours of symptom onset.[219,220] After 48 hours had elapsed, each of the national audits showed that CEA could be performed within 3–7 days and 14 days with low procedural risks.[218–220]

2.3.5.2. Carotid artery stenting. Performing CAS in the early time period after symptom onset is controversial and the literature contains conflicting data. A pooled series from four industry-sponsored registries ($n = 2104$) reported higher 30-day stroke rates (8.8%) when CAS was performed <14 days, compared with 5.9% when CAS was performed >14 days.[221] A doubling of stroke risk was also reported in the CAPTURE Registry ($n = 3500$) when CAS was performed <14 days of symptom onset.[223]

The Carotid Stenosis Trialists' Collaboration (CSTC) has published an individual patient meta-analysis involving 4138 symptomatic patients who were randomised to CEA or CAS within the four major multicentre RCTs (CREST, ICSS, EVA-3S, and SPACE).[224] Only a relative minority underwent CEA (11%) or CAS (14%) <48 hours of symptom onset. Among patients who were treated within 7 days of symptom onset, those treated by CAS were significantly more likely to suffer an adverse outcome (30-day death/stroke, 30-day any stroke, 30-day fatal or disabling stroke), compared with CEA (Table 17). The 30-day rate of death/stroke when CAS was performed within 7 days of symptom onset was 9.4%, versus 3.8% after CEA (OR 3.4 (95%CI 1.01–11.8). The CSTC concluded that for patients undergoing a carotid intervention within 7 days of symptom onset, CEA was significantly safer than CAS.[224] In an earlier individual patient meta-analysis of procedural risks in recently symptomatic patients randomised within EVA-3S, SPACE, and ICSS, patients undergoing CAS within 8–14 days of the most recent symptom incurred significantly higher 30-day death/stroke rates (8.1) versus 3.4% after CEA ($p = .04$).[225]

Very few CAS studies have published 30-day death/stroke rates stratified for delays from most recent symptom to undergoing CAS. Those that have published are summarised in Table 18. There are no data relating to outcomes after CAS using proximal flow reversal in large cohorts of recently symptomatic patients, especially in the first 7 days after symptom onset.

However, surgeons/interventionists participating in the RCTs were credentialed and may not represent "real world" practice. In a recent systematic review, Paraskevas observed that 72% of administrative dataset registries reported 30-day death/stroke rates in excess of the 6% threshold after CAS, while 28% reported stroke rates in excess of 10%.[70] Given that the term "recently symptomatic" includes any patient undergoing CAS/CEA <6 months

Table 15. Proportion of patients undergoing CEA in national audits within 0–2, 3–7, 8–14, and >15 days after onset of symptoms.

National Audit	0–2 days	3–7 days	8–14 days	≥15 days
Sweden[218] $n = 2596$	148/2596 (6%)	804/2596 (31%)	677/2596 (26%)	967/2596 (37%)
UK[219] $n = 23,235$	780/23,235 (3%)	5126/23,235 (22%)	6292/23,235 (27%)	11,037/23,235 (48%)
Germany[220] $n = 56,279$	5198/56,279 (9%)	19,117/56,279 (34%)	16,205/56,279 (29%)	15,759/56,279 (28%)

Table 16. 30-day death/stroke risks after CEA, stratified for delay from symptom onset to CEA in national audits of practice.

National Audit	0–2 days % (95% CI)	3–7 days % (95% CI)	8–14 days % (95% CI)	≥15 days % (95% CI)
Sweden[218] $n = 2596$	17/148 11.5% (6.8–17.8)	29/804 3.6% (2.4–5.1)	27/677 4.0% (2.6–5.8)	52/967 5.4% (4.0–7.0)
UK[219] $n = 23,235$	29/780 3.7% (2.5–5.3)	128/5126 2.5% (2.1–3.0)	132/6292 2.1% (1.8–2.5)	254/11,037 2.3% (2.0–2.6)
Germany[220] $n = 56,279$	157/5198 3.0% (2.6–3.5)	480/19,117 2.5% (2.3–2.7)	427/16,205 2.6% (2.4–2.9)	370/15,759 2.3% (2.1–2.6)

Table 17. 30-day outcomes following CEA and CAS, stratified for timing of the carotid intervention after symptom onset in a pooled meta-analysis of symptomatic patients randomised within CREST, ICSS, EVA-3S, and SPACE.[a]

	30-day outcomes		OR (95% CI)	$p =$
	CEA	CAS		
Any stroke/death				
<7 days	3/226 (1.3%)	24/287 (8.4%)	6.51 (2.00—21.21)	.002
>7 days	65/1819 (3.6%)	129/1806 (7.1%)	2.00 (1.49—2.67)	<.0001
Any stroke				
<7 days	3/226 (1.3%)	23/287 (8.0%)	6.27 (1.92—20.44)	.002
>7 days	62/1819 (3.4%)	122/1806 (6.8%)	1.98 (1.47—2.67)	<.0001
Fatal/disabling stroke				
<7 days	1/226 (0.4%)	9/287 (3.1%)	8.29 (1.07—64.28)	.04
>7 days	26/1819 (1.4%)	46/1806 (2.5%)	1.77 (1.10—2.85)	.02

[a] Based on data derived from Rantner et al.[224]

Table 18. 30-day death stroke risks following CAS, stratified for time from index symptom to intervention.

	0—2 days	3—7 days	8—14 days	>14 days
Setacci 2010[226]	1/26 (4.0%)			
Moratto 2012[227]	3/78 (3.8%)			
Al-Mubarak 1999[228]		3/44 (6.8%)		
Wach 2014[229]	5/70 (7.1%)	4/88 (4.5%)	1/36 (2.8%)	1/27 (3.7%)
SwedVasc 2015[230]	0/13 (0.0%)	4/85 (4.7%)	5/80 (6.3%)	6/145 (4.1%)

of symptom onset, this would suggest that the majority of patients undergoing carotid interventions within the first 7—14-day period in "real world" practice would probably be better treated by CEA.

However, in selected patients with an area of infarction involving less than one-third of the MCA territory, emergency CEA can be performed with 2—8% rates of death/stroke for stroke-in-evolution and 0—2% for crescendo TIAs.[235—237] These results compare favourably with the otherwise poor natural history of these conditions.

There are no RCT data for determining whether intravenous heparin administration is superior to antiplatelet therapy in preventing early recurrent stroke in patients with stroke in evolution or crescendo TIAs. In a series of 144 patients suffering a non-disabling stroke and who had a 50—99% stenosis and TCD evidence of embolisation, spontaneous embolisation rates were diminished in patients started on antiplatelet therapy, but not in those receiving heparin.[238] In two RCTs, comparing low molecular weight heparin (LMWH) versus aspirin monotherapy in acute stroke patients where antiplatelet/antithrombotic therapy was commenced within 48 hours of symptom onset, there was

Recommendation 40	Class	Level	References
When revascularisation is considered appropriate in symptomatic patients with 50—99% stenoses, it is recommended that this be performed as soon as possible, preferably within 14 days of symptom onset	I	A	172,173
Recommendation 41			
Patients who are to undergo revascularisation within the first 14 days after onset of symptoms should undergo carotid endarterectomy, rather than carotid stenting	I	A	224,225

2.3.5.3. Intervening in neurologically unstable patients. It is necessary to delay CEA in patients suffering a disabling stroke, as they face a higher risk of haemorrhagic transformation of an infarct or ICH.[231,232] Patients with a significant neurological deficit (modified Rankin ≥3), with an area of infarction exceeding one-third of the MCA territory and those who have altered consciousness should not undergo CEA until significant neurological improvement has occurred.

CEA in neurologically unstable patients (stroke-in-evolution, crescendo TIAs) carries a higher than average procedural risk.[233] A meta-analysis has reported that stroke/death rates after CEA were 20.2% (95% CI 12.0—28.4) in patients undergoing CEA for stroke in evolution and 11.4% (95% CI 6.1—16.7) in patients undergoing CEA for crescendo TIAs.[234] no compelling evidence that LWMH conferred any significant benefit over aspirin.[239,240] However, in a *post-hoc* analysis looking specifically at the prevalence of neurologic deterioration at 10 days, LMWH was associated with a significant reduction in ischaemic stroke progression (5%), compared with aspirin (12.7%), (OR 0.36, 95% CI 0.16—0.81), without an excess risk of cerebral haemorrhage.[241]

Other therapeutic strategies that might reduce spontaneous microembolisation in patients with recurrent TIAs or crescendo TIAs include TCD titrated intravenous dextran therapy[242] or tirofiban (intravenous glycoprotein IIb/IIa receptor antagonist).[243] Batchelder et al. showed that early institution of aspirin and clopidogrel (once parenchymal haemorrhage was excluded on CT/MRI) was associated with

significant reductions in spontaneous embolisation (21% down to 5%, OR 0.20, 95% CI 0.06—0.66, $p = .0047$) and a significant reduction in recurrent events prior to CEA, (13% down to 3%, OR 0.20, 95% CI 0.06—0.66, $p = .01$).[132]

In the absence of quality evidence, it would seem reasonable to offer heparin (plus aspirin) or dual antiplatelet therapy in patients with recurrent TIAs or crescendo TIAs prior to urgent CEA.

Recommendation 42	Class	Level	References
Revascularisation should be deferred in patients with 50—99% stenoses who suffer a disabling stroke (modified Rankin score ≥3), whose area of infarction exceeds one-third of the ipsilateral middle cerebral artery territory, or who have altered consciousness/drowsiness, to minimise the risks of postoperative parenchymal haemorrhage	I	C	231,232
Recommendation 43			
Patients with 50—99% stenoses who present with stroke-in-evolution or crescendo transient ischaemic attacks should be considered for urgent carotid endarterectomy, preferably <24 hours	IIa	C	233—237

2.3.6. Timing of carotid interventions after intravenous thrombolysis. An important concern when performing CAS/CEA after intravenous thrombolysis (IVT) is an increased risk of ICH following reperfusion of ischaemic cerebral tissue. A review of 13 series (361 patients), observed that the 30-day death/stroke rate was 3.6%, while the prevalence of ICH was 2.5%.[244] These outcomes were not significantly different to historical series (where thrombolysis was not used), suggesting publication bias. To achieve such low procedural risks, strict selection criteria for early CEA should be followed. These include (1) rapid neurological recovery of the patient after IVT (modified Rankin 0—2); (2) area of infarction less than one-third of the MCA territory; (3) recanalisation of a previously occluded MCA mainstem; (4) ICA stenosis 50—99%; and (5) no evidence of parenchymal haemorrhage or significant brain oedema.[244—246] Careful postoperative BP monitoring is mandatory[170] (Section 2.6.1.3.3). Contraindications to early CEA after IVT include (1) severe persistent neurological deficit (modified Rankin score ≥3); (2) anticipated high surgical risk; and (3) the presence of parenchymal haemorrhage and previous radical neck dissection or radiotherapy.[244] Given these strict selection criteria and contraindications, only 2—6% of patients undergoing acute IVT may be eligible for CEA.[245,247]

The optimal timing of CEA after IVT remains unknown, but antiplatelet and heparin therapy should be withheld for 24 hours after cessation of IVT[247] because of the heightened risk of haemorrhagic complications during this time period. The literature review observed delays ranging from 48 hours to 8 days, with one small study reporting higher rates of ICH if CEA was performed within 72 hours of IVT completion.[248] The largest published series (202 cases) reported 30-day death/stroke rates of 3.4% among patients who underwent CEA <14 days of IVT, compared with 5.1% in those undergoing CEA <7 days.[249] It is essential, however, that CEA patients who undergo treatment within a few days of completing IVT are monitored carefully and treated actively for post-CEA hypertension (Section 2.6.1.3.3).[170]

Only one study (involving six patients) has reported outcomes following early CAS after IVT.[250]

Recommendation 44	Class	Level	References
Early carotid endarterectomy (within 14 days) should be considered after intravenous thrombolysis in symptomatic patients if they make a rapid neurological recovery (Rankin 0—2), the area of infarction is less than one-third of the ipsilateral middle cerebral artery territory, a previously occluded middle cerebral artery mainstem has recanalised, there is a 50—99% carotid stenosis and no evidence of parenchymal haemorrhage or significant brain oedema	IIa	C	244—246
Recommendation 45			
It is recommended that intravenous heparin and antiplatelet therapy be withheld for 24 hours after completion of intravenous thrombolysis, but antiplatelet therapy should then be commenced before any carotid intervention is undertaken	I	C	247
Recommendation 46			
It is recommended that patients undergoing early carotid interventions after thrombolysis should have post-interventional hypertension actively treated to reduce the risks of parenchymal haemorrhage	I	C	244

2.3.7. Timing of carotid interventions after intracranial endovascular therapies. A meta-analysis of five randomised trials reported that emergency endovascular treatment of acute ischaemic stroke (mechanical thrombectomy [stent retrieval] and/or intra-arterial thrombolysis) was associated with a twofold improvement in functional outcome, compared with patients randomised to BMT. Interestingly, endovascular therapy was not associated with reduced mortality or an increased risk of symptomatic intracerebral haemorrhage.[251] A proportion of patients undergoing an emergency intracranial endovascular intervention will be found to have a significant extracranial ICA stenosis. There are currently no data to guide clinicians as to whether adjuvant CEA or CAS should be performed as a synchronous or staged intervention in these patients, but neuro-interventionists were advised not to "routinely" perform CAS at the time of mechanical thrombectomy in the ESCAPE trial.[252] In the Multicentre Randomised Clinical Trial of Ischaemic Stroke in the Netherlands (Mr CLEAN) study, 13% of patients underwent stent retrieval plus simultaneous CAS, but no data were provided about whether this strategy was associated with higher or lower procedural risks.[253]

2.3.8. Is there a subgroup with <50% stenosis who might benefit from surgery? An individual patient meta-analysis of symptomatic patients with <50% stenoses who were randomised within ECST, NASCET, and the VA trials[172,173] showed that CEA conferred no benefit over BMT (Section 2.3.3). The 5-year risk of stroke in 1746 patients with <30% stenoses who were randomised to CEA was 18.4%, compared with 15.7% on BMT. The 5-year risk of stroke in 1429 patients with 30—49% stenoses who were randomised to CEA was 22.8%, compared with 25.5% on BMT.[173] However, a small cohort of patients with <50% stenoses will still continue to suffer recurrent symptoms (despite BMT). In a recent review of outcomes in previously symptomatic patients with 20—49% stenoses at baseline, the risk of recurrent ipsilateral stroke at 3 years was 7.4%.[254]

In patients with <50% stenoses who report recurrent symptoms, it is important to ensure that medical treatment really has been optimised and that no other cause for the recurrent TIAs can be identified. If symptoms persist, despite optimal medical therapy, it may be reasonable to consider CEA/CAS, but this should not be undertaken without independent neurologist or stroke physician review.

Recommendation 47	Class	Level	References
Carotid endarterectomy or carotid stenting may be considered in recently symptomatic patients with <50% stenoses if they suffer recurrent symptoms despite best medical therapy and following multidisciplinary team review	IIb	C	

2.3.9. "High-risk for surgery" symptomatic patients. In patients considered high-risk for mortality/morbidity after CEA, CAS has been proposed as an alternative. "High-risk for CEA" is generally defined as anatomical and/or clinical factors that have the potential to increase complications following CEA, ranging from death, stroke, through to cranial nerve injury (CNI). The concept of "high-risk" is, however, open to misuse. This is because being "high-risk for CEA" can occasionally be misinterpreted as being "high-risk for stroke."[255] Criteria that are currently used to define a patient as being "high-risk for CEA" are based on those adopted by SAPPHIRE.[104] SAPPHIRE advised that the patient should have carotid territory symptoms within the preceding 180 days and have a 50—99% stenosis, plus at least one of the following: clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open-heart surgery); severe pulmonary disease; contralateral carotid occlusion; contralateral laryngeal-nerve palsy; previous radical neck surgery, cervical radiation therapy; recurrent stenosis after CEA; and age >80 years. While severe cardiac or pulmonary artery disease might increase the risk of CEA and the presence of a contralateral recurrent laryngeal nerve palsy is an accepted contraindication to CEA, the validity of certain "high-risk for CEA" criteria are open to debate. In addition, no RCT has evaluated whether CEA under locoregional anaesthesia is equivalent to (or safer) than CAS in symptomatic patients with severe cardiac or pulmonary disease.

2.3.9.1. Age. Age >80 is often cited as a "high-risk for CEA" criterion. However, meta-analyses of data from symptomatic patients in ICSS, CREST, EVA-3S, and SPACE[196] showed that increasing age (especially ≥70) was associated with increased stroke risks after CAS, but not CEA (Section 2.3.4.1.2). Possible explanations for the higher stroke rates after CAS in older patients include increased atherosclerotic burden, increased aortic arch calcification and wall disease, changes in vascular anatomy, and increasing carotid plaque vulnerability.[256]

2.3.9.2. Radiation therapy. Previous cervical radiation therapy is often cited as being associated with poorer outcomes after CEA. However, in a systematic review of 27 studies (533 patients) who underwent CAS ($n = 361$) or CEA ($n = 172$), the perioperative risk for "any cerebrovascular adverse event" was 3.9% (95% CI 2.3%—6.7%) following CAS versus 3.5% (95% CI 1.5%—8.0%) after CEA ($p = .77$).[257] However, the risk of temporary CNI after CEA was 9.2% (95% CI 3.7%—21.1%) versus none after CAS. After the perioperative period, recurrent TIA/stroke was significantly more common after CAS (4.9/100 person years) versus 2.8/100 person years after CEA ($p = .014$). In addition, restenosis >50% was significantly more common after CAS ($p < .003$).

2.3.9.3. Restenosis after carotid endarterectomy. A meta-analysis of observational patient data observed that in

patients with restenosis after CEA, CAS was not superior to redo CEA regarding perioperative stroke/death rate or further restenosis.[258] Thirteen studies involving 1132 patients who were treated by CAS ($n = 653$) or redo CEA ($n = 479$) reported that perioperative death/stroke did not differ between CAS and redo CEA (2.3% vs. 2.7%, OR 0.8, 95% CI 0.4—1.8). The risk of developing a second restenosis (median follow-up 13 months) was similar for both groups (HR 1.4, 95% CI 0.9—2.2). The prevalence of CNI was 5.5% after redo CEA, but the rate of permanent CNI was less than 1%. Restenosis after CEA is discussed in greater detail in Section 2.6.2.2.

Recommendation 48	Class	Level	References
In recently symptomatic patients with 50—99% stenoses and anatomical and/or medical comorbidities that are considered by the multidisciplinary team to make them "higher-risk for carotid endarterectomy," carotid stenting should be considered as an alternative to endarterectomy, provided the documented procedural death/stroke rate is <6%	IIa	B	104,105,189,198

2.3.9.4. "High-risk" criteria in population studies. The Centre for Medicare and Medicaid Services (CMS) defines physiologic high-risk variables as age >80 years, New York Heart Association class III, CCF, left ventricular ejection fraction <30%, unstable angina, MI ≤30 days, contralateral ICA occlusion, recent coronary artery bypass grafting or valve repair, and haemodialysis. Anatomical risk factors include contralateral laryngeal nerve palsy, restenosis after CEA, a history of cervical radiotherapy, high or low placed carotid lesions, and previous neck surgery.[259]

Symptomatic "high-risk" patients had a 9.1% risk of death/stroke or MI following CAS vs. 7.3% after CEA (OR 1.3, 95% CI 0.95—1.73, $p = .11$). Among CEA patients, age >80 (OR 1.4, 95% CI 1.02—1.8), congestive heart failure (OR 1.7, 95% CI 1.03—2.8), ejection fraction <30% (OR 3.5, 95% CI 1.6—7.7), angina (OR 3.9, 95% CI 1.6—9.9), contralateral occlusion (OR 3.2, 95% CI 2.1—4.7), and high anatomic lesions (OR 2.7, 95% CI 1.33—5.6) predicted an increased risk of perioperative stroke, MI, or death. The authors observed that while certain CMS "high-risk" criteria could identify patients at higher-risk for suffering adverse events after CEA, some "high-risk" criteria were more important than others. They concluded that CEA appeared safer than CAS for the majority of "high-risk for CEA" patients, while the benefits for CAS appeared to be limited to patients with restenosis and prior radiation therapy.[260]

The Vascular Study Group of New England (VSGNE) performed a multivariate analysis, which showed that independent risk factors for an increased risk of stroke, MI, or death at 1 year in CEA patients included increasing age, preadmission residence in a nursing home, CHF, diabetes, chronic pulmonary disease, any prior history of cerebrovascular disease, and contralateral ICA occlusion. Three SAPPHIRE criteria (abnormal stress test, restenosis after CEA, and history of radiotherapy) were not associated with an increased late risk.[261] These conflicting data, therefore, suggest that there is still no consensus regarding what constitutes being "high-risk for CEA." SAPPHIRE criteria should not be used uncritically to exclude symptomatic patients from CEA. Management decisions must be made on an individual patient basis, based on patient comorbidities, anatomical features, and the experience of CAS practitioners locally.

2.4. Carotid surgical techniques

2.4.1. Carotid endarterectomy

2.4.1.1. Preoperative checklist. The surgeon should ensure that the answers to a number of key questions are documented in the patient's case notes before performing CEA.[262] The aim is to minimise avoidable morbidity/mortality and to lessen the risk of medico-legal censure. Questions to be answered include: Has the indication for surgery been documented? Are there atypical symptoms that require further investigation? Is the degree of stenosis appropriate for recommending CEA? Have the procedural risks quoted to the patient been documented? Is the patient receiving optimal BMT? Is high carotid disease anticipated? Are there any pre-existing CNIs? Has the operative side been marked with an indelible pen?

Of these, four are particularly important. First, did the surgeon quote his/her own perioperative risks to the patient during the consent process, rather than using outcome data from RCTs? Second, if the patient has previously undergone carotid surgery (especially to the contralateral side), a total/partial thyroidectomy, or radical neck surgery, it is essential that the patient undergoes indirect laryngoscopy to ensure there is no evidence of a contralateral vocal cord palsy. Bilateral recurrent laryngeal nerve palsies can be fatal (as can bilateral hypoglossal nerve palsies). If a contralateral vocal cord palsy is identified, the reason for performing CEA should be urgently reviewed. If the patient was asymptomatic, the procedure should be cancelled and CAS considered as an alternative. If the patient was recently symptomatic, then CAS should still be considered. If it is not possible to perform CAS and the indication for intervening remains compelling, the patient should be warned about the consequences of bilateral recurrent laryngeal nerve palsies (permanent tracheostomy) and an Ear, Nose, and Throat (ENT) surgeon should be present at the time of extubation. In addition, the surgeon should not use a retrograde approach to the bifurcation, as this is associated with a significantly higher risk of recurrent laryngeal nerve injury (Section 2.4.1.6). Third, it is important to ensure that

the patient is receiving appropriate antiplatelet and statin therapy and that systolic BPs >180 mmHg have been excluded (Section 2.3.2.4.1). Finally, it is essential that the surgeon anticipates the likelihood of having to mobilise the upper ICA. If this is anticipated, the surgeon should take steps to ensure that this can be achieved safely. For less experienced surgeons, it might be appropriate to ask a more experienced colleague to either assist or take over the case. Alternatively, it may be necessary to plan for a more complicated exposure technique (Section 2.4.1.14). The risks associated with dissection of the upper ICA are higher (especially CNI) and this needs to have been discussed with the patient beforehand.

2.4.1.2. Staged or synchronous bilateral carotid interventions. A proportion of patients will present with bilateral 70—99% stenoses. Almost all will be either totally asymptomatic, or have one stenosis symptomatic and the other asymptomatic. It is extremely rare for bilateral severe ICA stenoses to be symptomatic, either simultaneously or within a short period of each other. The question arises whether synchronous bilateral CEAs should ever be considered. While it is feasible to undertake bilateral synchronous CEAs,[263] the most dangerous complication is inadvertent injury to both recurrent laryngeal and/or hypoglossal nerves, which can be fatal. Accordingly, if bilateral (synchronous) revascularisation is deemed absolutely necessary, it may be better to consider bilateral CAS. For most patients, however, staged bilateral CEAs would seem more appropriate, especially in the patient with a symptomatic 50—99% stenosis on one side and an asymptomatic 70—99% stenosis on the other.

2.4.1.3. General versus locoregional anaesthesia. A meta-analysis of 41 non-randomised studies (25,000 CEAs) reported that CEA under locoregional anaesthesia (LRA) was associated with a 40% RRR in 30-day death/stroke, compared with CEA under general anaesthesia (GA), as well as significant reductions in MI and respiratory complications.[264] The General Anaesthesia Local Anaesthesia (GALA) trial (3526 patients) is the largest RCT to date and reported no significant difference regarding perioperative death, stroke, or MI between GA (4.8%) and LRA (4.5%).[265] An updated Cochrane review,[266] which combined data from 14 RCTs (4596 patients), showed that CEA under LRA did not confer significant reductions in 30-day stroke (3.2%), compared with CEA under GA (3.5%).

Most studies on CEA under LRA include patients on aspirin monotherapy. However, with the increasing use of DAPT (especially in the early time period after onset of symptoms), there are concerns about haematoma formation. In a systematic review of 69 studies (n = 10,081 patients), combined deep and superficial cervical plexus blockade was associated with a significantly higher risk of major complications (OR 2.13, p = .006), when compared with superficial/intermediate blockade.[267] However, the "major complications" were inadvertent intravascular injection and respiratory failure/distress secondary to phrenic nerve and/or recurrent laryngeal nerve paralysis. There was no specific mention as to whether deep cervical plexus blockade was associated with an increased risk of haematoma formation. In UK guidelines on LRA in patients with coagulation abnormalities, there was no mention about any adverse effect relating to DAPT and no specific mention about whether it was safe to undertake deep cervical plexus blockade in CEA patients.[268] Moreover, guidelines published by the American Society of Regional Anesthesia refer mainly to spinal/epidural anaesthesia (with no reference to deep cervical plexus blockade) and they provide no advice regarding DAPT. In most clinical situations, the guidelines recommended cessation of antiplatelet therapy (especially clopidogrel) wherever possible.[269]

Accordingly, there are no published data on whether it is safe to perform deep cervical plexus blockade in CEA patients on DAPT.[270] With the likelihood that an increasing proportion of recently symptomatic patients will undergo CEA, while on DAPT, surgeons and anaesthetists who choose to perform CEA under LRA must establish local protocols regarding perioperative antiplatelet strategies and choice of anaesthesia. It would, however, be inappropriate to stop clopidogrel and delay CEA for 7—10 days, as this will increase the likelihood of the patient suffering an early recurrent embolic stroke (Section 2.3.5). Intraoperative ultrasound may enable safer infiltration of local anaesthetic, as it permits visualisation of the cervical transverse processes and VA.

Recommendation 49	Class	Level	References
It is recommended that choice of anaesthesia for carotid endarterectomy (general versus locoregional) be left to the surgical team's discretion	I	A	264—266

2.4.1.4. Volume outcome relationship. A meta-analysis of 25 studies (>900,000 CEAs, mainly from the USA) found a significant relationship between CEA in higher-volume centres and lower rates of 30-day death, stroke, and death/stroke, with a critical threshold of 79 cases per year per unit.[271] In another study, analysing outcomes following 18,248 CEAs in England, there was also a significant volume outcome relationship favouring higher-volume centres, with respect to lower mortality and reduced length of stay.[272] In the latter meta-analysis, the critical threshold was 35 CEAs per centre, per year. The most likely explanation for the difference between 35

CEAs per year in the UK analysis and 79 in the previous meta-analysis is probably because about 85% of CEAs in the UK are undertaken in symptomatic patients (associated with higher procedural risks), while the former meta-analysis will have included a greater proportion of asymptomatic patients (associated with lower procedural risks).

AbuRahma analysed the effect of surgeon volume on 30-day stroke/death in 953 CEAs. High-volume surgeons (>30 CEAs per year) had significantly lower 30-day stroke/death rates, compared with lower-volume surgeons. Death/stroke was significantly higher in non-vascular surgeons (general/cardiac surgeons vs. vascular surgeons) in asymptomatic patients (3.2% vs. 0.72%).[273] In a meta-analysis looking at outcomes stratified by hospital and surgeon volume, seven out of nine studies showed a significant inverse relationship for individual surgeon volume,[274] while seven out of eight studies reported that specialist vascular training was associated with significantly lower death/stroke rates after CEA, compared with general, cardiac and neurosurgical specialties, but only for lower volume surgeons. For high-volume surgeons, surgical specialty had no impact on outcome.[274]

2.4.1.5. Transverse or longitudinal incision? The traditional approach to the bifurcation is via a longitudinal anterior sternomastoid incision. Alternatively, CEA can be performed via a transverse incision, guided by preoperative DUS marking of the bifurcation. Bastounis reported that transverse incisions gave better cosmetic results with fewer CNIs.[275] By contrast, Marcucci reported no difference in the prevalence of CNI and commented that it was more difficult to insert a shunt if a transverse incision was used.[276] Ascher proposed a modified approach where DUS was used to identify the bifurcation and a smaller longitudinal incision then made, which can be extended as required. This significantly reduced incision length, and offered good cosmesis, with no excess CNI risk.[277] Surgeons can, therefore, use whichever incision they prefer. If DUS suggests that the bifurcation is not too high and there is a focal stenosis, a transverse skin crease incision will probably give the best cosmetic result. If, however, there is any question about the bifurcation being high, or if the lesion is extensive, a longitudinal incision remains preferable.

2.4.1.6. Antegrade versus retrojugular exposure. Retrojugular exposure avoids mobilising the hypoglossal nerve and may be associated with shorter operating times and may optimise access to the upper ICA. A retrojugular approach facilitates access to the upper ICA by sweeping anteriorly structures such as the sternocleidomastoid artery, hypoglossal nerve, and ansa cervicalis.[278] A meta-analysis of four non-randomised trials and two RCTs (740 CEAs) found no evidence that retrojugular (versus antegrade) exposure was associated with reductions in perioperative death (0.6% vs. 0.5%) or stroke (0.9% vs. 0.7%). However, the retrojugular approach was associated with significantly higher rates of recurrent laryngeal nerve palsy (8.1% vs. 2.2%), with no evidence of reduced rates of hypoglossal nerve injury (1.3% vs. 1.3%).[279]

Recommendation 50	Class	Level	References
The choice of carotid exposure (antegrade/retrojugular) should be left to the discretion of the operating surgeon	I	B	279

2.4.1.7. Carotid sinus nerve blockade. The rationale that routine carotid sinus nerve (CSN) blockade reduces haemodynamic instability during/after CEA, was not supported by a meta-analysis of four RCTs, which reported no evidence that CSN blockade reduced hypotension, hypertension, or arrhythmias after CEA.[280]

Recommendation 51	Class	Level	References
Routine carotid sinus nerve blockade is not recommended as there is no evidence it reduces the prevalence of perioperative hypotension, hypertension, and arrhythmias	III	A	280

2.4.1.8. Anticoagulation and protamine reversal. In an ECST subgroup analysis, "no heparin" administration prior to carotid clamping was associated with a significant increase in perioperative stroke.[169] There has been much controversy about whether it is safe to reverse heparin (using protamine), the concern being that any reduction in neck haematomas might be offset by a higher risk of postoperative thrombotic stroke. Only one, small RCT addressed this question, but was abandoned after recruiting only 64 patients because two patients randomised to protamine suffered a stroke because of early thrombosis.[282]

The proportion of US surgeons using protamine increased from 43% in 2003 to 62% by 2010 and the VSGNE Registry (10,059 CEAs) reported that heparin reversal with protamine was associated with significant reductions in re-exploration for neck haematoma (0.6% vs. 1.4%; $p = .001$), without any increase in perioperative stroke/death (1.1% vs. 1.0%) or perioperative MI (1% vs. 1.2%).[283] A similar finding was

made in a *post-hoc* analysis of 2107 CEA patients randomised within the GALA trial.[284] A systematic review and meta-analysis of outcomes in 3817 CEA patients receiving protamine and 6070 CEA patients not receiving protamine observed that protamine administration was associated with a significant reduction in the prevalence of neck haematoma requiring re-exploration (OR 0.42, 95% CI 0.22—0.8, $p = .008$) and no evidence that protamine was associated with an increased risk of perioperative stroke (OR 0.71, 95% CI 0.49—1.03, $p = .07$).[285]

Recommendation 52	Class	Level	References
Protamine reversal of heparin should be considered to prevent neck haematomas requiring re-exploration	IIa	B	283—285

2.4.1.9. Shunting: routine, never, selective? Temporary interruption of cerebral perfusion during carotid clamping can cause haemodynamic neurological deficits, which can be avoided by shunt insertion. Surgeons tend to be "routine," "selective," or "never" shunters, usually based on their training. There is a paucity of quality data for guiding practice.[281] While there are various methods for monitoring cerebral perfusion during carotid clamping (electroencephalography [EEG], stump pressure, back flow, TCD), the only modality that is 100% reliable is the patient's neurological status when CEA is performed under LRA. A Cochrane review of six RCTs (1270 CEAs) concluded that (based on poor quality data) no meaningful recommendations could be made regarding routine, selective, or never shunting.[286] Bennett evaluated 2081 CEA patients from the National Surgical Quality Improvement Programme (NSQIP) database (1368 without and 713 with a shunt) and found no differences regarding perioperative TIA/stroke (1.7% without vs. 2.4% with shunt).[287]

Recommendation 53	Class	Level	References
It is recommended that the choice of shunting (routine, selective, never) be left to the discretion of the operating surgeon	I	C	286

2.4.1.10. Carotid patching: routine, never, selective? Surgeons tend to be "routine," "selective," or "never" patchers. A meta-analysis of 10 RCTs (2157 patients), comparing routine patching with routine primary closure, observed that (i) routine patching was associated with significant reductions in perioperative ipsilateral stroke (patch 1.5% vs. 4.5% primary closure; OR 0.31, 95% CI 0.15—0.63, $p = .001$); (iii) routine patching was associated with significant reductions in 30-day ICA thrombosis (0.5% patch vs. 3.1% primary closure; OR 0.18, 95% CI 0.08—0.41, $p < .0011$); (iii) patients randomised to primary closure were three times more likely to return to theatre within 30 days (3.1% primary closure vs. 1.1% patched; OR 2.9, 95% CI 1.3—6.3, $p = .01$); (iv) there was no significant difference between routine patching and routine primary closure regarding perioperative death, fatal stroke, death/stroke, and CNI; and (v) patch type (polyester, polytetrafluoroethylene (PTFE), autologous vein, bovine pericardium) did not influence early outcomes.[288,289] Vein patch rupture is an extremely rare complication and is more likely if smaller calibre saphenous veins have been harvested from the ankle.[290]

With regard to long-term outcomes, routine patching (versus routine primary closure) was associated with significant reductions in (i) late ipsilateral stroke (1.6% patch vs. 4.8% primary closure; OR 0.3, 95% CI 0.2—0.6, $p = .001$); (ii) any stroke (2.4% patch vs. 4.6% primary closure; OR 0.49, 95% CI 0.3—0.9, $p = .002$); and (iii) restenosis (4.3% patch vs. 13.8% primary closure; OR 0.2, 95% CI 0.2—0.3, $p < .01$). No RCTs have compared routine with selective patching,[288,289] and there is no consensus on criteria for selective patching.

Recommendation 54	Class	Level	References
Routine patching is recommended, rather than routine primary closure. There is no evidence that patch type influences outcome	I	A	288,289

2.4.1.11. Eversion vs. traditional endarterectomy. During eversion CEA (eCEA), the ICA is transected obliquely at its origin and a cylinder of atheroma "expelled" via eversion of the outer media and adventitia. The distal intimal step is examined for residual flaps, which are then excised. The ICA is shortened (as required) and reanastomosed to the CCA. Advantages include no risk of prosthetic infection, it is quicker than patched CEA, bifurcation geometry is preserved, and it is possible to shorten the distal ICA where necessary. Disadvantages are that a shunt cannot be inserted until eversion is completed and there may be problems accessing the upper ICA (if distal disease has been underestimated). A meta-analysis has reported that eCEA was associated with a significantly higher incidence of post-CEA hypertension (OR 2.75, 95% CI 1.82—4.16), compared with conventional CEA (cCEA). By contrast, cCEA was associated with a significantly higher incidence of perioperative hypotension (OR 11.37, 95% CI 1.95—66.46).[291]

In a meta-analysis of 21 randomised and non-randomised studies comparing cCEA ($n = 7721$) with eCEA ($n = 8530$), eCEA was associated with significant reductions in perioperative stroke (OR 0.46, 95% CI 0.35—0.62), perioperative death (OR 0.49, 95% CI 0.34—0.69), and a significant reduction in late carotid occlusion (OR 0.48, 95% CI 0.25—0.90).[292] However, in a Cochrane review of five RCTs (2590 CEAs),[293] there were no statistically significant differences regarding (i) 30-day death/stroke, (ii) perioperative thrombosis, and (iii) late stroke. However, patients randomised to eCEA had a twofold reduction in late restenosis >50% (2.5%), compared with patients undergoing cCEA (5.2%) (OR 0.48, 95% CI 0.3—0.7). When the meta-analysis compared eCEA with patched CEA, however, there were no differences in late restenosis (2.5% eversion vs. 3.9% patched (HR 0.52, 0.2—1.7).[293] These data would, therefore, suggest that eCEA provides equivalent outcomes to cCEA, provided the arteriotomy is closed with a patch.

Recommendation 55	Class	Level	References
Eversion endarterectomy is recommended over routine primary arteriotomy closure	I	A	293
Recommendation 56			
The choice between eversion or patched endarterectomy should be left to the discretion of the operating surgeon	I	A	293

2.4.1.12. Treatment of coils and kinks. The management of patients with ICA coils/kinks in the absence of significant stenoses is controversial. Incidental coils/kinks are found in up to 16% of patients and half will have histological features consistent with fibromuscular dysplasia.[294] One RCT compared surgical correction versus BMT in 182 patients with hemispheric/non-hemispheric symptoms with an isolated coil/kink of the ICA, where neurologists performed postoperative assessments.[294] Patients randomised to surgical correction had a 0% rate of occlusion at a mean of 5.9 years follow-up, compared with 5.5% in those treated medically ($p = .02$). The risk of late stroke was 0% in surgically treated patients, compared with 6.6% in medically treated patients ($p = .01$). Unfortunately, meaningful interpretation of the data was confounded by 41% of the medically treated patients crossing over to surgical treatment because of recurrent hemispheric or ongoing non-hemispheric symptoms.

Recommendation 57	Class	Level	References
Surgical intervention for asymptomatic isolated coils/kinks of the internal carotid artery is not recommended	III	C	
Recommendation 58			
Symptomatic patients with isolated coils/kinks may be considered for surgical correction, but only following multidisciplinary team review and provided no other cause for transient ischaemic attack or stroke symptoms can be identified	IIb	B	294

2.4.1.13. Role of monitoring and quality control. There is no consensus as to whether a policy of monitoring or quality control reduces 30-day death/stroke after CEA.[170,295]

Quality control is not the same as monitoring. The role of monitoring is to ensure adequate brain perfusion, especially during carotid clamping and shunting. This can be achieved using TCD, or by performing CEA under LRA, measuring stump pressure, performing a subjective assessment of ICA backflow following carotid clamping, and near infra-red spectroscopy. Loss of cerebral electrical activity is assessed by somatosensory evoked potentials and EEG. The onset of any intraoperative neurological deficit can be accurately identified by performing CEA under LRA.

Quality control techniques aim to modify operative strategies to prevent technical error, including embolisation during carotid dissection (TCD), to ensure that the shunt is functioning (TCD, CEA under LRA), to identify residual luminal thrombus before flow restoration (angioscopy), to identify residual luminal thrombus after flow restoration (DUS, angiography), to diagnose large intimal flaps (angioscopy, DUS, angiography) to diagnose residual (untreated) stenoses (DUS, angiography), and to diagnose the very rare patient who thromboses the operated ICA during neck closure (diagnosed by increasing rates of embolisation followed by declining MCAV using TCD).[170]

Evidence suggests that targeted monitoring and quality control strategies may reduce perioperative death/stroke,[170,296] but reliance on a single monitoring or quality control strategy is unlikely to make any difference, because of the multiple causes of perioperative stroke (hypoperfusion, embolism, thrombosis, intracranial haemorrhage, hyperperfusion syndrome).

Recommendation 59	Class	Level	References
Targeted monitoring and quality control strategies may be considered to reduce the risk of perioperative stroke	IIb	C	170,296

2.4.1.14. Treatment of high internal carotid artery lesions. A high bifurcation or a stenosis extending behind the jaw can represent a technical challenge and increase the risk of CNI. If the person performing DUS assessment cannot image above the lesion, corroborative CTA/MRA imaging must be performed to evaluate operability. The presence of distal disease extension should prompt the surgeon to reconsider whether CEA is appropriate (e.g. in asymptomatic patients). If the patient is recently symptomatic and the surgeon is concerned about his/her ability to complete the procedure, CAS should be considered as an alternative.

In the presence of distal disease extension, advance planning is essential. Nasolaryngeal intubation enables the mouth to be closed, which then opens up the angle between jaw and mastoid process to facilitate distal access. Subluxation of the temporomandibular joint has to be undertaken preoperatively as it cannot be performed once the operation is under way. An alternative strategy (which can be performed once the operation is under way) involves extending the incision anterior to the ear with mobilisation of the superficial lobe of the parotid. This greatly increases access to the upper ICA, but usually requires the assistance of a specialist ENT or parotid surgeon.[297]

Intraoperatively, there are several techniques for optimizing access to the upper ICA, including division of the sternocleidomastoid artery (which tethers the hypoglossal nerve), division of the occipital branch of the external carotid artery (ECA), transection of the ansa cervicalis (which also tethers the hypoglossal nerve), and division of digastric and transection of the styloid process.

2.4.1.15. Role of wound drainage. The rationale for placing a wound drain following CEA is that it should prevent haematoma formation, which could compromise the airway in the early postoperative period and also predispose to abscess formation and/or late patch infection. There is, however, controversy as to whether drains make any difference. A RCT observed that routine drainage yielded a mean volume of 42 mL of blood, plus a median residual neck haematoma volume of 25 mL on DUS assessment (range 5—65). By contrast, the median residual haematoma volume in patients randomised to "no drains" was 31 mL (range 3—72).[298] Observational studies have reported that small calibre drains (10F) are ineffective, while 14F drains significantly reduce neck haematoma formation.[299] This is another area of surgical practice where surgeons tend to practice what they were taught, rather than being based on evidence. Despite the single RCT (which suggested that routine drainage was ineffective), it is likely that most surgeons remain "more comfortable" about routinely or selectively inserting a wound drain after CEA.

2.4.1.16. Ward, high dependency or intensive care postoperatively? All CEA and CAS patients benefit from 3—6 hours neurological and intra-arterial BP monitoring in the recovery area of theatre or angio suite following CEA/CAS. Relatively few patients require routine postoperative monitoring in a high dependency unit (HDU) or intensive care unit (ICU). The majority can be transferred back to the vascular ward for ongoing surveillance, involving hourly non-invasive BP and neurological monitoring for the first 24 hours and 4-hourly thereafter until discharge.

Evidence suggests that up to 40% of patients may require treatment for post-CEA hypertension in the early postoperative period.[300] Half of these will require treatment in the first 3 postoperative hours, but most require only a single bolus of intravenous labetalol to control their BP (Section 2.6.1.3.3). If there are no further spikes of hypertension, these patients can usually return to the vascular ward 2—3 hours later. Patients who require intravenous therapy to control BP should either remain in the recovery area of theatre (with ongoing intra-arterial BP monitoring) or be transferred to the HDU for continued intra-arterial BP monitoring. Two hours after intravenous treatment has completed and with no further surges in BP, it is reasonable to transfer the patient back to the vascular ward for ongoing monitoring. Any patient who suffers a major intraoperative cardiac event should, however, be transferred to the ICU or coronary care unit for further evaluation.

Recommendation 60	Class	Level	References
The surgeon should anticipate the presence of distal disease extension preoperatively and plan for this in advance	I	C	

2.4.2. Carotid bypass

2.4.2.1. Indications. Bypass is indicated in the following situations: extensive atherosclerotic disease, excessive coiling/kinking of the ICA above a stenosis, previous radiotherapy causing fibrosis of the ICA, excessive arterial wall thinning after CEA, large intimal flap on completion imaging, revascularisation following enbloc excision of a carotid body tumour, treatment of prosthetic patch infection, treatment of restenosis after CEA, treatment of fibromuscular dysplasia, and treatment of aneurysms.[301–307]

Recommendation 61	Class	Level	References
Extracranial to Intracranial bypass surgery is not recommended in patients with an extracranial internal carotid occlusion	III	A	308–310

2.4.2.2. Technique. Options include an interposition graft; end-to-side anastomosis to the distal CCA with end-to-side or end-to-end anastomosis to the distal ICA with ECA exclusion or bifurcation reconstruction (retaining the ECA) with a distal end-to-end anastomosis to the ICA. Conduits include reversed saphenous vein harvested from the thigh,[302,303,306] PTFE,[301,302,304,305] or polyester.[307] Early and late outcomes are summarised in Table 19. These data suggest that carotid bypass can be performed with low procedural risks and with good long-term patency. Notwithstanding the lack of RCTs, late patency with prosthetic conduits appear to be as good as with vein (possibly better). Interestingly, only three late graft infections were reported in the 594 patients (0.5%) with prosthetic conduits.[302,307]

2.4.3. Extracranial to intracranial bypass.

The rationale underpinning extracranial to intracranial bypass (EC-IC) is that in patients with an extracranial ICA occlusion, a bypass (usually from the superficial temporal artery to the MCA) will reduce the long-term risk of ipsilateral ischaemic stroke. A 1985 RCT concluded that EC-IC bypass conferred no benefit over BMT.[308] The trial was, however, criticised regarding selection criteria, method of randomisation, the large number of patients operated upon outwith the trial and the lack of haemodynamic criteria for trial entry. A subsequent Cochrane review, which included two RCTs and 19 observational studies ($n = 2591$), concluded that EC-IC bypass conferred no benefit over BMT in terms of late stroke prevention (RCTs: OR 0.99, 95% CI 0.79–1.23, $p = .91$; non-RCTs: OR 0.80, 95% CI 0.54–1.18, $p = .25$).[309] A third RCT was undertaken in 2011, which included only patients with a recently symptomatic extracranial ICA occlusion plus evidence of haemodynamic impairment in the ipsilateral cerebral hemisphere (increased oxygen extraction fraction using positron emission tomography).[310] The 2-year risk of ipsilateral stroke (including perioperative stroke/death) was 21.0% (95% CI 12.8–29.2) after EC-IC bypass, versus 22.7% (95% CI 13.9–31.6) in patients randomised to BMT ($p = .78$). Accordingly, there is still no role for EC-IC bypass in the routine management of patients with atherosclerotic ICA occlusion. The only exception might be the patient with persisting clinical and haemodynamic insufficiency, despite BMT, in whom the MDT has advised that EC-IC bypass might be appropriate.

2.5. Carotid artery stenting

2.5.1. Adjuvant medical therapy.

Pre-intervention statin therapy may reduce procedural complications (Section 2.3.2.3.3). It is recommended to start DAPT with aspirin (300 mg initially for up to 14 days followed by 75 mg daily if not already taking aspirin) and clopidogrel (75 mg daily) 3 days prior to CAS. Aspirin and clopidogrel should be continued for at least 1 month, followed by clopidogrel thereafter, unless the treating physician opts for an alternative long-term antiplatelet regimen (Section 2.3.2.1.3). Most operators administer 5000 IU of intravenous heparin prior to the procedure and 0.6–1.2 mg of atropine (or 0.6 mg glycopyrrolate) to prevent hypotension and bradycardia/asystole prior to balloon inflation.[311,312]

Recommendation 62	Class	Level	References
It is recommended that atropine or glycopyrrolate be administered prior to balloon inflation during carotid stenting to prevent hypotension, bradycardia, or asystole	I	B	311,312

2.5.2. Access (femoral, cervical, radial).

The most common access is via the common femoral artery (CFA), although direct CCA and brachial/radial artery access are alternatives. The latter may be preferable in patients with aorto-iliac tortuosity/occlusion. Direct CCA access via a cut down has recently been advocated as this avoids manipulation of wires and catheters within the aortic arch.

2.5.3. Choice of wires, access catheters, stent design.

For access into the CCA, a 0.035″ guide wire is used. For stent placement and balloon angioplasty (requiring rapid exchange systems) 0.014″ floppy tip guide wires are advised. Long sheaths or guiding catheters (6F–8F) are used to obtain a stable position in the CCA. ICSS reported significantly lower 30-day risks of death/stroke in CAS patients where closed cell designed stents were used (5.1%), versus 9.5% in patients where open cell designed stents were used (OR 10.53, 95% CI 0.31–0.91, $p = .024$).[313] There is currently no evidence that micromesh or dual layer stents reduce procedural risks after CAS.

Table 19. Early and late outcomes following carotid interposition bypass grafting.

Author	n =	Conduit type	30-day death/stroke	Primary patency	Late infection
Ricco[301]	198	PTFE	1/198 (0.5%)	98% @ 10 y	None
Dorafshar[302]	31	PTFE	1/31 (3.2%)	90% @ 4 y	1/31
Roddy[304]	22	PTFE	0/22 (0.0%)	95% @ 2 y	None
Veldenz[305]	51	PTFE	1/51 (1.9%)	96% @ 2 y	None
Dorafshar[302]	10	Vein	1/10 (10%)	80% @ 4 y	n/a
Lauder[303]	50	Vein	3/50 (6.0%)	83% @ 3 y	n/a
Koncar[307]	292	Polyester	19/292 (6.5%)	96% @ 32 m	2/292
Branchereau[306]	212	Vein	14/212 (6.6%)	92% @10 y	n/a

y = years.

2.5.4. Role of predilatation. Predilation is only undertaken in patients with high-grade stenoses (>80%), when it is anticipated that the stent or filter protection device cannot cross the lesion,[314] because predilatation may be associated with higher procedural stroke rates.

2.5.5. Use of cerebral protection devices. There is conflicting evidence (and opinion) regarding the role of cerebral protection devices (CPDs) in preventing stroke after CAS, despite it not being unusual to find embolic material in retrieved distal filters.[315] A meta-analysis of 22 studies (n = 11,655) reported significantly lower rates of perioperative stroke/death favouring the use of CPDs (OR 0.57, 95% CI 0.43—0.76, $p < .01$).[316] In addition, the best CAS results within RCTs were reported in CREST and ACT-1, where CPDs were mandatory and CAS practitioners were trained in their use.[97,189] By contrast, a meta-analysis of 30-day stroke in patients randomised to CAS within EVA-3S, SPACE, and ICSS found no evidence that CPD usage was associated with reduced perioperative stroke rates (OR 0.95, 95% CI 0.38—2.41, $p = .92$).[195] Proximal CPDs protect the brain by stopping or reversing blood flow within the carotid bifurcation. Their main advantages include being able to cross the stenosis with protection already in place and the avoidance of distally placed CPDs (such as filters), which may be associated with spasm or distal ICA dissection. It is advised, however, that proximal CPDs should be avoided in patients with severe ECA/CCA disease.[317] Overall, 30% will not tolerate proximal occlusion[318] and will develop neurological symptoms. In a series of 600 patients, the only clinical predictive factor of not being able to tolerate proximal occlusion was contralateral ICA occlusion.[318] A systematic review has reported that the relative risk reduction in peri-procedural stroke was 0.62 (95% CI 0.54—0.72) in favour of protected CAS, with significant benefit being conferred in both asymptomatic and symptomatic patients.[319]

These contradictory reports and the lack of high-quality data have led to conflicting opinions among CAS practitioners, with some claiming that CPDs are unnecessary, while others would never perform an unprotected CAS procedure. Given the lack of high-quality data, the recommendation in these guidelines is based on a broad consensus among CAS practitioners that CPDs should be considered when performing CAS.

Recommendation 63	Class	Level	References
The use of embolic protection devices should be considered in patients undergoing CAS	IIa	B	97,189,316,319
Recommendation 64			
Proximal protection devices are not recommended in patients with advanced common carotid disease, or those with external carotid artery disease (where an occlusion balloon is to be positioned in the external carotid artery) or in patients with contralateral occlusion and insufficient collateralisation	III	C	317

2.5.6. Role of peri-procedural monitoring. The presence of an experienced anaesthesiologist or physician capable of maintaining haemodynamic stability is mandatory and haemodynamic monitoring should be continued for at least 6 hours after the procedure.

2.5.7. Learning curve and the volume:outcome relationship. As with CEA, there are conflicting data regarding a volume:outcome relationship following CAS. In a systematic review of outcomes from four large case series and one registry, it was observed that in "active" CAS centres, it took almost 2 years of experience before 30-day death/stroke rates fell below 5%.[320] In an analysis of data derived from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample from 2006 to 2010, greater operator volume was associated with a lower rate of postoperative mortality and complications, as well as shorter lengths of stay and lower hospitalisation costs.[321] In a large "high-risk for CEA" registry, a lifetime experience of 72 CAS procedures was necessary to achieve a 30-day death/stroke rate <3% in asymptomatic non-octogenarian patients.[222] In an analysis of outcomes in Medicare beneficiaries, 30-day mortality was significantly higher when practitioners performed fewer than six CAS procedures per year, compared with >24 (OR 1.9, 95% CI 1.4—2.7, $p < .001$).[322] In a very large single-centre series involving 2124

successful CAS procedures, a lifetime experience of >100 CAS interventions was associated with significantly fewer perioperative strokes (OR 0.81, 95% CI 0.67—0.95), while a lifetime experience of <50 CAS procedures was a significant predictor of an increased risk of perioperative stroke ($p < .001$).[323] Finally, in a post-marketing evaluation of outcomes in 5841 patients in the CHOICE Registry (carotid stenting for high surgical risk patients: evaluating outcomes), the most important predictive feature for 30-day death/stroke/MI was an increased time interval between individual CAS procedures.[324]

An individual patient meta-analysis was undertaken in recently symptomatic patients who were randomised to CAS in EVA-3S, SPACE, and ICSS.[325] In contrast to what was reported (above), the 30-day risk of death/stroke was not influenced by lifetime CAS experience ($p = .8$). However, compared with high annual volume CAS operators (mean >5.6 cases per year) who incurred a 5.1% risk of death/stroke, 30-day death/stroke was significantly higher in operators with low annual CAS experience (mean 3.2 cases per year), who incurred a 10% rate of death/stroke (OR 2.3, 95% CI 1.36—3.87). Intermediate volume operators (mean 3.2—5.6 cases per year) incurred an 8.4% risk of death/stroke (OR 1.93, 95% CI 1.14—3.27).[325]

The authors of the pooled individual patient meta-analysis of 1546 recently symptomatic patients randomised within ICSS, EVA-3S, and SPACE concluded that CAS practitioners should be performing at least six CAS procedures each year.[325] By contrast, the Society for Cardiovascular Angiography and Interventions and the Society for Vascular Medicine advise that "in an era of low CAS volumes," 25 lifetime CAS procedures is reasonable for achieving competency, along with 10—15 CAS procedures annually to maintain competency,[326] provided that the 3% (asymptomatic) and 6% (symptomatic) thresholds are maintained.

2.6. Complications following carotid interventions

2.6.1. The first 30 days

2.6.1.1. Stroke after carotid endarterectomy

2.6.1.1.1. Intraoperative stroke. An intraoperative stroke is defined as any new focal neurological deficit (or worsening of a pre-existing deficit), which is apparent immediately following recovery from anaesthesia and with symptoms lasting for >24 hours. In practice, the majority follow intraoperative embolisation (during carotid dissection/mobilisation, after shunt insertion, after restoration of flow, after accumulation of platelet thrombi on the endarterectomy zone during neck closure) or (less commonly) hypoperfusion, which may be associated with carotid clamping or shunt malfunction. In a recent 25-year audit, most intraoperative strokes appeared to follow embolisation of retained luminal thrombus after restoration of flow, despite irrigation with heparinised saline prior to flow restoration.[170] The source of the emboli was bleeding from transected vasa vasorum following plaque removal. The ensuing thrombus is often densely adherent to the endarterectomy zone and can be resistant to blind irrigation. It can, however, be identified using completion angioscopy (prior to flow restoration) and removed.[170]

One of the advantages of performing CEA under LRA is that the timing of any new neurological deficit can be accurately determined. For patients undergoing CEA under GA, an abrupt change in the EEG may also predict the most likely time of onset of a new neurological deficit.[327] If the patient exhibits the triad of hemiplegia, homonymous hemianopia, and higher cortical dysfunction (aphasia/visuospatial neglect) upon recovery from anaesthesia, it is highly likely that either the ICA or MCA mainstem is occluded. If only one or two components of the triad are present, this is more likely to represent occlusion of one or more MCA branches.[328]

It is currently accepted practice that anyone recovering from anaesthesia with a new neurological deficit should undergo immediate re-exploration, to exclude accumulation of thrombus within the endarterectomy zone.[329] In a subanalysis of the causes of stroke in ACST-1, the rate of disabling/fatal stroke in patients who underwent immediate re-exploration was similar to those who did not undergo re-exploration.[330] However, the immediate priority is to identify patients with ICA thrombosis, as they will benefit from immediate exploration. Provided flow is restored within 1 hour, good neurological recovery can be expected. Although re-exploration will not benefit patients with MCA mainstem or branch embolism or haemodynamic stroke (other than being able to remove a source of embolisation), this cannot be avoided. For those with access to TCD, decision-making is easier as ICA occlusion will be associated with MCA velocities identical to those seen during carotid clamping.[170] DUS can assist in confirming whether there is flow within the endarterectomy zone, but air in the subcutaneous tissues often makes it difficult to interpret the findings in the early postoperative period. At re-exploration, the artery should be opened carefully and thrombus removed. If thrombus extends distally, this may be retrieved by careful retraction. If a Fogarty catheter is used, care must be taken to avoid distal trauma. Following thrombectomy, any technical errors should be corrected and a completion angiogram performed to ensure distal patency. Several small series have suggested that patients suffering embolic occlusion of the ipsilateral anterior or MCA arteries during (or immediately after) CEA can be treated by re-exploration (to remove any residual thrombus within the endarterectomy zone) followed by an intraoperative intra-arterial infusion of 500,000[331,332] or 1 million units of urokinase,[333] without incurring significant bleeding complications (Section 2.6.1.2.1). Urgent mechanical thrombectomy should also now be considered in patients with embolic occlusion of the MCA mainstem, especially as some CEA patients may not be eligible for intravenous thrombolysis (Section 2.6.1.2.1).

It would clearly be preferable to prevent intraoperative stroke. While no RCTs have been undertaken, targeted monitoring (TCD, EEG) and quality control assessment (completion angioscopy, DUS, angiography) have been associated with significant reductions in intraoperative embolisation, identification of luminal thrombus prior to restoration of flow and a decline in intraoperative stroke rates.[170,296,327]

2.6.1.1.2. Postoperative stroke. This is defined as any new focal neurological deficit (or worsening of a pre-existing deficit), following full recovery from anaesthesia and whose symptoms last more than 24 hours. The aetiology varies with

the time interval from surgery. In the first 6 hours, the most likely cause is ICA thrombosis or embolism from mural thrombus in the endarterectomy zone. After 12–18 hours have elapsed, stroke caused by the hyperperfusion syndrome (HS) or ICH become more likely.[170] Accordingly, if a neurological deficit becomes apparent in the first 6 postoperative hours, thromboembolic stroke should be assumed and the patient should return immediately to theatre for re-exploration, the rationale and management being the same as for intraoperative stroke.[327] A number of studies have shown that it may be possible to prevent early postoperative thromboembolic stroke by starting DAPT preoperatively (aspirin 75 mg, clopidogrel 75 mg).[128,170]

However, patients developing new neurological symptoms after 6 hours have elapsed require emergency extracranial and intracranial CTA. This will exclude ICA thrombus (which should be removed at re-exploration) or (more likely), intracerebral oedema, ICH, or parenchymal haemorrhage. ICH may require craniotomy in selected cases, but the majority are managed conservatively. Hyperperfusion syndrome stroke complicates about 1% of CEAs and is usually associated with post-CEA hypertension, headache, atypical migrainous phenomena, and focal onset seizures.[334] The neurological deficit with HS can either be caused by breakthrough oedema or haemorrhage, or it can be ischaemic, possibly because of activation of the coagulation cascade and inhibition of endothelial fibrinolysis.[335] HS is often associated with the development of patchy white matter oedema on CT/MRI. This is sometimes mistaken for evolving ischaemia on CT, but DWI-MRI will show that the oedema is vasogenic (as opposed to cytotoxic) and MRI perfusion imaging will show normal perfusion within the area of white matter oedema.[336] For some reason, patchy white matter vasogenic oedema may also affect the vertebrobasilar territory. Patients exhibiting symptoms suspicious of HS will usually have elevated BP and this should be actively treated (Section 2.6.1.3.3). Seizures should be controlled with intravenous titrated doses of lorazepam and appropriate anti-epileptic drugs under the supervision of a neurologist.

2.6.1.1.3. Predictors of stroke after carotid endarterectomy. ECST reported various features that were associated with an increased risk of perioperative stroke including (i) female gender (10.4% vs. 5.8%, $p = .0001$); (ii) peripheral vascular disease (12.0% vs. 6.1%, $p = .0001$); (iii) systolic BP (<120 mmHg = 3.4%; 121–159 = 6.5%; 160–180 = 7.7%; >180 mmHg = 13.0%, $p = .04$); and (iv) the type of presenting cerebrovascular event (retinal [3.2%], hemispheric stroke [6.3%], hemispheric TIA [9.1%], $p = .006$).[169]

NASCET also reported clinical/imaging features associated with a significant increase in stroke after CEA including (i) hemispheric versus retinal events (6.3% vs. 2.7%; OR 2.3, 95% CI 1.1–5.0); (ii) left vs. right CEA (6.7% vs. 3.0%; OR 2.3, 95% CI 1.4–3.6); (iii) contralateral occlusion (9.4% vs. 4.4%; OR 2.2, 95% CI 1.1–4.5); (iv) ipsilateral CT/MR infarct (6.3% vs. 3.5%; OR 1.8, 95% CI 1.2–2.8); and (v) irregular as opposed to smooth plaque (5.5% vs. 3.7%; OR 1.5, 95% CI 1.1–2.3).[337] A meta-analysis of 170 studies (>70,000 patients) observed that contralateral occlusion was associated with higher procedural stroke rates after CEA, but not after CAS.[338]

2.6.1.2. Stroke after carotid artery stenting. Although CPDs are often used, intra-procedural strokes can still occur from embolization into the contralateral hemisphere (from the aortic arch), or because of incomplete CPD deployment and/or malpositioning of the filter, or because of incomplete aspiration of debris when using balloon protection devices. In a limited number of cases, CPDs cannot be used because of technical reasons or patient intolerance.

2.6.1.2.1. Mechanical thrombectomy and thrombolysis. Techniques for treating patients who develop a new neurological deficit during CAS include mechanical thrombectomy and/or intra-arterial thrombolysis. Safe mechanical removal of embolic material from the main branches of the ICA (out to the distal M2-segment) is possible using dedicated neuro-interventional retrieval devices.[339] With the recently published positive results of various RCTs evaluating mechanical thrombectomy in acute ischaemic stroke,[251] most interventionists now advocate the use of stent-retrievers or thrombus aspiration in patients who experience an acute, new stroke during CAS secondary to acute ICA, M1, or M2 branch occlusion (Section 2.3.5.3).

Thrombolysis in the setting of acute distal ICA occlusion because of embolisation during CAS is rarely beneficial, because the embolus usually comprises plaque, rather than fibrin clot. In the event of acute stent thrombosis, thrombolysis should be considered. Thrombolytic agents currently in use include urokinase and recombinant tissue plasminogen activator (rTPA), which are delivered through the guiding catheter, diagnostic catheter, or a super-selectively placed microcatheter (ensuring that the catheter is positioned within the thrombus). High-dose urokinase regimens are generally administered (500,000 units of urokinase), with half being administered as an initial bolus. Alternatively, a continuous infusion (without bolus) of up to 1,250,000 units of urokinase over 90 min can be performed.

rTPA can be given as a 5-mg bolus, followed by slow infusion (maximum dose 20 mg). If any of the proximal thrombus dissolves, the tip of the microcatheter must be advanced into the proximal portion of any residual thrombus. Selective intra-arterial administration of 5-mg abciximab followed by a bolus of 5-mg abciximab intravenously has been effective in the treatment of neurological sequelae because of distal embolisation after CAS.[339]

No RCTs have addressed the treatment of acute stroke caused by ICA thrombosis, or M1/M2 segment embolic occlusions after CAS. The management should, however, be no different to stroke occurring without a prior carotid intervention. Accordingly, eligible patients with thromboembolic, ischaemic stroke after CAS should be considered for mechanical thrombectomy using neuro-interventional thrombectomy devices, provided they fulfil the criteria for inclusion in those trials (Section 2.3.5.3).

2.6.1.2.2. Predictors of stroke after carotid artery stenting. A Delphi consensus identified various imaging criteria that were associated with an increase in difficulty for “novices”

undertaking CAS including (i) type III aortic arch; (ii) bovine arch; (iii) arch atheroma; (iv) diseased ECA; (v) markedly angulated distal ICA; (vi) a long stenosis; and (vii) a pinhole stenosis.[340] In CAVATAS, increasing stenosis length was an independent risk factor for procedural stroke/death.[341] In a pooled analysis from EVA-3S, SPACE, and ICSS, CAS was associated with a threefold excess risk of death/stroke (compared with CEA) when performed in the first 7 days after onset of symptoms (9.4% vs. 2.8%; OR 3.4, 95% CI 1.01—11.8) after adjusting for age, sex, and nature of qualifying event.[225] A *post-hoc* analysis of ICSS data showed that CAS patients who had an age-related white-matter change (ARWMC) score of $\geq$7 on preoperative CT/MRI faced an increased risk of perioperative stroke, compared with patients whose ARWMC score was <7 (HR 2.76, 95% CI 1.17—6.51, $p = .021$). There was no association between ARWMC scores and perioperative stroke in patients treated with CEA (HR 1.18, 0.4—3.55, $p = .76$).[342] CAS was associated with a significantly higher risk of perioperative stroke (compared with CEA) in patients with an ARWMC score of $\geq$7 or more (HR 2.98, 1.29—6.93, $p = .011$), but there was no difference in risk between CEA and CAS in patients whose ARWMC score was <7.[342] More recently, CREST has reported that perioperative stroke rates were significantly higher after CAS in patients whose lesion length was >13 mm and sequential lesions extending remotely from the main ICA stenosis.[343]

2.6.1.3. Haemodynamic instability

2.6.1.3.1. Post-stenting hypotension. In a meta-analysis of 27 studies ($n = 4204$), 12% (95% CI 7—18) required treatment for peri-procedural hypotension, 12% (95% CI 7—19) required treatment for bradycardia, while 13% (95% CI 8—17) were treated for both hypotension and bradycardia. Persistent haemodynamic instability (>1 hour vasopressor support) affected 19% (95% CI 13—27) of CAS patients.[344] There was a statistically significant association between increasing age and haemodynamic instability. Lesions within 10 mm of the carotid bifurcation and the site of minimum lumen diameter were associated with bradycardia and there was a statistically significant association between a history of ipsilateral CEA and persistent haemodynamic instability after CAS.[344] Haemodynamic instability after CAS usually resolves and its clinical significance seems relatively minor. Meta-analyses have not shown any statistically significant differences between patients with or without haemodynamic instability after CAS in terms of perioperative death (OR 2.99, 95% CI 0.34—26.06); stroke (OR 1.0, 95% CI 0.57—1.75); stroke/death (OR 1.51, 95% CI 0.98—2.33); TIA (OR 0.86, 95% CI 0.47—1.61); or any major adverse event rate (OR 1.31, 95% CI 0.73—2.34).[344]

Measures for preventing haemodynamic instability include adequate hydration and withholding antihypertensive medications on the morning of CAS. Continuous ECG monitoring, invasive BP monitoring and venous access are mandatory. Glycopyrrolate (a synthetic atropine derivative) was compared with atropine in a retrospective study (115 CAS procedures) and found to be more effective in preventing postoperative bradycardia and hypotension (30% vs. 72%, $p = .002$, and 2.5% vs. 36%, $p = .001$), respectively. In addition, there were lower rates of postoperative hypertension (2.5% vs. 16%, $p = .047$). However, glycopyrrolate conferred no benefit regarding peri-procedural tachycardia, BP changes, vasopressor use, or cardiac complications. No significant differences in procedural neurologic and access site complications were observed.[345]

The treatment of post-CAS hypotension requires administration of i.v. crystalloids plus volume expanders. This strategy may, however, be inadequate because of decreased peripheral vascular resistance (secondary to loss of sympathetic tone) and not underlying hypovolaemia. Titrated intravenous vasopressors (dobutamine, dopamine, norepinephrine, phenylephrine) may be necessary to maintain systolic BP >90 mmHg. The influence of vasopressor type (on outcome) was evaluated in a retrospective study involving 42 patients requiring vasopressor treatment after CAS.[346] The mean vasopressor infusion time was 32 hours for dopamine, compared with 24 hours for norepinephrine ($p = .052$) and 22 hours ($p = .028$) for phenylephrine. The mean length of stay in the coronary care unit was 47 hours for dopamine, compared with 37 hours for the norepinephrine/phenylephrine groups combined ($p = .056$). Major adverse events, including MI, arrhythmias, and cardioversion were significantly more common in patients receiving dopamine, than in patients receiving norepinephrine or phenylephrine ($p = .04$). Midodrine (a selective α-1 agonist) that causes arteriolar and venous vasoconstriction without stimulating cardiac β-adrenergic receptors is well tolerated and is as effective as intravenous dopamine in the treatment of hypotension after CAS.[347]

2.6.1.3.2. Post-endarterectomy hypotension. Post-CEA hypotension has been attributed to exposure of carotid sinus baroreceptors to the pulse pressure, without the dampening effect of the excised plaque.[348] The clinical relevance of post-CEA hypotension is variable, with some reporting that it increases perioperative stroke and MI,[349] whereas others believe it to be a benign phenomenon.[348] There is no consensus regarding what BP threshold should be used for treatment. The management of post-CEA hypotension is the same as for post-CAS hypotension.

Recommendation 65	Class	Level	References
First-line treatment of post-carotid intervention hypotension should be the administration of intravenous crystalloids together with volume expanders. If this fails to improve blood pressure, titrated intravenous vasopressors (dobutamine, dopamine, noradrenaline, phenylephrine) should be considered to maintain systolic blood pressure >90 mmHg	IIa	C	346

2.6.1.3.3. Post-endarterectomy hypertension. Postoperative hypertension affects up to two-thirds of patients undergoing CEA, depending on the definition used.[300] Several theories have been proposed, including denervation of the carotid bulb and increased cerebral norepinephrine and/or renin production by the central nervous system.[350–352] Post-CEA hypertension is associated with preoperative hypertension,[300,353] GA,[264] and eCEA.[291] The association between GA and post-CEA hypertension is attributed to increased neuroendocrine stress hormone levels. The association between eversion CEA and post-CEA hypertension is attributed to denervation of the carotid bulb, via circumferential transection at the origin of the ICA.[354] In a systematic review and meta-analysis, patients undergoing eCEA were significantly more likely to require vasodilator therapy for the treatment of post-CEA hypertension compared to patients undergoing cCEA (OR 2.75 (95% CI 1.82–4.16) $p < .0001$).[291] In a recent prospective study involving 100 CEA patients, Newman observed that poorly controlled preoperative BP and impaired baroreceptor function (but not impaired autoregulation) were associated with a significantly higher prevalence of post-CEA hypertension.[300] Intraoperative variables that predicted a significantly increased risk of post-CEA hypertension included poorly controlled or labile hypertension at induction of anaesthesia. No other variable (including the magnitude of MCA velocity increase with flow restoration) was predictive of post-CEA hypertension.[355]

Poorly treated post-CEA hypertension has been associated with postoperative TIA/stroke,[353,356] and is a risk factor for neck haematoma formation, HS, and ICH.[170,334,357] There are a variety of strategies for treating post-CEA hypertension,[170,358] but the need for intravenous antihypertensive therapy becomes less common once the patient resumes their normal antihypertensive medications. Vascular units should have written guidance for treating post-CEA hypertension so that treatment decisions are not delayed.

2.6.1.3.4. Post-stenting hypertension. As with CEA, most patients with post-CAS hypertension were treated with antihypertensive drugs prior to the procedure. Symptomatic post-CAS hypertension (HS, ICH) is reported in up to 3% of patients.[359] The management is the same as for CEA.

Recommendation 66	Class	Level	References
It is recommended that intra-arterial blood pressure monitoring be continued for the first 3–6 hours after carotid endarterectomy and carotid stenting, followed by hourly noninvasive blood pressure monitoring for the first 24 hours	I	C	
Recommendation 67			
It is recommended that vascular units have written criteria for treating post-carotid intervention hypertension	I	C	170

2.6.1.4. Wound haematoma after carotid endarterectomy. VSGNE reported that re-exploration for neck haematoma was required in 1.2% of CEA patients on aspirin, 0.7% on clopidogrel, and 1.4% in patients taking aspirin and clopidogrel.[360] ICSS reported that the prevalence of haematoma requiring re-exploration was 3.4%.[361] There is no evidence that DAPT significantly increases the risk of neck haematoma formation.[132,360,362] The role of protamine reversal in reducing re-exploration for neck haematoma formation after CEA has been discussed in Section 2.4.1.8. Small calibre suction drains do not appear to reduce the prevalence of haematoma, whereas larger calibre drains may help[299] (Section 2.4.1.15). Most haematomas occur in the first 6 hours after CEA, often after a period of untreated hypertension.[357] Any evidence of stridor or tracheal deviation mandates immediate evacuation.

Recommendation 68	Class	Level	References
Any patient who develops a postoperative neck haematoma in association with stridor or tracheal deviation must be re-explored immediately	I	C	

2.6.1.5. Cranial nerve injury. In a meta-analysis of 16,749 CEA patients from four RCTs, eight prospective, and 14 retrospective studies, the prevalence of CNI was 4.2% for the recurrent laryngeal nerve, 3.8% for the hypoglossal nerve, 1.6% for the mandibular branch of the facial nerve, 0.2% for the glossopharyngeal nerve, and 0.2% for the spinal accessory nerve.[363] Significant predictors for CNI were urgent procedures and re-exploration for bleeding/neurological deficit. The meta-analysis observed that the prevalence of CNI had diminished over the last 30 years.[363]

In ICSS, the incidence of CNI was 5.5% in 821 CEA patients.[361] However, only 11 (1.3%) had symptoms at 30 days and the CNI was disabling in only one patient (0.12%) at 6 months (modified Rankin Score >3). In CREST, the prevalence of CNI was 4.3% in 1151 patients, the most common injuries being glossopharyngeal/vagus (41%), mandibular branch of the facial nerve (30%), and hypoglossal (25%). Horner's syndrome complicated 4% of CEAs. In CREST, one-third of CNIs resolved within 30 days, with 81%

resolved by 1 year. In terms of HRQoL analyses in CREST, CNI had an impact on eating and swallowing at 2–4 wks, but not thereafter.[364] This would suggest that although CNI is more common after CEA and is responsible for eating/swallowing problems in the first 2–4 wks, few are disabling in the long term.

CNIs can be avoided by good anatomical knowledge, by dissecting close to the arterial wall and by careful use of forceps, retractors, cautery, and clamps. A useful manoeuvre to minimise injury to the hypoglossal nerve is division of the sternocleidomastoid artery, which tethers the nerve. The hypoglossal nerve can then be indirectly retracted by applying a tie to the divided ansa cervicalis. Injuries to the mandibular branch of the facial nerve can be minimised by avoiding jaw retraction and by curving the skin incision posteriorly toward the mastoid process. In a RCT involving 1126 CEA patients, perioperative administration of dexamethasone reduced temporary CNIs, without reducing the prevalence of permanent CNIs.[365]

2.6.1.6. New postoperative cerebral ischaemic lesions. ICSS undertook a substudy in which CEA and CAS patients underwent DWI-MRI 1–7 days before treatment, followed by a second scan 1–3 days after treatment, and a third scan 27–33 days after treatment,[366] each analysed by blinded investigators. Sixty-two of 124 CAS patients (50%) and 18/107 CEA patients (17%) had at least one new DWI lesion on the first post-treatment scan (OR 5.21, 95% CI 2.78–9.79, $p < .0001$). When the scans were repeated at 1 month, there were persisting changes on fluid-attenuated inversion recovery (FLAIR) MR sequences in 28/86 CAS patients (33%), compared with 6/75 CEA patients (8%) (OR 5.93, 95% CI 2.25–15.62, $p = .0003$).[366] In a meta-analysis of two RCTs and 18 non-randomised studies (CAS = 989; CEA = 1115), the incidence of new DWI-MRI cerebral lesions was significantly greater after CAS than CEA (40% vs. 12%; OR 5.17, 95% CI 3.31–8.06, $p < .00001$).[367]

The clinical relevance of new DWI-MRI lesions is unknown. There is no evidence that these lesions predispose towards cognitive impairment, but this would require long-term studies and large numbers of patients. ICSS published follow-up data in the cohort who underwent pre- and postoperative MRI imaging.[368] The 5-year incidence of recurrent stroke/TIA was 22.8% in CAS patients with new DWI lesions, compared with 8.8% in CAS patients with no new DWI-MRI lesions (HR 2.85, 95% CI 1.05–7.72, $p = .04$). ICSS concluded that new ischaemic brain lesions after CAS may be a marker for an increased risk of recurrent cerebrovascular events and that DWI-positive patients might benefit from more aggressive and prolonged DAPT.[368]

2.6.2. Late complications

2.6.2.1. Prosthetic patch infection. In a review of 30 published case series (130 patients), patch infection complicated 0.4–1.8% of CEAs.[369] One-third presented within 2 months of the original procedure (usually with a preceding wound complication), while two-thirds presented after 6 months had elapsed, usually with a chronic sinus or pseudoaneurysm formation. Patch rupture or anastomotic dehiscence was relatively rare and mostly involved infections occurring within the first 2 months.[369] Staphylococci and streptococci were the underlying infective organisms in 90% of cases. Because an increasing proportion of coagulase-negative staphylococci are resistant to flucloxacillin, it is reasonable to start patients on intravenous vancomycin (or teicoplanin) while awaiting definitive cultures.

DUS is the first-line investigation and can reveal patch corrugation (which may precede the diagnosis of overt infection by 11 months[370]), the presence of deep collections, and/or pseudoaneurysm formation. DUS should, however, be supplemented by CTA in patients being considered for open exploration or insertion of a covered stent. Patch excision and arterial reconstruction with autologous vein (patch/bypass) is the "gold standard" treatment.[370,371] Patch excision and reconstruction with prosthetic material should be avoided because of high rates of reinfection.[369] There have been limited reports ($n = 5$) of using covered stents to treat patch infection (good initial results), but no long-term data are available.[369]

Recommendation 69	Class	Level	References
Patch excision and autologous venous reconstruction is recommended for most patients with prosthetic patch infection	I	C	369,371
Recommendation 70			
Insertion of a covered stent may be considered in selected "high-risk for surgery" patients with suspected prosthetic patch infection	IIb	C	369
Recommendation 71			
Patch excision and prosthetic reconstruction is not recommended for patients with patch infection after carotid endarterectomy	III	C	369

2.6.2.2. Restenosis after carotid interventions

2.6.2.2.1. Pathophysiology. "Recurrent" lesions within 4–6 wks of CEA represent residual atherosclerotic lesions, rather than restenoses. Restenosis usually begins 3–6 months postoperatively, secondary to neointimal hyperplasia. Restenoses developing after 24 months most likely

represent recurrent atherosclerosis. Factors associated with restenosis include smoking, hypertension, female gender, diabetes, small carotid diameter, residual stenoses, and primary closure after CEA.[73,99]

2.6.2.2.2. Surveillance for restenosis after endarterectomy and stenting. DUS criteria for diagnosing restenoses after CEA and CAS are different to imaging an untreated carotid artery (Section 2.1.5). Following CEA, it has been proposed that the PSV threshold for diagnosing a >50% restenosis should be 213 cm/s and 274 cm/s for diagnosing a >70% restenosis.[372] DUS criteria for diagnosing "in-stent restenosis" after CAS are summarised in Table 20. As can be seen, PSV threshold velocities are much higher than after CEA for diagnosing >50% and >70% restenoses.[373,374] However, the need to use higher PSV thresholds for diagnosing >50% ICA restenoses after CAS was not confirmed in a recent substudy from ICSS.[375]

DUS surveillance enables monitoring of disease progression in the contralateral ICA, which is more common than ipsilateral restenosis, with progression being dependent on disease severity at the time of CEA. The data are, however, conflicting as to its benefit. Patients with >50% contralateral stenoses have been reported to be five times more likely to progress during follow-up.[376,377] Ballotta undertook serial surveillance of contralateral ACS following CEA and reported that progression from a moderate (50–69%) to a severe (70–99%) stenosis was associated with an increased risk of TIA/stroke, with >80% of events occurring in the latter patient group.[378] No data, however, were provided for ipsilateral stroke rates alone.

By contrast, in a series of 151 CEA patients who underwent serial postoperative imaging of the non-operated ICA, cumulative freedom from stroke in the non-operated hemisphere was 99%, 96%, and 86% at 1, 5, and 10 years, respectively (mean stroke incidence = 1% per annum). Only one stroke in the contralateral hemisphere was preceded by a TIA and no stroke was associated with a severe (>70%) ICA stenosis.[379] Ten patients (7%) whose contralateral stenosis was <50% at baseline progressed to a severe stenosis during follow-up, but only three became symptomatic. In each case, however, onset of symptoms preceded recognition of disease progression. The study concluded that none of the observed strokes could have been prevented by postoperative surveillance.[379]

2.6.2.2.3. Prevalence of restenosis. A recent meta-analysis identified 11 RCTs which reported rates of restenosis >70% or occlusion after CEA and CAS.[380] RCTs were used (rather than observational studies) because they are prospective, they are conducted with greater scientific rigour, selection bias is reduced through randomisation and independent observers adjudicate most endpoints.[380] The weighted incidence of "restenosis >70% or occlusion" is detailed in Table 21.

A previous meta-analysis reported that CAS was associated with significantly higher >70% restenosis rates than after CEA (OR 2.41, 95% CI 1.28–4.53, $p = .007$).[195] In CAVATAS, however, most patients randomised to endovascular therapy were treated by balloon angioplasty. When the meta-analysis was confined to the five RCTs using primary stenting, the difference in severe restenosis rates between CEA and CAS was not statistically significant (OR 1.97, 95% CI 0.67–5.79).[195]

2.6.2.2.4. Restenosis and recurrent ipsilateral symptoms. There are conflicting data about whether there is any association between restenosis after CEA or CAS and recurrent ipsilateral symptoms. Table 22 summarises surveillance data from seven RCTs involving CEA patients ($n = 2839$) and four RCTs involving CAS patients ($n = 1964$). The principal investigators of each RCT were asked to check whether the diagnosis of restenosis >70% or occlusion was made before or after stroke onset and to provide details about the status of the asymptomatic ipsilateral ICA stenosis on the last DUS surveillance scan immediately preceding stroke onset.[380] There was no association between a previously asymptomatic "restenosis >70%" and late ipsilateral stroke in CAS patients. Only 1/125 patients with a restenosis >70% after CAS (0.8%) at 50 months' follow-up suffered a late ipsilateral stroke, compared with 37/1839 (2.0%) in CAS patients who did not develop a restenosis >70% (OR 0.87, 95% CI 0.24–3.21, $p = .8339$). Overall, 97% of all late ipsilateral strokes after CAS occurred in patients without a restenosis >70%.[380]

Table 20. Duplex velocity criteria for diagnosing in-stent restenosis after CAS.

In-stent restenosis	Peak systolic velocity	End diastolic velocity	ICA/CCA ratio
>50%	>220 cm/s		≥2.5
>70%	≥300 cm/s	≥90 cm/s	≥3.8

Based on data from Lal[373] and Stanziale.[374]

Table 21. Meta-analysis of the prevalence of restenosis >70% or occlusion in surveillance data from RCTs involving CEA and CAS.[a]

	No. of RCTs	No. of patients	Mean follow-up (months)	Restenosis >70% or occlusion % (95% CI)
Any CEA	11	4249	47	5.8% (4.1–8.2)
Patched CEA	5	1078	32	4.1% (2.0–8.4)
CAS or angioplasty	6	2916	60	10.3% (6.4–16.4)
CAS	5	2716	62	10.0% (6.0–16.3)

[a] Data derived from Kumar et al.[380]

Table 22. Meta-analysis of the prevalence of late ipsilateral stroke in CEA/CAS patients with and without an asymptomatic "restenosis >70% or occlusion" in the constituent RCTs.[a]

Procedure No. of RCTs No. of patients	Mean follow-up (months)	Stroke ipsilateral to >70% restenosis[b]	Stroke ipsilateral to restenosis <70%	OR (95% CI)
Any CEA 7 RCTs ($n = 2810$)	37	7/135 5.2%	40/2704 1.2%	4.77 (95% CI 2.29—9.92), $p < .0004$, $I^2 = 0\%$
CAS 4 RCTs ($n = 1964$)	50	1/125 0.8%	37/1839 2.0%	0.87 (0.24—3.21), $p = .8339$, $I^2 = 0\%$

[a] Data derived from Kumar et al.[380]

[b] All restenoses had been asymptomatic prior to stroke onset.

By contrast, a severe asymptomatic restenosis >70% after CEA did appear to be associated with a significantly higher risk of late ipsilateral stroke. Seven of 135 patients (5.2%) with a previously asymptomatic restenosis >70% prior to stroke onset suffered a late ipsilateral stroke at a median of 37 months' follow-up, compared with 40/2704 (1.2%) in patients without a restenosis >70% (OR 4.77, 95% CI 2.29—9.92, $p < .0001$).[380] However, 85% of late ipsilateral strokes after CEA occurred in patients without a restenosis >70%.[380] There were insufficient data to perform subgroup analyses in patients undergoing patched or eversion CEA.

2.6.2.2.5. Management of restenosis

2.6.2.2.5.1. Symptomatic restenoses. No RCTs have evaluated whether symptomatic restenoses should be treated medically or by redo CEA/CAS. It has, however, become customary to adopt the same treatment criteria that are used to select symptomatic patients with primary atherosclerotic stenoses (Section 2.3.3). Accordingly, if a patient reports ipsilateral carotid territory symptoms and has a 50—99% restenosis after CEA or CAS, they should undergo redo CEA or CAS within 14 days of symptom onset. Supervising clinicians should ensure that all patients receive optimal medical treatment (Section 2.2.1). Patients with recent symptoms with a <50% ipsilateral restenosis should be treated medically, in much the same manner as if they had presented without having undergone a previous CEA or CAS (Section 2.3.3). The choice of redo CEA or CAS should be based on MDT review, local surgeon/interventionist experience, and patient choice. In a meta-analysis of 13 studies ($n = 1132$ patients), there was no difference in 30-day death/stroke between CAS (3.1%) and redo CEA (3.7%) when treating recently symptomatic patients with 50—99% restenoses (OR 0.8, 95% CI 0.3—2.6).[258]

2.6.2.2.5.2. Asymptomatic restenoses. This remains a highly controversial subject. No RCT has evaluated whether BMT or redo CEA/CAS (+BMT) is the optimal treatment strategy for patients with asymptomatic >70% restenoses after CEA or CAS. Despite an intuitive belief that most asymptomatic restenoses are benign, a recent meta-analysis reported that two-thirds of patients undergoing treatment for restenoses were asymptomatic,[258] suggesting that many surgeons and interventionists were uncomfortable about not intervening in asymptomatic patients with restenoses >70%.

Kumar's meta-analysis suggested that patients developing an asymptomatic restenosis >70% after CAS would gain little or no benefit from reintervention, as the risk of stroke is very small (0.8% over 4 years)[380] (Table 22). However, the presence of an asymptomatic >70% restenosis after CEA was associated with a significantly higher risk of late ipsilateral stroke, compared with patients without a severe restenosis (Table 22).

The meta-analysis observed that, based on the data in Table 22, approximately 6% of patients undergoing CEA will develop a restenosis >70% (or occlusion) over a mean of 47 months. This means that approximately 1700 CEA patients would need to undergo DUS surveillance to identify 100 patients with an asymptomatic restenosis >70%. The presence of an untreated, asymptomatic restenosis >70% after CEA was associated with a 5% risk of late ipsilateral stroke (Table 22). If one assumes that all undergo reintervention, a maximum of five ipsilateral strokes will be prevented. However, 95/100 would ultimately undergo an unnecessary reintervention, two to three would suffer a perioperative stroke following CAS or redo CEA[258] and about 5% would suffer a CNI after redo CEA.[258] In effect, a policy of aggressively intervening in 100 patients with an asymptomatic >70% restenosis after CEA could only ever prevent about two to three ipsilateral strokes in the long term. Moreover, despite serial surveillance and reintervening in all patients with asymptomatic 70—99% restenoses after CEA, 85% of all late ipsilateral strokes destined to happen would still occur in patients with no evidence of a restenosis >70% (Table 22).

However, two subgroups with asymptomatic restenoses >70% do warrant DUS surveillance and reintervention. The first would be any patient developing neurological symptoms with carotid clamping during CEA under LRA, or during balloon inflation (proximal flow reversal) during CAS. The second would be patients who developed significant electrophysiological changes during carotid clamping or whose mean MCA velocities fell below 15 cm/s on TCD monitoring

during carotid clamping under GA. A threshold of 15 cm/s has been shown to correlate with loss of cerebral electrical activity.[381] In both subgroups, progression to occlusion may be more likely to be associated with a major haemodynamic stroke.

2.6.2.2.5.3. Redo endarterectomy or stenting? If a decision has been made to intervene, there are two options including surgery (redo CEA, bypass) or CAS, neither of which have been subject to randomised comparison. In a 2015 meta-analysis of 13 observational studies, where redo CEA was compared with CAS,[257] there was no difference in 30-day stroke/death (2.3% after CAS vs. 2.7% after redo CEA, OR 0.8, 95% CI 0.4—1.8). There was also no difference in the prevalence of recurrent restenosis >70% (4% after CAS vs. 7.7% after redo CEA). Redo CEA was associated with a 5.5% risk of CNI (mostly temporary) and a 2.7% risk of bleeding complications. CAS was associated with access site complications (1.9%), arrhythmia (1.4%), technical failure (1.3%), and residual stenosis (0.3%).[258]

Recommendation 72	Class	Level	References
Patients suffering a late ipsilateral stroke/TIA in the presence of an ipsilateral 50—99% restenosis should undergo redo carotid endarterectomy or carotid artery stenting	I	A	172
Recommendation 73			
It is recommended that patients suffering a late ipsilateral stroke/transient ischaemic attack in the presence of an ipsilateral <50% restenosis should be treated medically	I	A	172
Recommendation 74			
Reintervention may be considered in carotid endarterectomy patients with an asymptomatic 70—99% restenosis, following multidisciplinary team review	IIb	B	380
Recommendation 75			
It is recommended that carotid stent patients who develop an asymptomatic restenosis >70% are treated medically	I	A	380
Recommendation 76			
Serial surveillance and reintervention for asymptomatic restenoses >70% is recommended in patients who developed neurological symptoms during carotid clamping under local anaesthesia, or during balloon inflation (or proximal flow reversal) during carotid stenting	I	C	
Recommendation 77			
Serial surveillance and reintervention for asymptomatic restenoses >70% is recommended in carotid endarterectomy patients who developed significant electrophysiological changes during carotid clamping or whose mean middle cerebral artery velocities fell below 15 cm/s on transcranial Doppler monitoring during carotid clamping under general anaesthesia	I	C	
Recommendation 78			
When a decision has been made to undertake revascularisation in patients with a restenosis, it is recommended that the choice of redo endarterectomy or stenting should be based on multidisciplinary team review, local surgeon/interventionist preference, and patient choice	I	C	

2.7. Management of concurrent coronary and carotid disease

The presence of carotid stenosis/occlusion is associated with an increased risk of perioperative stroke in patients undergoing coronary artery bypass (CABG), but whether carotid disease is a risk factor, rather than an aetiological factor, has been the subject of considerable debate.

2.7.1. Is carotid disease an important cause of stroke during cardiac surgery? The prevalence of stroke after CABG is 1—2%.[382] The prevalence of carotid "stenosis >50%" in unselected CABG patients is 9%, while the prevalence of "stenosis >80%" is 7%.[382] A meta-analysis reported that CABG patients with "50—100%" carotid stenoses faced a 7% risk of perioperative stroke, increasing to 9% in patients with 80—100% stenoses.[383] High as these risks might seem, it is important to consider how occlusion and the patient's neurological status influences stroke risk after CABG. CABG patients reporting a prior history of TIA/stroke and those with carotid occlusion incur a much higher risk of post-CABG stroke. D'Agostino observed that the rate of post-CABG stroke was 18% in patients with a previously symptomatic unilateral carotid stenosis, increasing to 26% in symptomatic patients with bilateral stenoses who then underwent isolated CABG.[384] A systematic review suggested that CABG patients with carotid occlusion incurred an 11% risk of stroke after CABG.[382]

After excluding patients with symptomatic carotid disease (who are definitely at higher risk of post-CABG stroke) and those with occlusion (who cannot undergo CEA), the risk of perioperative stroke in a recent systematic review fell to ≤2.0% in CABG patients with unilateral (non-operated) asymptomatic 50—99%, 70—99%, and 80—99% carotid stenoses.[383] In the same systematic review, 6.5% of patients with bilateral ACS suffered a perioperative stroke, while 9.1% either died or had a stroke during CABG.[383]

The aetiology and laterality of perioperative stroke in 4674 CABG patients screened preoperatively for carotid disease found that 86% of strokes could not be attributed to carotid disease.[382] In a pooled series of 23,557 patients undergoing CABG without prophylactic CEA/CAS, 95% of 476 postoperative strokes could not be attributed to carotid disease.[385—387] Accordingly, most of the available evidence suggests no causal relationship between a significant, asymptomatic unilateral stenosis and post-CABG stroke, that is other aetiologies may play a more important role, particularly aortic arch atheroembolism. As CABG patients increase in age, so too does the prevalence of severe carotid disease, severe aortic arch disease, and post-CABG stroke (Table 23).[22,382,388]

Interestingly, the presence of a carotid bruit was the only significant predictor of severe aortic arch atherosclerotic disease,[389] while a >70% carotid stenosis on DUS was an independent predictor of severe aortic arch disease.[390] In a 2015 systematic review of predictors associated with stroke after CABG, Mao found seven variables associated with an increased risk of post-CABG stroke including increasing age, prior stroke/TIA, carotid stenosis, history of PAD, unstable angina, prolonged cardiopulmonary bypass, and postoperative atrial fibrillation.[391]

2.7.2. What is the value of screening patients undergoing cardiac surgery? Given the low prevalence of stroke after CABG, routine screening for ACS before CABG cannot be supported. Clinical/imaging factors associated with an increased likelihood of finding a severe carotid stenosis in CABG patients include increasing age, carotid bruit, history of prior stroke/TIA, and left main stem disease.[382,392]

2.7.3. Are carotid interventions indicated in cardiac surgery patients? The many different causes of stroke during CABG and the lack of a clear causal association with ACS mean that routine prophylactic carotid revascularization is unlikely to reduce the prevalence of post-CABG stroke. However, some CABG patients will benefit from a staged/synchronous carotid intervention. The literature supports staged or synchronous carotid interventions in CABG patients with a history of stroke/TIA,[384] but is less supportive of prophylactic CEA/CAS in CABG patients with unilateral 70—99% asymptomatic stenoses, where the stroke risk may only be about 2%.[383,393] The evidence would, however, support prophylactic CEA (or CAS) in patients with bilateral asymptomatic 70—99% stenoses, or a 70—99% stenosis with contralateral occlusion.[383]

Table 23. Prevalence of post-CABG stroke and its association with age and prevalence of carotid and aortic arch disease.

Age	Prevalence of post-CABG stroke[382]	Prevalence of carotid stenosis >70% on screening[a 22]	Prevalence of aortic arch disease[388]
50—59	1—2%	0.2% M:0.1% F	9%
60—69	2—3%	0.8% M:0.2% F	18%
70—79	4—7%	2.1% M:1.0% F	22%
≥80	8—9%	3.1% M:0.9% F	33%

M = males; F = females.

[a] Prevalence of carotid stenosis based on population screening, not screening in CABG patients.

However, a RCT has challenged this interpretation of the literature.[394] Illuminati randomised 185 CABG patients with unilateral, asymptomatic 70—99% carotid stenoses to staged/synchronous CEA prior to CABG or isolated CABG followed by CEA at a later date (deferred CEA). Thirty-day mortality was 1% in each group, while 30-day death/stroke rate was 4% (deferred CEA) and 1% (staged/synchronous CEA) (p = ns). Interestingly, the 90-day death/stroke rate was 9% with deferred CEA versus 1% for staged/synchronous CEA. The authors concluded that prophylactic CEA was potentially beneficial in CABG patients with unilateral asymptomatic 70—99% carotid stenoses to reduce the 90-day risk of ipsilateral stroke, rather than perioperative stroke.[394]

2.7.4. What carotid surgical/endovascular options are available? Interventional strategies include: (1) staged CEA followed by CABG; (2) staged CABG followed by CEA; (3) synchronous CEA and CABG; (4) staged CAS followed by CABG; and (5) "same day" CAS + CABG. Table 24 summarises the findings of several meta-analyses published over the last two decades. The majority of patients (>80%) would have been neurologically asymptomatic with unilateral ICA stenoses and the majority reported 30-day death/stroke rates of 7—8%.

Table 25 presents similar data, this time from administrative dataset registries, which are more likely to reflect "real world" practice. Thirty-day death/stroke ranged from 6% to 10% in predominantly asymptomatic patients, with the highest procedural risks being observed in patients with a history of stroke/TIA who underwent either staged/synchronous CEA + CABG (14%) or CAS − CABG (44%).[404]

One systematic review[400] suggested that performing CABG off-pump was associated with the lowest rates of post-CABG stroke, attributed to no cannulation of a diseased aortic arch. However, Gopaldas[406] found no evidence to support this in patients undergoing either staged or synchronous carotid interventions (Table 25).

CAS might be an alternative to CEA. In an updated meta-analysis (Table 24), which included 2727 patients who underwent staged or "same day" CAS-CABG, the overall 30-day death/stroke rate was 7.9%.[401] The majority (80%) were neurologically asymptomatic with a unilateral carotid stenosis, in whom the 30-day death/stroke rate was 6.7% after CAS + CABG with a death/stroke/MI rate of 8.5%. Given the low rates of stroke in asymptomatic patients with unilateral stenoses undergoing isolated CABG, it is unlikely that CAS + CABG (or CEA + CABG) will benefit the

Table 24. Meta-analyses of pooled 30-day outcomes from different revascularisation strategies in patients with combined carotid and cardiac disease.

Procedure	*n* =	Death	Stroke	MI	Death/stroke	Death/stroke/MI
Staged CEA then CABG (all)						
Brener 1996[395]	407	9.4%	5.3%	11.5%		
Borger 1999[396]	920	2.9%	3.2%		5.7%	
Naylor 2003[397]	917	3.9%	2.5%	6.5%	6.1%	10.2%
Sharma 2015[398]	7552	3.4%	1.9%		6.2%	
Staged CABG then CEA (all)						
Brener 1996[395]	213	3.6%	10.0%	2.7%		
Naylor 2003[397]	302	2.0%	5.8%	0.9%	7.3%	
Synch CEA + CABG (all)						
Brener 1996[395]	2308	5.6%	6.2%	4.7%		
Borger 1999[396]	844	4.7%	6.0%		9.5%	
Naylor 2003[397]	7753	4.6%	4.6%	3.6%	8.7%	11.5%
Sharma 2015[398]	17469	4.0%	4.3%	3.6%	7.9%	
Synch CEA + CABG (symptomatic)						
Naylor 2003[399]	514	5.8%	6.8%	1.9%	7.6%	8.1%
Synch CEA + CABG (asymptomatic)						
Naylor 2003[399]	925	3.6%	3.7%	2.2%	4.5%	4.5%
Synch CEA + CABG (off pump)						
Fareed 2009[400]	324	1.5%			2.2%	3.6%
Synch CEA + CABG (pre bypass)						
Naylor 2003[399]	5386	4.5%	4.5%	3.6%	8.2%	11.5%
Synch CEA + CABG (on bypass)						
Naylor 2003[399]	844	4.7%	2.1%	2.9%	8.1%	9.5%
Same day CAS + CABG (all)						
Paraskevas 2016[401]	531	4.5%	3.4%	1.8%	5.9%	6.5%
Staged CAS-CABG (all)						
Guzman 2008[402]	277	6.8%	7.6%		12.3%	
Naylor 2009[403]	760	4.2%	5.5%	1.8%	9.1%	9.4%
Paraskevas 2016[401]	2196	4.8%	5.4%	4.2%	8.5%	11.0%

CABG = coronary artery bypass graft; CAS = carotid stenting; CEA = carotid endarterectomy; MI = myocardial infarction; off pump means CABG done without cardiopulmonary bypass; pre-bypass, on bypass indicates when CEA was performed relative to cardiopulmonary bypass; synch = synchronous.

Table 25. 30-day procedural risks after CEA + CABG stratified for treatment strategy from large administrative dataset registries.

	Procedure		*n* =	Death	Stroke	Death/stroke
Dubinsky 2007[405] NIS 1993–2002	Staged/synch CEA + CABG	All cases	7073	5.6%	4.9%	9.7%
Timaran 2008[404] NIS 2000–2004	Staged/synch CEA + CABG	All cases	25,249	5.4%	3.9%	8.6%
	Staged CAS + CABG		862	5.2%	2.4%	6.9%
	Staged/synch CEA + CABG	Symptomatic	948		14.2%	
	Staged CAS + CABG	Symptomatic	25		44.0%	
Gopaldas 2011[406] NIS 1998–2007	Staged CEA + CABG	All cases	6,153	4.2%	3.5%	7.1%
	Synchronous CEA + CABG		16,639	4.5%	3.9%	7.7%
	Staged CEA + CABG	Off bypass	2004	4.0%		7.0%
	Staged CEA + CABG	On bypass	4149	4.3%		7.7%
	Synchronous CEA + CABG	Off bypass	5280	4.2%		6.5%
	Synchronous CEA + CABG	On bypass	11,359	4.5%		7.4%

NIS = National Inpatient Sample, synch = synchronous; all cases = symptomatic and asymptomatic; off bypass = CABG was done off cardiopulmonary bypass.

asymptomatic patient with unilateral stenoses. Another important finding from the systematic review was that performing staged or same-day CAS + CABG in patients with a prior history of TIA/stroke was associated with a 15% 30-day risk of death/stroke.[401]

Using propensity scoring, Shishehbor evaluated three approaches to carotid revascularisation in CABG patients with predominantly asymptomatic carotid disease, staged CEA-CABG (n = 45), staged CAS-CABG (n = 110), and combined CEA-CABG (n = 195). Staged CAS-CABG and combined CEA-CABG were associated with similar rates of death, stroke, and MI in the short term, with both being better than staged CEA-CABG.[407] Mortality was comparable across all treatment strategies in the early period, whereas higher stroke rates were observed in the combined CEA-CABG group and higher MI rates in the staged CEA-CABG

group at 1 year. Outcomes significantly favoured staged CAS-CABG after the first year.[407]

The requirement for DAPT after CAS can be a problem for the staged CAS-CABG approach, as it increases the risk of MI between the two procedures, as well as increasing the risk of perioperative bleeding during urgent or emergency CABG. However, evidence suggests that CAS can be performed on the same day as CABG using aspirin/heparin cover, with thienopyridine antiplatelet agents being started 6–12 hours after CABG.[401,408,409]

2.7.5. Managing patients with unstable coronary artery disease The Carotid Artery Revascularization and Endarterectomy (CARE) registry involved 255 patients who underwent CAS and 196 who underwent CEA prior to urgent cardiac surgery. The 30-day rate of death/stroke and MI was 15% after CAS and 22% after CEA,[410] which is considerably higher than reported in Tables 24 and 25. CARE did not, however, separate staged CEA-CABG and combined CEA + CABG and significant regional variations existed in practice, with 60% of carotid interventions being undertaken in asymptomatic patients.

Recommendation 79	Class	Level	References
Routine screening for carotid disease prior to open-heart surgery is not recommended	III	C	
Recommendation 80			
Ultrasound screening for carotid disease prior to coronary bypass should be considered in patients aged>70 years, those with a history of transient ischaemic attack or stroke, a carotid bruit or left mainstem disease so that the patient can be better informed of the increased risks associated with coronary artery bypass surgery in patients with concurrent carotid disease	IIa	C	382,392
Recommendation 81			
Staged or synchronous carotid intervention should be considered in coronary artery bypass surgery patients with a history of stroke or transient ischaemic attack in the preceding 6 months and a 50–99% carotid stenosis	IIa	B	382,384
Recommendation 82			
Staged or synchronous carotid endarterectomy should be considered, instead of stenting plus coronary bypass, in patients with a history of stroke or transient ischaemic attack in the preceding 6 months and a 50–99% carotid stenosis	IIa	B	397,399,401,404
Recommendation 83			
A staged or synchronous carotid intervention is not recommended in coronary artery bypass patients with an asymptomatic unilateral 70–99% carotid stenosis for the prevention of stroke after coronary bypass	III	B	383
Recommendation 84			
A staged or synchronous carotid intervention may be considered in coronary artery bypass patients with bilateral asymptomatic 70–99% carotid stenoses, or a 70–99% stenosis with contralateral occlusion	IIb	C	383
Recommendation 85			
The choice between carotid endarterectomy and carotid stenting in asymptomatic patients in whom a carotid intervention is deemed necessary prior to coronary artery bypass should be based on the urgency of performing surgery, choice of antiplatelet strategy during coronary bypass, individual patient characteristics, symptom status, and local expertise	IIa	C	

2.8. Carotid disease and major non-cardiac surgery

Vascular surgeons are often asked to advise on how to manage a patient undergoing major non-cardiac surgery who has a concurrent severe ACS. Should prophylactic CEA or CAS be considered to reduce the risk of perioperative stroke?

2.8.1. Prevalence of stroke after major non-cardiac surgery. The prevalence of perioperative stroke depends on the nature and complexity of the surgical procedure, the presence of risk factors and (most particularly) the timing of major surgery after a recent TIA or stroke (Table 26).

Table 26. Prevalence of perioperative stroke stratified for type of procedure.

Author	Population	*n* =	Stroke risk
Axelrodt 2004[411]	Major vascular surgery	5296 aortic	0.5%
		7299 lower limb bypass	0.4%
		7442 major amputation	0.6%
Sharifpour 2014[412]	Major vascular surgery	8077 major amputation	0.7%
		21,962 lower limb bypass	0.5%
		7888 open aortic	0.8%
		9823 EVAR	0.5%
Jørgensen 2014[413]	Non-cardiac, including vascular	481,113	0.1%
Sonny 2014[414]	Non-cardiac including vascular	2110	2.6%
Kikura 2008[415]	General, orthopaedic, thoracic, non-carotid vascular	36,634	0.3%
Parvizi 2007[416]	Knee arthroplasty	1636	0.4%
Bateman 2009[417]	Hemicolectomy	131,067	0.7%
	Hip replacement	201,235	0.2%
	Lung resection	39,339	0.6%
Huang 2010[418]	Caesarean section	303,862	0.05%
Mashour 2011[419]	Non-cardiac (low risk) general, orthopaedic, urology, ENT, plastics, thoracic, gynaecology	523,059	0.1%
Biteker 2014[420]	Non-cardiac, non-vascular	1340	2.3%

EVAR = endovascular aortic aneurysm repair.

The prevalence of perioperative stroke was <1% in all but two cohorts undergoing major (non-cardiac operations) in Table 26, suggesting that (for the vast majority of patients) perioperative stroke during major non-cardiac surgery is rarely a major problem.

2.8.2. Prediction of stroke after major non-cardiac surgery. Table 27 summarises features associated with an increased risk of perioperative stroke after non-cardiac surgical procedures. The most consistent were increasing age and a history of previous stroke.

2.8.3. Timing of major surgery after recent stroke. One of the main findings from Table 27 was how the timing of major non-cardiac operations after a recent stroke impacted on perioperative stroke. In a large Danish national study of adult patients undergoing 481,183 elective, non-cardiac operations, 7137 (1.5%) were undertaken in patients with a prior history of stroke. In the latter cohort, the risk of perioperative stroke was 11.9% when elective non-cardiac operations were performed within 3 months of stroke onset, declining to 4.5% where 3–6 months had elapsed and 1.8% where 6–12 months had elapsed. This compares with 0.1% in patients who had no history of prior stroke.[413]

2.8.4. Is there a role for prophylactic carotid endarterectomy or stenting? Patients undergoing non-cardiac, non-vascular major surgery with three or four cardiovascular risk factors (age, coronary disease, renal failure, hypertension, diabetes, smoking, body mass index >35 kg/m^2, chronic obstructive pulmonary disease, previous TIA) incurred a 0.7% incidence of perioperative stroke. With five or more risk factors, the incidence of perioperative stroke increased to 1.9%.[419,420] It is therefore important to review the overall cardiovascular risk profile in patients undergoing major non-cardiac, non-vascular surgical procedures as part of the consent process.[418,421] Most perioperative strokes are ischaemic and secondary to cardiac embolism. The perioperative period also involves complex haemodynamic stresses involving hypercoagulable and systemic inflammatory responses, all of which increase the risk of perioperative stroke, especially if anticoagulation or antiplatelet therapies need to be withdrawn.

The role of prophylactic carotid revascularisation in patients with ACS undergoing major non-cardiac, non-vascular surgical procedures has been evaluated in one RCT and one non-randomised study. Ballotta randomised 79 patients with severe ACS to prophylactic CEA within 1 wk of the major surgical procedure (n = 40), versus a deferred CEA after the major surgical procedure (n = 39). There were no perioperative deaths or strokes in either group. Two deferred patients (5%) suffered a minor stroke 65 and 78 days after their major surgical procedure, while awaiting CEA.[422]

Sonny performed a retrospective study to determine whether the presence of ACS predisposed patients who were undergoing non-cardiac, non-carotid surgery to a heightened risk of perioperative stroke. During a 5-year period, 2110 patients had carotid DUS performed within 6 months before or 1 month after their operation. Thirty-seven per cent of patients had at least one ACS >50%, while 13% had >70% stenoses. Of the 2110 patients included, 112 (5%) died within 30 days and 54 (3%) suffered a postoperative stroke. Neither of the stenosis thresholds (>50%, >70%) was associated with an increased risk of perioperative stroke.[414] Where possible, statin and antiplatelet therapy should not be stopped prior to major non-vascular surgical procedures in patients with asymptomatic 50–99% carotid stenoses.[423] The decision to temporarily withdraw anticoagulant therapy should be made on an individual patient basis following a review of whether the bleeding risk exceeds the risk of thromboembolic stroke.

Recommendation 86	Class	Level	References
Patients undergoing elective, non-cardiac surgery with a history of stroke or transient ischaemic attack within the preceding 6 months should undergo carotid artery imaging	I	B	413
Recommendation 87			
Patients with a history of stroke or transient ischaemic attack in the preceding 6 months who are to undergo elective, non-cardiac surgery with an ipsilateral 50—99% carotid stenosis should undergo carotid revascularisation before elective non-cardiac surgery	I	A	172,413
Recommendation 88			
It is recommended that, where possible, elective non-cardiac surgery should be delayed for 6 months in patients with a history of recent stroke and no significant carotid disease. The decision to proceed with semi-urgent elective surgery will have to be individualised, based on the underlying pathology	I	B	413
Recommendation 89			
Routine carotid imaging in asymptomatic patients undergoing non-cardiac surgery procedures is not recommended	III	B	411,412
Recommendation 90			
Patients undergoing major non-cardiac, non-vascular surgical procedures should undergo a comprehensive cardiovascular risk assessment to aid the consent process regarding the risk of perioperative stroke	I	B	419,421
Recommendation 91			
Wherever possible, statin and antiplatelet therapy should not be stopped prior to major non-vascular surgical procedures in patients with asymptomatic 50—99% carotid stenoses. Anticoagulant therapy withdrawal should be based on an assessment of thromboembolic and haemorrhagic risks	III	B	423
Recommendation 92			
Prophylactic carotid endarterectomy and carotid stenting are not recommended in patients with asymptomatic carotid stenoses prior to major non-cardiac, non-vascular surgical procedures	III	B	414,422

2.9. Occlusive disease of proximal common carotid and innominate arteries

2.9.1. Introduction. The incidence of significant stenosis or occlusion affecting the origins of aortic arch branch vessels is 0.5—6.4%, with a relatively higher frequency affecting the innominate or left subclavian arteries, as opposed to the left CCA.[424] Total CCA occlusion is relatively rare, affecting 2—4% of patients undergoing angiography for symptomatic cerebrovascular disease.[425] Patients with a symptomatic arch origin stenosis have a 2.3% annual risk of developing a stenosis affecting another arch branch vessel,[424] while tandem occlusive disease affecting the carotid bifurcation may be present in up to 17% of patients.

2.9.2. Clinical presentation. Left CCA lesions give rise to left hemispheric and left retinal symptoms. Left subclavian lesions give rise to vertebrobasilar and/or left upper extremity symptoms, while innominate lesions can involve three territories (right carotid, vertebrobasilar, and right upper extremity). Occlusive lesions involving branches of the aortic arch are generally atherosclerotic, but arteritis (Takayasu's, radiation) and dissection should be considered in younger patients.

2.9.3. Indications for revascularisation. Indications for revascularising arch branch origin lesions are similar to those for performing CEA. The natural history of isolated CCA or innominate stenoses is unknown. In patients with neurological sequelae or upper extremity ischaemia, the indication for revascularisation is relatively straightforward. There is no evidence supporting open or endovascular interventions in asymptomatic patients.

2.9.4. Endovascular versus open surgical reconstruction. There is controversy regarding the optimal intervention for patients with innominate artery disease, as there is often

Table 27. Predictors for perioperative stroke following major non-cardiac procedures.

Author	Population	Stroke predictors	OR (95% CI)
Axelrodt 2004[411]	Major vascular surgery	Aortic operation	1.7 (1.0–2.8)
Sharifpour 2014[412]	Major vascular surgery	Each 1 y increase in age	1.02 (1.01–1.04)
		Cardiac history	1.4 (1.1–1.9)
		Females	1.5 (1.1–1.9)
		History of stroke	1.7 (1.3–2.3)
		Acute/chronic renal failure	2.0 (1.4–3.0)
Parvizi 2007[416]	Knee arthroplasty	Age	1.2 (1.0–201.2)
		BMI	1.0 (1.0–1.1)
Kikura 2008[415]	General, orthopaedic, thoracic, non-carotid vascular	Age >70 y	23.6 (9.6–58.1)
		High-risk surgery	1.5 (1.1–2.2)
		Diabetes	2.2 (1.4–3.3)
		Coronary disease	2.3 (1.3–4.1)
		CCF	1.7 (1.1–2.7)
		AF	5.5 (2.8–10.9)
		Prior stroke	7.1 (4.6–11)
Bateman 2009[417]	Hemicolectomy, hip replacement, lung resection	Renal impairment	3.0 (2.5–3.5)
		AF	2.0 (1.7–2.3)
		Prior stroke	1.6 (1.3–2.1)
		Valvular heart disease	1.5 (1.3–1.9)
		CCF	1.4 (1.2–1.7)
		Diabetes	1.2 (1.0–1.4)
Mashour 2011[419]	Non-cardiac, non-neurosurgery, general, orthopaedics, urology, ENT, plastics, thoracic, gynaecology, minor vascular	Acute renal failure	3.6 (2.3–5.8)
		History of stroke	2.9 (2.3–3.8)
		History of TIA	1.9 (1.3–2.6)
		On dialysis	2.3 (1.6–3.4)
		Hypertension	2.0 (1.6–2.6)
		COPD	1.8 (1.4–2.4)
		Smoking	1.5 (1.1–1.9)
Biteker 2014[420]	Non-cardiac, non-vascular	Age	2.5 (1.01–3.2)
		History of stroke	3.6 (1.2–4.8)
Jørgensen 2014[413]	Non-cardiac	Stroke <3 months	67.6 (52.3–87.4)
		Stroke 3–6 months	24.0 (15.0–38.4)
		Stroke 6–12 months	10.4 (6.2–17.4)

BMI = body mass index.

multivessel involvement. Until 30 years ago, supra-aortic occlusive disease could only be treated by open surgery. Transposition of the CCA on to the subclavian artery provides direct autogenous revascularisation, but this may not always be feasible. Open CCA endarterectomy can be performed via an open or retrograde semi-closed endarterectomy. However, with recent advances in hybrid interventions, most innominate or proximal CCA stenoses/occlusions are now treated by open retrograde angioplasty and stenting.[424] In the largest published series of primary stenting for 145 aortic side branch origin lesions in 114 patients, the technical success rate was 97% and there were no strokes or deaths at 30 days. During a mean follow-up of 52 months (range 2–163), restenosis-free survival was 96% and 83% at 12 and 60 months, respectively.[424]

2.9.5. Open revascularisation: cervical versus transthoracic reconstruction. Techniques for reconstructing arch vessels include bypass via a transthoracic or extra-thoracic (cervical) approach. The transthoracic approach involves a median sternotomy or the less invasive "trap-door" technique. Cervical reconstructions are less invasive and are associated with fewer procedural risks. Patients with an isolated subclavian or CCA lesion (with a patent ipsilateral carotid or subclavian artery) should undergo transposition or bypass via a cervical approach. Saphenous vein was previously the first-choice conduit, but it is often small in calibre and more prone to kinking/angulation than prosthetic grafts, which otherwise offer durable patency and low morbidity.[426] At the other end of the spectrum is the patient with involvement of all three arch branches, where graft outflow must arise from the aorta via a median sternotomy. Transthoracic reconstructions can be performed with acceptably low morbidity/mortality. Moreover, the transthoracic approach is associated with significantly better long-term patency.[427]

2.9.6. Tandem proximal inflow and internal carotid artery disease. "Tandem disease" involves lesions affecting the innominate artery or proximal CCA, in addition to significant disease within the ipsilateral ICA. Historically, most were treated by total open procedures, but most now undergo a hybrid approach where open retrograde angioplasty/stenting of the innominate or proximal CCA is followed by CEA.[428]

Recommendation 93	Class	Level	References
Open or endovascular interventions to treat proximal common carotid artery or innominate artery stenoses/ occlusions are not recommended in asymptomatic patients	III	C	
Recommendation 94			
Most proximal common carotid artery and innominate stenoses should be considered for treatment via open retrograde angioplasty and stenting	IIa	C	424

2.10. Unresolved issues relating to managing carotid artery disease

The Writing Group identified key issues relating to the investigation and management of carotid artery disease that need to be addressed to better inform future guidelines. These include:

Should the "accepted" risk thresholds for performing CEA or CAS be reduced from 6% in symptomatic patients and 3% in asymptomatic patients?

Should the time threshold for a patient being defined as "recently symptomatic" (currently 6 months) be reduced?

The need to develop a validated algorithm for identifying "high-risk for stroke" asymptomatic patients in whom to target CEA and CAS.

To determine whether asymptomatic carotid disease contributes towards cognitive decline and whether CEA/CAS can reverse or prevent this?

Whether measurement of plasma biomarkers to evaluate excessive endothelial and coagulation system activation has any potential for guiding risk stratification in patients with asymptomatic carotid disease.

Should all recently symptomatic patients be started on dual antiplatelet therapy once parenchymal haemorrhage is excluded on CT/MRI and then be continued through the perioperative period?

Relevance of new DW-MRI lesions after CEA and CAS. Do these contribute towards a higher rate of recurrent stroke or cognitive decline?

In patients undergoing emergency stent retrieval thrombectomy for acute ischaemic stroke because of an ICA or MCA (M1/M2) occlusion, is it safe to perform CAS to treat concurrent extracranial ICA stenoses during the same procedure?

Which recently symptomatic patients with 0–49% ICA stenoses might benefit from urgent CEA or CAS?

What is the optimal timing for performing CEA or CAS after intravenous thrombolysis?

How should the presence of a tandem distal ICA severe stenosis influence management decisions in recently symptomatic patients with 50–99% ICA stenoses?

Can we accurately define patients who really are "high-risk for CEA" in whom one should preferentially perform CAS?

Can we accurately define patients who really are "high-risk for CAS" in whom one should preferentially perform CEA?

What is the optimal method for protecting the brain during CAS: none, distal filter, proximal protection, transcarotid approach?

Is it safe to perform CEA under locoregional anaesthesia if the patient is taking dual antiplatelet therapy?

Does intravenous heparin therapy confer any additional benefit over mono or dual antiplatelet therapy in patients who present with crescendo TIAs?

Is CEA under locoregional anaesthesia safer than CAS in "high-risk for CEA" patients with significant cardiac or chronic pulmonary disease?

Is there any role for testing antiplatelet resistance prior to CEA or CAS?

3. MANAGEMENT OF VERTEBRAL ARTERY DISEASE

3.1. Introduction

3.1.1. Burden of vertebrobasilar stroke. One-fifth of ischaemic strokes affect the vertebrobasilar territory, otherwise termed the posterior circulation.[429] Vertebrobasilar events receive much less attention than those affecting the carotid territory, but data suggest they are associated with a similarly high risk of early recurrent stroke.

3.1.2. Aetiology of vertebrobasilar stroke. The causes of vertebrobasilar stroke/TIA are similar to those affecting the anterior circulation,[430] including cardioembolism, large artery thromboembolism, and small artery disease. Atherosclerosis of the vertebral or basilar arteries accounts for 20–25% of strokes. Stenoses mostly occur at the VA origins, but they can affect the distal VA and basilar arteries. Intracranial stenoses are more common in individuals with a sub-Saharan African or East Asian ethnic origin, compared with Caucasians. Thromboembolism appears to be the main cause of ischaemia in patients with VA stenoses. This is supported by the detection of circulating emboli on TCD distal to the stenosis and by the temporal risk profile in patients with symptomatic stenoses, which shows a high early risk of recurrent stroke followed by a much lower risk, despite the continued presence of a stenosis.

Haemodynamic compromise was previously thought to be the main cause of vertebrobasilar symptoms. However, studies suggest that this is less common than previously thought. In the New England posterior circulation registry, only 13/407 patients (3%) had symptoms secondary to haemodynamic ischaemia and this was most commonly seen in patients with bilateral intracranial VA disease.[431] Cardiac embolism, usually from atrial fibrillation, accounted for a quarter of posterior circulation strokes/TIAs. An additional quarter resulted from disease of the small penetrating arteries, resulting in lacunar stroke. These penetrating arteries arise from the intracranial vertebral, basilar, and posterior cerebral arteries.[431]

3.1.3. Symptoms attributable to vertebral artery disease. The vertebrobasilar system supplies the brainstem, cerebellum, occipital lobes, and (in most patients) the inferior temporal lobes and most of the thalami. Accordingly, ischaemia can give rise to a wide range of symptoms, including vertigo, ataxia, eye movement disorders, bilateral limb weakness, complete visual loss (cortical blindness), and hemianopia.[430] However, vertebrobasilar events can also include symptoms that are classically attributable to presumed anterior circulation ischaemia, including unilateral weakness or numbness. In a consecutive series of 407 patients with posterior circulation stroke in a tertiary referral centre, the most common symptoms were dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%), and nausea/vomiting (27%). The most common signs were unilateral limb weakness (38%), gait ataxia (31%), unilateral limb ataxia (30%), dysarthria (28%), and nystagmus (24%).[432]

3.1.4. Imaging strategies in vertebral artery disease. MRI is more sensitive than CT for imaging posterior circulation ischaemia/infarcts, particularly in the brainstem.[433] This reflects the higher resolution of MRI over CT for identifying infarcts, especially small ones in the brainstem or cerebellum, because MRI is less prone to artefact than CT. DWI is the most sensitive MRI technique for detecting acute ischaemia or infarction. DW-MRI may be positive for up to 2 wks after onset of ischaemia, although it can occasionally be negative, particularly with very small brainstem infarcts.[434]

DUS is less sensitive at detecting VA stenoses than carotid stenoses.[435] The VA can often, but not always, be visualised on DUS, but the more distal VA segments cannot be imaged directly and the presence of a stenosis is often only inferred from waveform abnormalities. If waveform abnormalities are present, however, they have a high specificity.[436] DUS provides direct/indirect evidence of abnormal VA flow, including lesions located proximally or distally.[437] DUS can estimate VA size and direction of flow and can differentiate between hypoplasia, stenosis, occlusion, and aplasia of the VA. However, it has low sensitivity, especially for the deeply located proximal VA segment.[436,438] DUS can also indirectly suggest the presence of subclavian steal syndrome with pre-steal (transient mid-systolic flow deceleration), partial steal (flow reversal during systole), and complete subclavian steal (retrograde flow persisting throughout the cardiac cycle).

In the presence of VA origin occlusion, flow through collaterals may be seen, while stenoses may be visualised as turbulent flow or waveform dampening. An intra-stenotic to post-stenotic PSV_{VA} ratio >2.2 has been validated as the optimal criterion for diagnosing a proximal VA stenosis $\geq$50%, with a sensitivity and specificity of 96% and 89%, respectively.[439] Beyond stenosis grading, VA diameters that differ by $>$25% are considered non-symmetrical.[440] Hypoplasia in the V2 segment is defined as a diameter $\leq$2.5 mm and a significant decrease in flow velocities as compared with the contralateral side and an increase in ipsilateral flow resistance index >0.85.[441]

Historically, intra-arterial angiography was the "gold standard" for diagnosing atherosclerotic VA disease. However, because of angiography-related stroke, it has been replaced by non-invasive imaging, especially CEMRA and CTA. Both allow visualisation of the entire vertebrobasilar system, thereby enabling simultaneous detection of extra- and intracranial VA and basilar stenoses. CEMRA provides better visualisation of the vertebrobasilar system, particularly the proximal VA, than non-contrast MRA techniques, such as time of flight imaging.[435] In a study comparing CTA, CEMRA, and DUS, against the "gold standard" of intra-arterial digital subtraction angiography, CEMRA and CTA were found to have high sensitivity and specificity and were better than DUS for evaluating the VAs.[439]

Recommendation 95	Class	Level	References
Colour Duplex ultrasound is recommended as the first-line imaging strategy in patients with suspected vertebrobasilar ischaemia, but must be followed by either contrast-enhanced magnetic resonance angiography or computed tomography angiography before any decisions on intervention are made	I	B	438,439

3.2. Secondary prevention in asymptomatic patients

3.2.1. Optimal medical therapy

3.2.1.1. Risk factor control. There have been no specific RCTs evaluating the effect of risk factor control in patients with asymptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for ACS (Section 2.2.1.1).

Recommendation 96	Class	Level	References
A healthy diet, smoking cessation, and physical activity are recommended for all patients with asymptomatic vertebral artery disease	I	C	24—27

3.2.1.2. Antiplatelet therapy. There have been no specific RCTs evaluating the effect of antiplatelet therapy in patients with asymptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for ACS (Section 2.2.1.2).

3.2.2. Screening for asymptomatic vertebral artery disease. There have been no specific RCTs evaluating the effect of screening in patients with asymptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for ACS (Section 2.2.2).

Recommendation 97	Class	Level	References
Low-dose aspirin (75—325 mg daily) or clopidogrel (75 mg daily) if aspirin-intolerant, is recommended in asymptomatic patients with vertebral stenoses for the prevention of myocardial infarction and other vascular events	I	C	

3.2.1.3. Lipid-lowering therapy. There have been no specific RCTs evaluating the effect of statin therapy in patients with asymptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for ACS (Section 2.2.1.3).

3.2.3. Interventions for asymptomatic vertebral artery disease. The risk of stroke in patients with asymptomatic VA stenoses is much lower than for symptomatic VA stenoses. In a hospital-based study of 3717 patients with atherosclerotic arterial disease, 7.6% had asymptomatic VA stenoses of >50% on DUS.[442] The annual stroke risk was 0.2% in patients with isolated asymptomatic VA stenoses and 0.8% for those with VA and carotid artery stenoses.

Recommendation 98	Class	Level	References
Statin therapy is recommended for the prevention of late stroke, myocardial infarction, and other cardiovascular events in patients with asymptomatic vertebral artery stenoses	I	C	

3.2.1.4. Treatment of hypertension. There have been no specific RCTs evaluating the effect of antihypertensive therapy in patients with asymptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for ACS (Section 2.2.1.4).

Recommendation 99	Class	Level	References
Antihypertensive treatment is recommended for patients with hypertension and asymptomatic extracranial vertebral artery stenoses to maintain long-term blood pressure <140/90 mmHg	I	C	

3.2.1.5. Treatment in diabetic patients. There have been no specific RCTs evaluating the effect of therapy for diabetes in patients with asymptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for ACS (Section 2.2.1.5).

3.3. Tertiary prevention in recently symptomatic patients

3.3.1. Optimal medical therapy

3.3.1.1. Risk factor control. There have been no specific RCTs evaluating the effect of risk factor control in patients

Recommendation 100	Class	Level	References
In diabetic patients with asymptomatic vertebral artery stenoses, strict glycaemic control is recommended	I	C	
Recommendation 101			
In diabetic patients with asymptomatic vertebral artery stenoses, the target blood pressure should be <140/85 mmHg	I	B	48

Recommendation 102	Class	Level	References
Population screening for asymptomatic vertebral artery stenoses is not recommended	III	C	

Recommendation 103	Class	Level	References
Asymptomatic vertebral artery atherosclerotic lesions should not be treated by open or endovascular interventions	III	C	442

with symptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for symptomatic carotid stenoses (Section 2.3.2.1).

Recommendation 104	Class	Level	References
A healthy diet, smoking cessation, and physical activity are recommended for all patients with symptomatic vertebral artery disease	I	C	

3.3.1.2. Antiplatelet therapy. There have been no specific RCTs evaluating the effect of antiplatelet therapy in patients with symptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for symptomatic carotid stenoses (Section 2.3.2.2).

3.3.1.3. Lipid-lowering therapy. There have been no specific RCTs evaluating the effect of risk factor control in patients with symptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for symptomatic carotid stenoses (Section 2.3.2.3).

3.3.1.4. Treatment of hypertension. There have been no specific RCTs evaluating the effect of antihypertensive therapy in patients with symptomatic VA stenoses. Accordingly, it

Recommendation 105	Class	Level	References
Antiplatelet therapy is recommended in symptomatic patients with 50—99% stenoses not undergoing vertebral interventions. First-choice therapy is clopidogrel 75 mg daily or aspirin 75 mg daily plus modified release dipyridamole 200 mg twice daily. If intolerant of dipyridamole or clopidogrel, aspirin monotherapy (75—325 mg) should be used. If aspirin- and clopidogrel-intolerant, use modified release dipyridamole 200 mg twice daily	I	A	121—124,126
Recommendation 106			
It is recommended that patients undergoing vertebral artery stenting should receive dual antiplatelet therapy with aspirin (75—325 mg daily) and clopidogrel (75 mg daily). Clopidogrel should be started at least 3 days prior to stenting or as a single 300 mg loading dose in urgent cases followed by 75 mg daily. Aspirin and clopidogrel should be continued for at least 4 wks after stenting and then optimal long-term secondary preventive antiplatelet therapy should be continued indefinitely	I	C	
Recommendation 107			
Long-term aspirin plus clopidogrel therapy is not recommended in symptomatic patients undergoing open surgery or stenting of vertebral artery stenoses unless indicated for cardiac reasons	III	C	
Recommendation 108			
Concurrent gastro-protection therapy or proton pump inhibition with pantoprazole should be considered in patients prescribed clopidogrel who have one or more factors that increase the patient's risk of gastrointestinal bleeding (prior history of gastrointestinal bleeding, older age, *Helicobacter pylori* infection, concomitant use of aspirin, or other non-steroidal anti-inflammatory agents, anticoagulants, selective serotonin re-uptake inhibitors and steroids)	IIa	B	148—151

Recommendation 109	Class	Level	References
Statin therapy is recommended for the prevention of stroke, myocardial infarction, and other cardiovascular events in patients with symptomatic vertebral artery stenoses	I	C	

is reasonable to adopt the same strategy that has been recommended for symptomatic carotid stenoses (Section 2.3.2.4).

Recommendation 110	Class	Level	References
Antihypertensive treatment is recommended for patients with hypertension and symptomatic extracranial vertebral artery stenoses to maintain long-term blood pressure <140/90 mmHg	I	A	45,47

3.3.1.5. Treatment in diabetic patients. There have been no specific RCTs evaluating the effect of therapy for diabetes in patients with symptomatic VA stenoses. Accordingly, it is reasonable to adopt the same strategy that has been recommended for symptomatic carotid stenoses (Section 2.3.2.5).

Recommendation 111	Class	Level	References
In diabetic patients with symptomatic vertebral artery stenoses, strict glycaemic control is recommended	I	C	
Recommendation 112			
In diabetic patients with symptomatic vertebral artery stenoses, the target blood pressure should be <140/85 mmHg	I	B	48

3.3.2. Interventions in recently symptomatic patients. It was previously thought that vertebrobasilar events had a more benign prognosis than carotid events. Consequently, patients were less rigorously investigated and did not always receive intensive secondary prevention. Recent evidence, however, suggests that VA stenoses are associated with higher rates of early recurrent stroke, with a risk profile similar to (or worse) than that for carotid disease. Evidence suggests that the 90-day risk of recurrent stroke is 7% in patients with no VA stenoses, 16% in patients with extracranial VA stenoses, and 33% in those with intracranial VA or basilar artery stenoses.[443]

The evidence would, therefore, suggest that any intervention in symptomatic vertebrobasilar patients should probably be undertaken early after symptom onset.[443] This is not, however, reflected in several RCTs. In CAVATAS, the mean interval between symptom onset and randomisation was 92 days (range 5—376), while the mean interval between randomisation and endovascular treatment was 45 days (range 7—148 days).[444] In the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study,[445] the mean delay between qualifying event and stenting was 73 days (median 29, range 1—959 days). In the Vertebral Artery Stenting Trial (VAST), the median interval between last symptom and randomisation was 25 days (IQR 11—50), while the delay between randomisation and stenting was 7 days (0—12).[446]

3.3.2.1. Role of vertebral revascularisation in "positional vertigo.". It is not unusual for a diagnosis of "positional" vertebrobasilar ischaemia to be made in patients presenting with dizziness or vertigo during lateral neck rotation or extension. Historically, these symptoms have been attributed to VA "nipping" in the bony foramina of the transverse processes of the cervical vertebrae. However, while occasional diagnoses have been corroborated using CTA/MRA/DSA, most are probably made without any further investigation. As a consequence, patients may then be turned down for major surgery on the mistaken belief that they might be at high risk for perioperative stroke because of a misdiagnosis of vertebrobasilar ischaemia. A systematic review of the literature[447] observed that out of 20 published studies, seven reported no changes in VA or posterior cerebral artery (PCA) blood flow, while 13 described varying changes (reversal, complete occlusion, reduced flow). In a series of 46 patients with an accessible window for TCD and who presented with dizziness/vertigo on head movement, none exhibited any change in extracranial VA flow during head turning/extension and none had reversal of VA flow. There were also no changes in PCA flow characteristics (directionality/flow velocities) during head turning. In this series, 74% were referred to a balance clinic, where 94% noted an improvement following entry into a vestibular rehabilitation programme,[448] presumably because of successful treatment for benign positional vertigo.

3.3.3. Open surgical management. Access to the VA is less easy than for the ICA. This is the main reason why surgery is less commonly undertaken to treat symptomatic stenoses.[430] Surgical approaches to lesions at the VA origin include transposition to the ipsilateral CCA, VA reimplantation, vein bypass grafting from the subclavian artery. Reconstruction of the distal VA can treat stenoses or occlusions within the V2/V3 segments, but worldwide experience is limited.

A variety of techniques have been reported for reconstructing the distal VA V3 segment (from C2 to where the VA perforates the dura). These include transposition (suitable only for C1—C2 reconstructions) and bypass grafting. Transposition procedures using the ECA or occipital artery rely on the size and patency of the donor artery and are indicated if there is no suitable graft available. Graft conduits include reversed saphenous vein, prosthetic, and other autologous grafts (e.g. radial artery).[449] The only available data available are from non-controlled studies, which are vulnerable to publication bias and selective reporting of favourable results. These have reported early complication rates of 2.5—25% for VA reconstructions, with perioperative mortality rates of 0—4% and mortality rates of 2—8% for distal artery reconstruction.[449—452]

3.3.4. Endovascular treatment

3.3.4.1. Stenting vs. medical therapy. Few data are available regarding extracranial VA stenting in the early time period after onset of symptoms. A review of 600 cases of symptomatic VA stenoses (symptoms within 6 months) treated with angioplasty ± stenting stratified the stenoses according to whether they were proximally or distally located.[453] Stenting of the proximal VA was technically successful in 99%, with a mortality of 0.3% and a perioperative stroke rate of 1.3%. Following stenting, there was a low rate of annual recurrent stroke (0.6%), although there was a 25% restenosis rate. By contrast, stenting or angioplasty of the distal VA was associated with higher morbidity (10.6% for stenting, 7.1% for angioplasty), with mortality rates of 3.2% and 3.7%, respectively.[453]

A systematic review, involving 1000 patients undergoing extracranial VA stenting, reported a periprocedural stroke risk of 1.1%.[454] However, high restenosis rates (25—30%) complicated VA origin stenting. The systematic review observed that the use of drug eluting stents (DES) was associated with lower rates of restenosis compared with bare metal stents (BMS) (11% vs. 30%) after a mean follow-up of 24 months,[453] although not all case series have shown this association.[455,456] The available data suggest that interventions involving intracranial VA stenoses were associated with higher procedural risks than for extracranial lesions. However, this has to be balanced against the much higher risk of recurrent stroke for patients with intracranial VA stenoses.[443]

There are few RCT data to guide practice. CAVATAS randomised 16 patients with symptomatic VA stenoses to angioplasty or BMT.[444] None developed recurrent symptoms, but many patients were recruited months after their last TIA/stroke, that is well beyond the high-risk period for recurrent stroke.

The VAST study randomised 115 symptomatic patients with >50% intra- or extracranial VA stenoses. Fifty-seven were randomised to stenting and 58 to BMT.[446] Three stented patients suffered a stroke, MI, or vascular death within 30 days of treatment, versus one in the BMT group. During a median 3-year follow-up, seven stented patients (12%) and four (7%) in the BMT group experienced a stroke in the territory of the symptomatic VA.[446] During follow-up, there were eight "any" strokes in the stented group and seven in the BMT group. VAST was stopped prematurely because of regulatory issues and was underpowered to show any significant difference between stenting and BMT. There was no evidence of any benefit favouring stenting. It did, however, suggest that the risk of stenting for patients with intracranial VA stenoses was relatively high. This is very similar to data from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis Trial (SAMMPRIS).[457] SAMMPRIS compared stenting (Wingspan stent) against BMT in 450 patients with symptomatic intracranial stenoses, of whom 60 (13%) had stenoses of the VA or basilar arteries. Basilar artery stenoses were associated with particularly high rates of periprocedural ischaemic stroke following stenting (21% vs. 7% for other arteries).[458]

A systematic review, involving 672 symptomatic patients in four RCTs and six non-randomised studies between 2007 and 2015, and which compared outcomes between percutaneous transluminal angioplasty (PTA) plus BMT versus BMT alone, observed no significant benefit from PTA + BMT over BMT alone (Table 28).[459]

Not included in Feng's meta-analysis was the Vertebral Artery Ischaemia Stenting Trial (VIST), which presented its results at the European Stroke Organisation Conference in 2016.[460,461] VIST randomised 182 patients with symptomatic intra- and extracranial VA stenoses between BMT versus angioplasty with or without stenting. Almost all, however, underwent stenting. It had been hoped to recruit 540 patients, but funding was stopped because of slow recruitment. Of the 91 patients randomised to stenting, the procedure was not performed in 30 (33%). The main reason in 23 patients (77%) was the finding of a stenosis <50% on DSA at the time of the planned stenting. Selection prior to randomisation had been on the basis of CTA or MRA. Of the 61 patients in the stent group, the stenosis was extracranial in 48 (79%) and intracranial in 13 (21%). Mean follow-up was 3.5 years. The primary endpoint was any stroke during follow-up and on "intention to treat"

Table 28. 30-day and long-term outcomes in a meta-analysis of PTA + BMT versus BMT in patients with symptomatic vertebral artery stenoses.[a]

Endpoint	30-day		Long-term	
	PTA + BMT	BMT	PTA + BMT	BMT
Posterior circulation TIA	16.7%	0.0% $p = .09$	10%	38% $p = .11$
Posterior circulation infarction	1.8%	1.7% $p = .99$	6%	12% $p = .51$

[a] Data derived from Feng et al.[459]

analyses, this occurred in five patients (including one fatal stroke) in the stent group and in 12 patients (including two fatal strokes) in the medical group (HR 0.40, 95% CI 0.14—1.13, $p = .08$), which trended in favour of stenting. However, after adjusting for time from last symptom to randomisation, which was significantly shorter in the stented arm, the results became significant with a HR of 0.34 (95% CI 0.12—0.98, $p = .04$). As the majority of patients in VIST had extracranial stenoses, drawing firm conclusions on the benefit of stenting intracranial stenoses was not possible, but the risk of peri-procedural stroke appeared to be higher for intracranial stenoses (zero for stenting of extracranial stenoses, 2/13 [15%] following stenting of intracranial stenoses). Higher stroke risks associated with stenting of intracranial stenoses was also observed in the SAMMPRIS study.[457]

The fact that VIST (like VAST before it) stopped early, means that the study was inevitably underpowered to make definitive conclusions. However, while awaiting corroboration in larger RCTs, the VIST findings suggest that stenting of recently symptomatic extracranial VA stenoses may be appropriate in selected patients, especially those with recurrent symptoms, despite risk factor modification and optimal BMT.[460,462]

Angioplasty with stent placement seems to aid durability. Specifically designed stents for the VA are not available and coronary balloon-expandable stents are typically used because they have a low crossing profile, limited foreshortening, and easy navigation through tortuous vessels. Although self-expanding stents are more difficult to deploy as precisely as balloon-expandable stents (especially in ostial lesions), they can be reserved for extracranial VA stenting in vessels with too large a diameter for using coronary stents (>4 mm). Late stent fracture with in-stent restenosis is a problem with endoluminal therapies at the VA origin. A recent meta-analysis of non-randomised studies suggested that there was no difference between DES and BMS regarding technical success, clinical success, and peri-procedural complications in the treatment of extracranial VA stenoses. However (compared with DES), BMS-treated patients had significantly higher rates of recurrent symptoms (2.8% vs. 11.3% (OR 3.3, $p = .01$) and restenoses (15.5% vs. 33.6%, OR 0.38, $p = .001$)[464] (Section 3.4.2).

3.3.4.5. Cerebral protection devices. Procedures can be performed with or without CPDs, although VAs are sometimes too small to accommodate them. One large review found distal protection was only used in 2% of cases.[462]

Recommendation 113	Class	Level	References
Patients with recurrent vertebrobasilar territory symptoms (despite best medical therapy) and who have a 50—99% extracranial vertebral artery stenosis may be considered for revascularisation	IIb	B	446,449,451,460,461
Recommendation 114			
No one should have a diagnosis of "positional vertigo" attributed to nipping of the vertebral arteries on head movements, unless corroborated by computed tomographic, magnetic resonance or digital subtraction angiography	III	C	447,448

3.3.4.2. Adjuvant medical therapy. Protocols regarding dual antiplatelet therapy, statins and intravenous heparin are the same as for CAS (Sections 2.3.2.2.3 and 2.3.2.3.3).

3.3.4.3. Access. Most procedures are performed via a femoral approach (93%), although transbrachial (3%) and trans-radial access (5%) have been used.[462] The procedure is usually performed under LA, thereby enabling continuous neurologic monitoring.

3.3.4.4. Choice of wires, access catheters, stent design. A 5F/6F guiding catheter or long-access sheath (when working via the CFA) is navigated to a stable position in the subclavian artery. The VA ostium is cannulated and the stenotic lesion crossed with 0.014- or 0.018-inch guide wires and treated using small coronary balloons and stents. Both monorail and over-the-wire systems are available, but the former has the advantage of using standard-length wires, making catheter exchange simpler. Despite high technical success rates, VA angioplasty (alone), especially when used for the treatment of disease at the VA origin, appears to have high rates of restenosis.[463]

3.3.4.6. Predilatation. The risks associated with predilatation in extracranial VA stenting have never been reported. It is reasonable to perform predilatation when the stent cannot pass through the VA stenosis.

3.4. Complications after vertebral interventions

3.4.1. Complications after surgical reconstructions. Relatively few surgeons have experience of performing significant numbers of open VA reconstructions. Accordingly, the results reported from large personal series by the small number who do, may not actually represent "real world" practice. Table 29 details 30-day rates of death, stroke (including laterality), and death/stroke after proximal and/or distal VA reconstructions in the contemporary literature.

Patency rates ranged from 84% to 100% at 30 days,[449,451,465—467] with one series of 352 VA reconstructions reporting early occlusion rates of 7%.[449] While 30-day death/stroke rates after proximal and/or distal VA reconstructions (Table 29) were relatively low

Table 29. Morbidity and mortality after vertebral artery reconstructions.

Author	Operation	*n* =	% sympt	Death	Any stroke	Carotid stroke	VB stroke	Death/stroke
Habozit 1991[468]	All VA ops	109	100%	1.8%	2.8%	0.9%	1.8%	4.6%
	VA ops only	73		0.0%	1.4%			1.4%
	VA + carotid	36		5.5%	5.5%			11%
Berguer 2000[451]	All VA ops	369	94%	2.2%	3.2%	2.2%	1.1%	3.8%
	Prox VA ops	252		1.6%	2.8%	2.8%	0.0%	
	Distal VA ops	117		3.4%	4.3%	0.9%	3.4%	
	VA ops only	286			2.4%			
	VA + carotid	83			6.0%			
Kieffer 2002[449]	Distal VA	352	94%	2.0%	3.4%	2.0%	1.4%	3.4%
	VA ops only	264		0.4%	2.3%	1.1%	1.1%	2.3%
	VA + carotid	88		6.8%	6.8%	3.4%	3.4%	6.8%
Hanel 2009[467]	Proximal VA	29		0.0%	0.0%	0.0%	0.0%	0.0%
Ramirez 2012[466]	All VA ops	74	82%	4.1%	4.1%		2.6%	6.8%
	VA ops only	39			2.6%	0.0%		5.1%
	VA + carotid	35			5.7%			8.5%
Coleman 2013[465]	Distal VA ops	41	91%	0.0%	2.4%			2.4%
	VA ops only	35		0.0%	0.0%			0.0%
	VA + carotid	6		0.0%	33%			33%

(2–7%), there was evidence of a trend across all published series that procedural risks were significantly higher when vertebral reconstructions were combined with carotid procedures (30-day death/stroke rate 8–11%). Paralysis of the spinal accessory nerve complicated 1–13% of procedures, averaging 7%, while Horner's syndrome (temporary or permanent) complicated 2–21% of procedures.[449,465–467]

3.4.2. Procedural risks following vertebral artery stenting.

In a review of outcomes in 20 non-randomised studies involving 1767 undergoing VA stenting, only five strokes (0.3%) were reported as occurring in the perioperative period. The rate of procedural TIA was 9/1767 (0.5%), while access complications occurred in 13 patients (0.7%) and eight procedures (0.5%) were complicated by dissection.[469] In this series, perioperative stroke was extremely rare. In the absence of specific studies on the treatment of stroke after VA stenting, no specific recommendations can be made other than advising that they should probably be treated in the same way as after CAS (Section 2.6.1.2).

3.4.3. Restenosis after vertebral artery stenting.

Risk factors for in-stent restenosis (ISR) include tortuosity of the extracranial VA, diameter of the stent,[470] diabetes mellitus, smoking, small VA diameters, and long stenoses (>10 mm).[471] The SSYLVIA study enrolled 61 patients, where 18 had stenoses located within the extracranial VA. SSYLVIA observed that 43% of BMS that were placed in the extracranial VA had ISR after 6 months. The proportion with ISR was considerably higher in ostial VA lesions, compared with pre-posterior inferior cerebellar artery VA lesions and intracranial lesions (67%, 25%, and 32%, respectively).[445]

In meta-analyses, the prevalence of >50% ISR after VA stenting varied from 0 to 45%,[454,471] reflecting heterogeneity regarding study duration, type of follow-up imaging, post-procedural medical therapy, and technical factors such as stent diameter. Table 30 summarises the findings from four systematic reviews on predominantly retrospective, single-centre case studies. Eberhardt combined data from over 300 endovascular interventions for symptomatic atherosclerotic disease of extracranial VAs and reported

Recommendation 115	Class	Level	References
Combined carotid and vertebral artery revascularisations should not be performed during the same procedure	III	C	449,451,465,466

Table 30. Meta-analyses on rates of restenosis after VA stenting.

Author	Years	*n* =	BMS *n* =	DES *n* =	Mean follow-up	Mean ISR %	ISR BMS	ISR DES
Eberhardt 2006[453]	1966–2005	313	n/a	n/a	12 mo	25.7%	na	na
Stayman 2011[454]	na	980	340	196	24 mo	n/a	30%	11.2%
Antoniou 2012[462]	1981–2011	1010	801	209	n/a	23%	na	12%
Langwieser 2014[473]	Up to 2013	457	287	170	n/a	n/a	23.7%	8.2%
Tank 2016[464]	2006–2012	304	148	156	14 mo DES 20 mo BMS	24.4%	33.6%	15.5%

mo = months.

that 26% had significant ISR at 12 months.[453] Stayman[454] combined 27 studies (980 patients) and observed that restenosis rates were lower with DES than with BMS (11.2% vs. 30%). In a more recent systematic review of 42 studies published between 1981 and 2011 (1099 patients), ISR was 23%. However, among 151 patients treated with DES, only 12% developed a significant restenosis.[462] Langwieser analysed nine studies comparing BMS and DES.[473] DES were associated with significantly lower rates of restenosis (8.2%), compared with BMS (23.7%, $p = .0001$) and significantly lower rates of symptomatic restenosis (4.7%) compared with BMS (11.6%, $p = .005$). In a more recent systematic review of studies published between 2006 and 2012, when compared with DES, BMS had significantly higher rates of recurrent symptoms (2.8% vs. 11.3%, OR 3.32, $p = .011$) and restenoses (OR 2.63; $p = .001$).[464]

Although DUS can identify proximal VA stenoses, the resolution of currently available ultrasound equipment is sub-optimal for the assessment of recurrent stenoses, especially within stented vessels. Hence, unlike with recurrent stenoses after CEA/CAS, surveillance imaging after VA endovascular interventions is challenging. While DSA remains the "gold standard," its routine use cannot be justified, especially as recurrent events after VA interventions are very low. Accordingly, for those who advocate imaging surveillance after VA interventions, DUS may be performed after VA stenting of ostial or proximal VA segments at 6 and 12 months and yearly thereafter. Any suspected lesions should be corroborated by CTA or MRA before considering catheter angiography.[73,453,476]

Recommendation 116	Class	Level	References
When extracranial vertebral artery stenting is being considered, drug eluting stents should be considered in preference to bare metal stents	IIa	C	462,464,473

Recommendation 117	Class	Level	References
Digital angiography for serial surveillance after vertebral artery interventions is not recommended	III	B	
Recommendation 118			
Serial non-invasive imaging of the extracranial vertebral arteries may be considered in patients who have undergone open or endovascular interventions	IIb	C	454,462

3.5. Surveillance strategies after vertebrobasilar reconstructions

Open revascularisation procedures for proximal VA lesions are associated with high rates of symptomatic improvement and low rates of recurrent stenoses. Hanel reported late outcomes in 29 patients undergoing proximal VA reconstructions. Only two developed recurrent symptoms attributable to vertebrobasilar insufficiency, while only one of 14 patients in surveillance developed a recurrent VA stenosis.[467] Kakino reported no cases of restenosis on follow-up angiography and no recurrent strokes during a mean follow-up of 54 months after VA to subclavian artery transposition.[474] Restenosis rates after endovascular treatment are detailed in Table 30.

The relationship between VA restenoses and recurrent symptoms is unclear. After VA stenting, ISR affects 11–45% of patients,[454,472] while stent fracture is not uncommon and has been associated with a higher prevalence of recurrent events.[471] The pathophysiology of stent fracture and ISR is probably mechanical irritation from the fractured struts causing smooth muscle proliferation and impaired re-endothelisation within the proximal VA. However, in another study, three out of 12 patients developed stent fractures and all remained asymptomatic.[475]

3.6. Unresolved issues relating to vertebral artery disease

The Writing Group identified a number of key issues relating to the investigation and management of atherosclerotic VA disease that need to be addressed to better inform future guidelines. These include:

Is there a role for early stenting in recently symptomatic patients with extracranial VA stenoses?

What is the optimal way to manage a recently symptomatic patient with an intracranial VA stenosis?

Should all recently symptomatic patients with vertebrobasilar TIA/stroke be started on dual antiplatelet therapy once parenchymal haemorrhage has been excluded?

Does the location of VA stenoses in symptomatic patients influence decisions regarding intervention or medical therapy?

What is the optimal method of detecting VA restenosis (CEMRA or CTA) after stenting with BMS or DES?

How best to manage patients with >70% asymptomatic restenoses after VA stenting?

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ACKNOWLEDGEMENTS

The Writing Group, ESVS guidelines committee, and the reviewers of this document would like to acknowledge the contribution of Dr Paola de Rango (Writing Group member) who sadly died during the preparation of these guidelines.

The Writing Group would like to acknowledge the assistance of Mr Athanasios Saratzis for undertaking additional statistical analyses during the preparation of these guidelines and Dr Stephen Murphy who assisted with reviews of the literature.

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