CLINICAL PRACTICE GUIDELINE DOCUMENT

Editor's Choice – European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease

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ABBREVIATIONS AND ACRONYMS

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACE	Aspirin and Carotid Endarterectomy Trial
ACES	Asymptomatic Carotid Emboli Study
ACS	Asymptomatic carotid stenosis
ACSRS	Asymptomatic Carotid Stenosis and Risk of Stroke Study
ACST	Asymptomatic Carotid Surgery Trial (1 & 2)
ACT-1	Asymptomatic Carotid Trial-1
AHA	American Heart Association
APRx	Antiplatelet therapy
ARR	Absolute risk reduction
ARWMC	Age related white matter change
AF	Atrial fibrillation
BA	Basilar artery
BES	Balloon expandable stent
BMS	Bare metal stent
BMI	Body mass index
BMT	Best medical therapy
BP	Blood pressure
CA	Carotid angioplasty
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAS	Carotid artery stenting
CAVATAS	Carotid & Vertebral Artery Transluminal Angioplasty Study
CaW	Carotid web
CCA	Common carotid artery
CCF	Congestive cardiac failure
CEA	Carotid endarterectomy
CCEA	Conventional carotid endarterectomy
CEMRA	Contrast enhanced magnetic resonance angiography
CETC	Carotid Endarterectomy Trialists Collaboration
CFA	Common femoral artery
CI	Confidence Interval
CNI	Cranial nerve injury
CNO	Carotid near occlusion
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COPD	Chronic obstructive pulmonary disease
CoW	Circle of Willis
CPD	Cerebral protection device
CREST	Carotid Revascularisation *vs.* Stenting Trial
CSTC	Carotid Stent Trialists Collaboration
CT	Computerised tomography
CTA	Computerised tomography angiography
CVR	Cerebral vascular reserve
DAPT	Dual antiplatelet therapy
DBP	Diastolic blood pressure
DES	Drug eluting stent
DLS	Dual layer stent
DM	Diabetes mellitus
DOAC	Direct oral anticoagulant
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
DWI	Diffusion weighted imaging
EAS	European Atherosclerosis Society
ECA	External carotid artery
ECEA	Eversion carotid endarterectomy
ECG	Electrocardiogram
EC-IC	Extracranial intracranial
ECST	European Carotid Surgery Trial
EEG	Electroencephalography
EJVES	European Journal of Vascular and Endovascular Surgery
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESO	European Stroke Organisation
ESVS	European Society for Vascular Surgery
EVA-3S	Endarterectomy *vs.* Stenting in patients with Symptomatic Severe carotid Stenosis
FLAIR	Fluid attenuated inverse recovery
FFT	Free floating thrombus
GA	General anaesthesia
GC	Guidelines Committee
GWC	Guideline Writing Committee
HDU	High Dependency Unit
HR	Hazard ratio
HRF	High risk feature
HS	Hyperperfusion syndrome
HTPR	High on treatment platelet reactivity
ICA	Internal carotid artery
ICH	Intracerebral haemorrhage
ICSS	International Carotid Stenting Study
IPH	Intraplaque haemorrhage
IA	Innominate artery
ISR	In stent re-stenosis
ITU	Intensive therapy unit
i.v.	Intravenous
JBA	Juxtaluminal black area
LAA	Large artery atherosclerosis
LDL-C	Low density lipoprotein cholesterol
LMWH	Low molecular weight heparin
LRA	Locoregional anaesthesia
MCA	Middle cerebral artery
MDT	Multidisciplinary team
MES	Micro-embolic signals
MI	Myocardial infarction

MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Score
MT	Mechanical thrombectomy
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NIBL	New ischaemic brain lesion
NIHSS	National Institutes of Health Stroke Score
OR	Odds Ratio
PAD	Peripheral arterial disease
PCA	Posterior cerebral artery
PCSK9	Proprotein convertase subtilisin/kexin type 9
PPI	Proton pump inhibitor
PSV	Peak systolic velocity
PTFE	Polytetrafluoroethylene
QC	Quality control
QIP	Quality improvement programme
RCT	Randomised controlled trial
rTPA	Recombinant Tissue Plasminogen Activator
RLN	Recurrent laryngeal nerve
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 & Aggressive Medical Management for Preventing Recurrent Stroke & Intracranial Stenosis
SBP	Systolic blood pressure
SCS	Symptomatic carotid stenosis
SVS	Society for Vascular Surgery (North America)
SPACE	Stent Protected Angioplasty *vs.* Carotid Endarterectomy
SSEP	Somatosensory evoked potentials
TCD	Transcranial Doppler
TCAR	Transcarotid artery revascularisation
TFCAS	Transfemoral carotid artery stenting
TIA	Transient ischaemic attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TRA	Transradial artery access
TT	Thrombolytic therapy
UFH	Unfractionated heparin
USPSTF	US Preventive Services Taskforce
VACS	Veterans Affairs Co-operative Study
VA	Vertebral artery
VAST	Vertebral Artery Stenting Trial
VB	Vertebrobasilar
VISSIT	Vitesse Intracranial Stent Study for Ischaemic Stroke Therapy
VAST	Vertebral Artery Ischaemia Stenting Trial
VKA	Vitamin K antagonist
VQI	Vascular Quality Initiative
VSGNE	The Vascular Surgery Group of New England

WHAT IS NEW IN THE 2023 GUIDELINES?

Each section has been revised or rewritten and five new sections added: (i) management of free floating thrombus (section 4.13), (ii) management of carotid webs (section 4.14), (iii) management of symptomatic patients with an ipsilateral 50—99% carotid stenosis and atrial fibrillation (AF) (section 4.16), (iv) planning carotid interventions in anticoagulated patients (section 4.2.6), and (v) timing of carotid interventions in patients with acute ischaemic stroke undergoing thrombolysis (section 4.8). The 2023 European Society for Vascular Surgery (ESVS) carotid and vertebral guidelines also highlight similarities/discrepancies with the 2021 American Heart Association (AHA) guidelines on the management of stroke/transient ischaemic attack (TIA),[1] the 2021 European Stroke Organisation (ESO) guidelines on carotid endarterectomy (CEA) and carotid artery stenting (CAS),[2] the 2021 German-Austrian guidelines on the management of carotid disease,[3] and the 2021 Society for Vascular Surgery (SVS) guidelines on the management of patients with carotid and vertebral artery disease.[4] There are 133 recommendations, of which, 84 are unchanged, 11 have been "regraded" since 2017 and 38 are new. The 2023 ESVS guidelines benefit from 289 new references (240 published between 2017 and 2022), including 39 primary or secondary analyses from randomised controlled trials (RCTs),[5—43] 71 systematic reviews and/or meta-analyses,[44—94], [95—114] and data from 50 vascular registries or quality initiative programmes (QIPs).[115—164]

There is an expanded section on "best medical therapy" (BMT) in asymptomatic (section 3.1) and symptomatic patients (section 4.2). There are new sections on the role of combination antiplatelet therapy (APRx) in recently symptomatic patients (section 4.2.2.2), including the peri-operative period (sections 4.2.2.3 and 4.2.2.4); thresholds for treating hypertension (section 4.2.8); and targets for lipid lowering therapy (section 4.2.7.3). There is a rewritten section on the relationship between asymptomatic carotid stenosis (ACS) and cognitive impairment (section 3.10). Since 2017, there is evidence that ACS patients with impaired cerebral vascular reserve (CVR) may be more likely to develop cognitive decline, but there remains no compelling evidence that CEA or CAS improves or prevents cognitive impairment. In the section on timing of CEA after thrombolysis (TT), meta-regression analyses suggest that a delay of six days after lysis completion should be considered before performing CEA, to maintain 30 day death/stroke rates within the 6% recommended threshold (section 4.8). The impetus towards treating symptomatic patients as soon as possible after transient ischaemic attack (TIA) or minor stroke is retained (section 4.5), with CEA being preferred over transfemoral CAS (TFCAS) when interventions are performed in the first 7 — 14 days after symptom onset (section 4.5.4). Whilst transcarotid artery revascularisation (TCAR) has emerged as a promising new CAS technology since 2017, only one registry[118] has reported outcomes stratified for delays from symptom onset to TCAR (section 4.5.5). The recommendation that patients with 60—

99% ACS in the presence of one or more clinical or imaging features that make them higher risk for stroke on best medical therapy, and who should be considered for CEA or CAS has been retained (section 3.6), but 80—99% ACS was not added to the high risk criteria. The rationale underlying this decision is detailed in section 3.6. The section on CAS techniques has been expanded to reflect advances in technology since 2017 (section 6) and there is an updated section on carotid interventions after mechanical thrombectomy (MT) (section 4.9). The guidelines conclude with a list of "unanswered questions", which highlight areas for future research (section 13), and a new section on Information for the Patient (section 14).

NEW RECOMMENDATIONS IN THE 2023 GUIDELINES

New Class I recommendations

11. For patients with asymptomatic carotid stenosis who are undergoing carotid endarterectomy, lower dose aspirin (75—325 mg daily) rather than higher dose aspirin (> 325 mg daily) is recommended.
23. For symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting following a transient ischaemic attack or minor ischaemic stroke, short term aspirin plus clopidogrel for 21 days followed by clopidogrel monotherapy, or long term aspirin plus dipyridamole modified release is recommended.
24. For recently symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole monotherapy or ticagrelor monotherapy is recommended.
25. For recently symptomatic carotid stenosis patients in whom carotid endarterectomy is being considered, it is recommended that neurologists/stroke physicians and vascular surgeons develop local protocols to specify preferred antiplatelet regimens (combination therapy *vs.* monotherapy), so as not to delay urgent carotid surgery.
29. For symptomatic patients undergoing carotid endarterectomy on aspirin monotherapy, lower dose aspirin (75 — 325 mg daily) rather than higher doses (> 325 mg daily) is recommended.
30. In symptomatic carotid stenosis patients undergoing carotid endarterectomy who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole modified release monotherapy (200 mg twice daily) is recommended.
35. For symptomatic carotid stenosis patients who do not reach their lipid targets on maximum doses or maximum tolerated doses of statins, ezetimibe (10 mg daily) is recommended.
58. For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus within the carotid artery, therapeutic anticoagulation is recommended.
63. For patients with a transient ischaemic attack or minor ischaemic stroke in the presence of newly diagnosed or known atrial fibrillation and an ipsilateral 50—99% carotid stenosis, comprehensive neurovascular work up with multidisciplinary team review is recommended to determine whether urgent carotid revascularisation or anticoagulation alone is indicated.
64. For patients who have been started on anticoagulation (on the basis that cardiac embolism was considered the most likely cause of their transient ischaemic attack or stroke) but who then report recurrent event(s) in the territory ipsilateral to a 50—99% carotid stenosis whilst on therapeutic levels of anticoagulation, carotid endarterectomy or carotid artery stenting is recommended.
66. For patients undergoing carotid endarterectomy, it is recommended that the operation be performed by trained vascular surgeons, rather than by surgeons from other specialties.
91. For patients experiencing a peri-operative stroke, it is recommended to differentiate between an intra-operative and a post-operative stroke.
92. For patients who develop an ipsilateral neurological deficit after flow is restored following carotid clamp release when carotid endarterectomy is performed under locoregional anaesthesia, immediate re-exploration of the carotid artery is recommended.
93. For patients who develop an ipsilateral or contralateral stroke at any time period following carotid endarterectomy or carotid artery stenting, urgent diagnostic neurovascular imaging of both carotid arteries and the brain is recommended.

New Class IIa recommendations

10. For patients with >50% asymptomatic carotid stenosis who are intolerant or allergic to aspirin, clopidogrel 75 mg daily should be considered. If intolerant or allergic to both aspirin and clopidogrel, dipyridamole monotherapy (200 mg twice daily) should be considered.
14. For patients with asymptomatic carotid stenosis with dyslipidaemia who are intolerant of statins, with or without ezetimibe, lipid lowering therapy with PCSK9 inhibitors should be considered.
27. For recently symptomatic patients with a 50—99% carotid stenosis who are to undergo carotid endarterectomy, peri-operative combination antiplatelet therapy should be considered, and should be started after imaging has excluded intracranial haemorrhage.
28. In recently symptomatic patients with a 50—99% carotid stenosis who are to undergo carotid endarterectomy where antiplatelet monotherapy is preferred to combination therapy, aspirin (300—325 mg daily for 14 days, followed by 75—162 mg daily) should be considered.
36. For symptomatic carotid stenosis patients who are intolerant of, or not achieving target low density lipoprotein levels on statins, with or without ezetimibe, additional or alternative treatment with PCSK9 inhibitors should be considered
49. For patients with acute ischaemic stroke due to a symptomatic 50—99% carotid stenosis who have received intravenous thrombolysis, delaying carotid endarterectomy or carotid stenting by six days following completion of thrombolysis should be considered.
54. For recently symptomatic patients with 50—99% stenoses and contralateral carotid occlusion or previous cervical radiation therapy, the choice of carotid endarterectomy or carotid artery stenting should be considered on an individual basis.
62. For patients with confirmed ocular ischaemia syndrome and a 50—99% ipsilateral carotid stenosis, carotid endarterectomy or carotid stenting should be considered to prevent further ischaemia induced retinal neovascularisation.

77.	For patients undergoing carotid endarterectomy, intra-operative completion imaging with angiography, duplex ultrasound or angioscopy should be considered in order to reduce the risk of peri-operative stroke.
79.	For patients undergoing carotid endarterectomy, selective wound drainage should be considered.
82.	For patients selected to undergo carotid artery stenting, transradial or transcarotid artery revascularisation should be considered as an alternative to transfemoral carotid artery stenting, especially where transfemoral access may confer a higher risk of complications.
83.	For patients undergoing carotid artery stenting, decisions regarding stent design (open cell, closed cell) should be considered at the discretion of the operator.
85.	For patients undergoing carotid artery stenting, when pre-dilatation is planned, balloon diameters <5 mm should be considered in order to reduce the risk of peri-procedural stroke or transient ischaemic attack.
88.	For patients undergoing carotid artery stenting, decisions regarding choice of cerebral protection (filter, proximal flow reversal) should be considered at the discretion of the operator.
New Class IIb recommendations	
51.	For a patient with acute ischaemic stroke undergoing intracranial mechanical thrombectomy with a tandem 50–99% carotid stenosis and a small area of ipsilateral infarction, synchronous carotid stenting may be considered in the presence of poor antegrade internal carotid artery flow or poor collateralisation via the circle of Willis after mechanical thrombectomy.
57.	For patients with carotid near occlusion and distal vessel collapse with recurrent carotid territory symptoms (despite best medical therapy), carotid endarterectomy or carotid artery stenting may be considered only after multidisciplinary team review.
59.	For patients presenting with recent carotid territory symptoms and free floating thrombus who develop recurrent symptoms whilst receiving anticoagulation therapy, surgical or endovascular removal of the thrombus may be considered.
61.	For symptomatic patients with a carotid web in whom no other cause for stroke can be identified after detailed neurovascular work up, carotid endarterectomy or carotid artery stenting may be considered to prevent recurrent stroke.
84.	For patients undergoing elective carotid artery stenting, dual layer mesh covered stents may be considered.
90.	For patients undergoing transfemoral carotid stenting, at least twelve carotid stent procedures per year (per operator) may be considered an appropriate operator volume threshold to maintain optimal outcomes.
101.	In selected high risk for surgery patients or emergency patients with suspected prosthetic patch infection, insertion of a covered stent may be considered, as part of the three stage EndoVAC technique
New Class III recommendations	
60.	For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus, intravenous thrombolysis is not recommended.
86.	For patients undergoing carotid artery stenting, post-dilation is not recommended when the residual stenosis is <30%, in order to reduce haemodynamic instability.
128.	For patients presenting with a vertebrobasilar territory transient ischaemic attack or stroke and a 50–99% vertebral artery stenosis, routine stenting is not recommended.

New recommendations included in the European Society for Vascular Surgery 2022 clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease in comparison to the previous 2017 guidelines. Numbers correspond to the numbers of the recommendations in the guideline document.

UNANSWERED QUESTIONS FROM THE 2017 GUIDELINES

In the 2017 guidelines, a series of "unanswered questions" were identified as being priorities for future research.[165] These involved scenarios where there were either no data, or conflicting evidence that did not allow recommendations to be made. The current guidelines have addressed some of the questions (see below). "Unanswered questions" arising from the 2023 guidelines are detailed in section 13.

Is there a validated algorithm for identifying higher risk of stroke ACS patients?

The six "higher risk of stroke on BMT" criteria in the 2017 ESVS guidelines have been corroborated by a 2020 meta-analysis of 64 observational studies,[67] with the new data summarised in section 3.6.

Does ACS cause cognitive decline and can this be reversed or prevented by CEA or CAS?

A 2021 systematic review identified significant associations between ACS and cognitive impairment (section 3.7), but without clear evidence of a causal relationship, apart from in patients with impaired CVR.[87] Impaired CVR is an ESVS criterion for being at higher risk of stroke on BMT in patients in whom CEA (should) or CAS (may) be considered. A second systematic review found no evidence that CEA/CAS significantly improved cognitive function in ACS patients.[46]

Should symptomatic patients start combination anti-platelet therapy once parenchymal haemorrhage is excluded on computed tomography (CT) or magnetic resonance imaging (MRI)?

Addressed in sections 4.2.2.2 and 4.2.2.4. A meta-analysis of RCTs[59] showed that early institution of combination APRx significantly reduced non-fatal ischaemic and haemorrhagic stroke, fatal ischaemic stroke, moderate to severe functional disability, and poor quality of life at 90 days *vs.* aspirin alone in patients with a high risk TIA or minor ischaemic stroke. The 2023 guidelines include a new algorithm detailing various peri-operative combination APRx strategies.

What is the relevance of new DW-MRI lesions after CEA and CAS, and do they contribute towards higher rates of recurrent stroke or cognitive decline?

Since 2017, a large study involving patients undergoing non-cardiac surgery reported that post-operative new ischaemic brain lesions (NIBLs) were associated with cognitive impairment, and increased rates of recurrent stroke/TIA.[166] The International Carotid Stenting Study (ICSS) also showed that NIBLs were associated with higher rates of recurrent stroke/TIA[167] (section 7.1.6).

Which recently symptomatic patients with < 50% stenoses might benefit from urgent CEA or CAS?

Addressed in section 4.10. In selected patients experiencing recurrent TIAs or minor ischaemic stroke, despite BMT and who have a < 50% stenosis, CEA or CAS may be considered, but only after multidisciplinary team (MDT) review.

What is the optimal timing for CEA or CAS after intravenous TT after acute ischaemic stroke?

Addressed in section 4.8. Meta-regression analyses of non-randomised studies showed that performing CEA early after TT was associated with significantly higher risks, with the absolute risk of stroke/death being reduced to within the current 6% accepted risk threshold after six days had elapsed after TT.[66] There remains debate as to whether CEA should be deferred for six days in all TT patients, or only in those with CT/MRI evidence of acute infarction.

Which symptomatic patients are at 'high risk for CEA' in whom one should preferentially perform CAS?

Addressed in section 4.11 Vascular registries have proposed several clinical and imaging criteria that were considered to make a patient higher risk for CEA. However, many have now been shown to be incorrect.

Which symptomatic patients are at 'high risk for CAS' in whom one should preferentially perform CEA?

Addressed in section 7.1.2.1 and includes anatomical variables associated with increases in peri-operative stroke,[16] age > 70,[16] performing transfemoral CAS < 7 days after TIA/stroke,[170] long or sequential carotid stenoses,[171] heavy calcification,[172] and a high age related white matter change (ARWMC) score.[173]

What is the optimal brain protection method during transfemoral CAS: none, distal filter, proximal protection?

The role of cerebral protection and evidence for varying types of protection systems are addressed in section 6.5. There are no RCT data, but expert consensus remains that some form of protection should be used during CAS.

Is there a role for stenting in symptomatic patients with extracranial vertebral artery (VA) stenoses?

Addressed in section 12.6.2.1, which includes a 2019 meta-analysis of three RCTs.[77] Recommendations remain unchanged; VA stenting should be considered only in patients with recurrent symptoms despite BMT.

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

Addressed in section 12.6.2.1, which includes a 2019 meta-analysis of three RCTs.[77] The 2023 guidelines recommend BMT, rather than stenting.

Should symptomatic patients with vertebrobasilar TIA/stroke be started on combination APRx once parenchymal haemorrhage is excluded on CT/MRI?

No RCTs have addressed this question in patients with vertebrobasilar (VB) symptoms. However, a meta-analysis of three RCTs[59] in patients with minor ischaemic stroke or TIA (which included VB patients) showed that early institution of combination APRx significantly reduced non-fatal ischaemic and haemorrhagic stroke, fatal ischaemic stroke, moderate to severe functional disability and poor quality of life at 90 days *vs.* aspirin alone (section 4.2.2.2). Recommendations regarding APRx in VB patients are the same as for carotid territory stroke/TIA.

What is the optimal method for detecting VA re-stenoses after stenting?

Duplex ultrasound (DUS) may be performed after stenting of ostial or proximal VA lesions (section 12.7). Suspected re-stenoses should be corroborated by CT angiography (CTA) or MR angiography (MRA). Distal VA interventions require surveillance with CTA/MRA.

How should > 70% asymptomatic re-stenoses after VA stenting be managed?

Only one registry (n = 72) has addressed this question[174] (section 12.6.5.2). Re-intervention did not significantly reduce stroke/TIA at one year (*vs.* BMT patients), but 33% of treated patients developed recurrent re-stenoses. Recurrent re-stenoses were significantly more likely to occur after balloon angioplasty than redo stenting.

1. METHODOLOGY

1.1. Purpose of the guidelines

ESVS has prepared guidelines for treating patients with atherosclerotic carotid and VA disease, in succession to the 2009 and 2017 versions.[165,175] Non-atherosclerotic pathologies (arteritis, fibromuscular dysplasia, dissection, aneurysm) are not included as they will be the subject of a separate guideline. Potential users include vascular surgeons, neurologists, angiologists, stroke physicians, primary care doctors, cardiologists, and interventional radiologists. A key aim is to optimise "shared decision making", where the patient has choice and control over how they prefer to be treated and how their care is delivered. This requires the doctor to provide as much evidence based information as possible regarding all available treatment options (i.e., not just those preferred by the treating doctor), together with a balanced discussion of risks, benefits, and potential consequences in a manner the patient understands, and which takes account of his/her preferences. Guidelines promote standards of care but are not a legal standard of care. They are a "guiding principle" and care delivered depends on patient presentation, choice, comorbidities, and setting (techniques available, local expertise). The 2023 guidelines are published in the *European Journal of Vascular and Endovascular Surgery* (*EJVES*), as an online open access publication, as well as being free to access via the ESVS website. They will also be available on a dedicated ESVS App.

1.2. Compliance with AGREE II standards

AGREE II reporting standards for assessing the quality and reporting of practice guidelines were adopted during preparation of the 2023 guidelines[176] and a checklist is available (Appendix A). There was no formal evaluation of *Facilitators and Barriers* and the guidelines did not have the scope to go into detail regarding health economics, largely because individual countries have different processes for determining cost acceptability.

1.3. Guideline Writing Committee

Guideline Writing Committee (GWC) members were selected by the GWC chairs and ESVS Guidelines Committee (GC) chair to represent clinicians involved in decision making in patients with atherosclerotic carotid and VA disease. The GWC comprised vascular surgeons, stroke physicians/neurologists, interventional radiologists, and interventional cardiologists (see Appendix B for specialty and institution). Views and preferences for the target population were not sought directly, but Mr Chris Macey of the Irish Heart Foundation and the Stroke Alliance for Europe collaborated in preparing section 14 (Information for Patients). GWC members provided disclosure statements regarding relationships that could be perceived as conflicts of interest (these are filed and available at ESVS headquarters via info@esvs.org). GWC members received no financial support from any pharmaceutical, device, or industry body, to develop the guidelines.

1.4. Evidence collection

A video conference was held on 6 July 2020, at which topics and tasks were allocated. The GWC met monthly (by video conference) to review progress. Search strategies were undertaken for each of the 46 subsections, using Medline, Embase, and the Cardiosource Clinical Trials and Cochrane databases to 31 December 2020, plus reference checking of cited papers. Hand searches were undertaken of publications in 11 journals between 2017 and 2020 including: *EJVES*, the *Journal of Vascular Surgery*, *Annals of Vascular Surgery*, *Stroke*, *The Journal of Stroke and Cerebrovascular Disease*, *Neurology*, *Lancet Neurology*, *Cerebrovascular Diseases*, the *International Journal of Stroke*, *Stroke and Vascular Neurology*, and the *European Stroke Journal*. At the request of the GC, selected articles published between January and December 2021 were included if they added important information that influenced decision making and recommendations. Only peer reviewed publications were included, following the Pyramid of Evidence principle (Tables 1 and 2). Multiple RCTs or meta-analyses of multiple RCTs were at the top, then single RCTs or large non-randomised studies (including meta-analyses of large non-RCTs), meta-analyses of small non-RCTs, observational studies, case series, and large prospective audits. Expert opinion was at the bottom of the pyramid, while case reports and abstracts were excluded. The evidence used in each of the 38 new recommendations is detailed in the Tables of Evidence (Appendix C).

1.5. Studies commissioned for the guidelines

Four systematic reviews/meta-analyses were commissioned: (i) the association between ACS and cognitive impairment;[87] (ii) the effect of carotid interventions on cognitive function in ACS patients;[46] (iii) the effect of timing of carotid interventions on outcomes in the early time period after symptom onset;[52] and (iv) the effect of timing of carotid interventions on outcomes in patients with acute ischaemic stroke undergoing TT.[66]

1.6. Recommendations

The European Society of Cardiology (ESC) system was used to develop classes of recommendation and levels of evidence.[177] The strength (class) is graded from I to III, with I being the strongest (Table 1). The letters A, B, C denote evidence levels (Table 2), with A being the highest.

Table 1. Classes of recommendations according to the ESC (European Society of Cardiology)

Class of recommendation	Definition	Suggested wording
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective	Is recommended
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	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended, should not be done

Table 2. Levels of evidence according to the ESC (European Society of Cardiology)

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses of randomised trials
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 experts and/or small studies, retrospective studies, registries

Recommendations were developed by GWC members assigned to each section and all GWC members then reviewed each completed section and approved the final wording and grading of the recommendation. During preparation of the first (and subsequent) drafts, GWC members participated in video conferences where the wording and grading of all

recommendations were checked before being submitted for external review. If there was not unanimous agreement to begin with, regarding the grading/wording of recommendations, discussions were held to decide how this might be achieved. Ultimately, the wording and grading of all published recommendations secured unanimous agreement among the GWC, although a majority vote (11:3) was taken on the decision not to include 80—99% ACS as a "high risk of stroke on medical therapy" criterion in ACS patients (section 3.6).

Since 2017, the GC undertook a review of the criteria for grading the class and level of evidence, to ensure these were standardised for future ESVS guidelines, especially regarding subgroup analyses from RCTs. A modified ESC system was used to classify the level of evidence and to determine the strength of recommendation. In this modified system, RCT meta-analyses are level A; larger non-RCT meta-analyses are level B; while meta-analyses of small non-randomised studies are level C. Furthermore, predefined subgroup analyses of RCTs or large RCT subgroup analyses can be level A, while other subgroup analyses of RCTs should be considered level B. As a consequence, while the wording of 11 recommendations remains essentially unchanged (compared with 2017), grades of evidence have been revised and the relevant recommendation box is highlighted as having been "changed".

1.7. Review process

There were three rounds of external review, involving 25 reviewers (16 GC members plus nine external reviewers). Review comments were assessed by the co-chairs, who coordinated a response to each comment via a formal revision process and GWC video conferences. The final version was approved by GWC members before submission to *EJVES* Editors on 6 April 2022.

1.8. Audit and update plan

These guidelines will be updated every four years. Vascular centres are encouraged to audit implementations made as a result of the guidelines. Audit cycles should be repeated and changes implemented. There are many ways to perform clinical audit and it is now a requirement for most centres to be registered with local audit committees.

2. INTRODUCTION

Primary prevention aims to reduce the clinical impact of ACS and VA stenoses (to prevent TIA or stroke). The goal of secondary prevention is to prevent recurrent TIA, stroke or vascular events in patients presenting with TIA or ischaemic stroke, secondary to carotid or VA stenoses.

2.1. Definition of stroke and transient ischaemic attack

The term "cerebrovascular accident" has been replaced with TIA or stroke. Because many studies in carotid stenosis patients pre-dated debates about whether to classify TIA/stroke as time based or tissue based,[178] this guideline has retained time based definitions. TIA is an episode of focal brain, retinal, or spinal cord dysfunction lasting $<$ 24 hours, which is of a non-traumatic, vascular origin.[179] Crescendo TIAs refer to multiple TIAs in a short time period, defined by some as more than two TIAs in 24 hours,[180] or at least three events in seven days,[181] with full recovery between. Stroke is a sudden onset focal (rather than global) neurological dysfunction, with symptoms lasting $>$ 24 hours (or causing death in $<$ 24 hours), which is of non-traumatic, vascular origin.[179] Stroke in evolution refers to a fluctuating neurological deficit (without full recovery), or a progressively worsening neurological deficit over 24 hours.[180]

2.2. Burden of stroke

In a European population of 715 million, 1.4 million strokes occur annually.[127] Stroke accounts for 1.1 million deaths annually in Europe and is the second commonest cause of death after coronary artery disease (CAD).[127] It is suggested that the number of Europeans living with stroke as a chronic condition may increase by 25% from 3.7 million (2015) to 4.6 million (2035), as a result of the ageing population.[155] Including indirect costs, European health systems spent € 45 billion annually on stroke care in 2015.[155] In the United States of America, total stroke costs were $ 49.5 billion (€ 43.9 billion) in 2015 — 2016,[182] and are expected to increase to $ 129 billion (€ 114 billion) by 2035.[183]

2.3. Aetiology of stroke

Of strokes, 15—20% are haemorrhagic (intracranial [ICH], subarachnoid), while 20% of ischaemic strokes are vertebrobasilar (VB). The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification for TIA/ischaemic stroke includes five categories: (1) large artery atherosclerosis (LAA): defined as $\geq$ 50% stenosis or occlusion of an extra- or intracranial artery); (2) cardioembolic; (3) small vessel occlusion; (4) other aetiologies (arteritis, dissection); and (5) undetermined aetiology (two potential causes, no cause identified, incomplete investigations).[184] In 2 204 ischaemic stroke patients, LAA was responsible for 16.6% of strokes. An ipsilateral 50—99% carotid stenosis was identified in 8%, while carotid occlusion or intracranial disease accounted for 3.5% each.[185] In another prospective study (883 patients with carotid territory symptoms), 4% had 50—69% ipsilateral carotid stenoses, while 8% had 70—99% stenosis. Overall, 12.5% had an ipsilateral 50—99% stenosis, while another 5.2% had ipsilateral occlusion.[121] The proportion of LAA strokes may be declining, in association with proportional increases in cardioembolic stroke,[186] attributed to declines in total cholesterol, low density lipoprotein cholesterol (LDL-C), blood pressure (BP), increases in high density lipoprotein cholesterol,[187] and substantial increases in APRx, antihypertensive, and statin prescriptions.[186] Between 2002 and 2014, there was a 30% decline in the prevalence of 60—99% carotid stenoses and a 36% decline in 80—99% stenoses in patients referred to a TIA/stroke service.[187]

2.4. Methods for measuring carotid artery stenosis severity

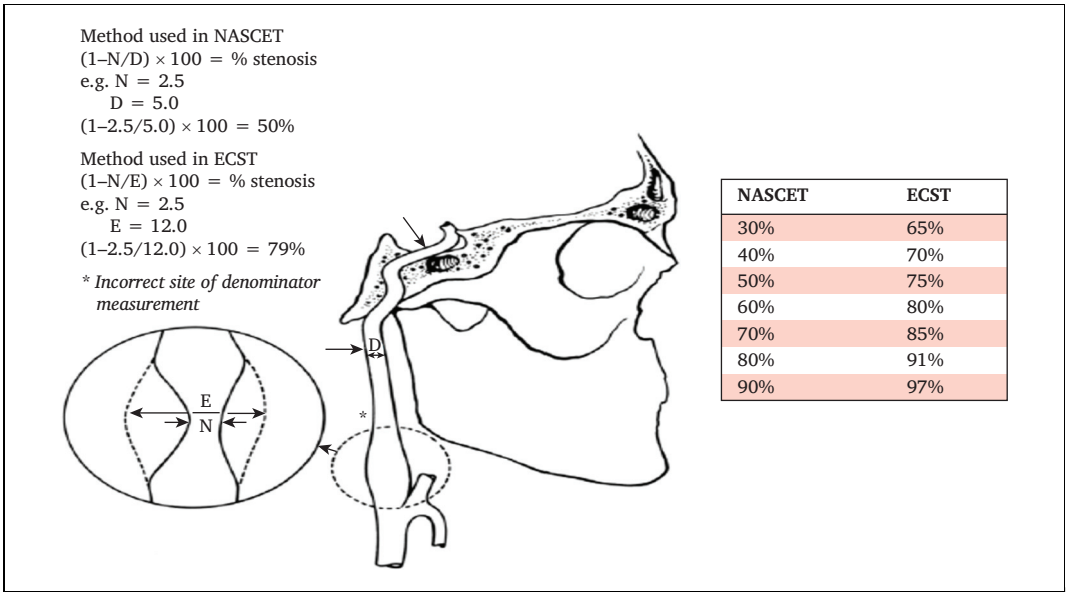
The European Carotid Surgery Trial (ECST)[188] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[189] adopted different methods for measuring stenosis (Figure 1).

Both methods used residual lumen diameter as the numerator. In ECST, the denominator was the estimated vessel diameter where the residual lumen was measured (usually the carotid bulb). In NASCET, the denominator was the diameter of disease free internal carotid artery (ICA) above the stenosis, where vessel walls were parallel. A 50% NASCET stenosis equates to a 75% ECST, while a 70% NASCET stenosis equates to an 85% ECST (Figure 1).[190] Uncertainty about methods used can lead to inappropriate patient selection (exclusion) for interventions.[191] The NASCET method has been adopted in the current guidelines, unless stated otherwise. The NASCET method does not permit measurement of stenosis severity in large volume plaques in dilated carotid bulbs. Here, the lumen may be slightly less than that of the distal ICA, so NASCET records a $<$ 50% stenosis, while ECST measures $>$ 70%. Symptomatic patients with large volume plaques consistent with an ECST $>$ 70% stenosis should, therefore, be considered for revascularisation.

The NASCET method has limitations regarding chronic near occlusion (CNO) with distal vessel collapse (section 4.12) unless the contralateral ICA is used as the denominator. In the RCTs, angiographic criteria for differentiating between CNO and a severe stenosis without distal collapse included at least two of (i) delayed contrast filling above ipsilateral stenosis; (ii) recruitment of circle of Willis (CoW) or distal ICA collaterals; (iii) diameter of distal ipsilateral ICA less than contralateral ICA; and (iv) distal ICA diameter equal to or less than diameter of the ipsilateral external carotid artery (ECA).[17] CNO with complete vessel collapse and a "threadlike" distal lumen (previously known as string sign, slim sign, or subocclusion) and CNO with partial vessel collapse have a prevalence $<$ 10% in patients with significant carotid disease.[192] Because angiograms are not routinely performed, CTA criteria have been developed to differentiate CNO from a 90— 95% stenosis with no distal vessel collapse, including (i) residual lumen $\leq$ 1.3 mm; (ii) ipsilateral distal ICA diameter $\leq$ 3.5 mm; (iii) ratio of ipsilateral distal ICA diameter to contralateral ICA $\leq$ 0.87; and (iv) ratio of ipsilateral distal ICA diameter to ipsilateral ECA diameter $\leq$ 1.27.[193]. It has also been proposed that the combination of distal ICA diameter $\leq$ 2 mm and an ICA diameter ratio $\leq$ 0.42 offers better prognostic discrimination.[194]

2.5. Imaging strategies in carotid artery disease

During ECST and NASCET, all participants underwent intra-arterial angiography. This policy has now been abandoned because of angiogram related stroke. In the Asymptomatic Carotid Atherosclerosis Study (ACAS), 30 day death/stroke after CEA was 2.3%, but half of the peri-operative strokes were angiogram related.[195] Colour DUS is the first line imaging modality due to low cost and accessibility and there are consensus criteria for diagnosing stenosis severity.[196—198] Alternatives include CTA or MRA which can simultaneously image the aortic arch, supra-aortic trunks, carotid bifurcation, distal ICA and intracranial circulation, which is important if CAS is being considered. Contrast enhanced MRA (CEMRA) has higher accuracy than non-contrast MRA (time of flight) but requires paramagnetic contrast agents (gadolinium). In a *Health Technology Assessment* meta-analysis of 41 non-randomised studies, DUS, MRA and CTA were equivalent in detecting significant stenoses,[199] but it was advised that centres relying on DUS before CEA should perform a second DUS, preferably by a second operator.[199] A combination of two imaging modalities (DUS + CTA or DUS + MRA) improves accuracy and is routine practice in many centres.[200] Table 3 summarises the sensitivity and specificity of DUS, CTA, and CEMRA, compared with the gold standard of digital



NASCET	ECST
30%	65%
40%	70%
50%	75%
60%	80%
70%	85%
80%	91%
90%	97%

Figure 1. North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) methods for measuring carotid stenosis severity.

Table 3. Sensitivity and specificity of duplex ultrasound (DUS), computed tomographic angiography (CTA), and contrast enhanced magnetic resonance angiography (CEMRA), compared with digital subtraction angiography (DSA)* in imaging of carotid artery disease

		DUS	CTA	CEMRA
Sensitivity – %	Occlusion	97	97	99
	Stenosis	89	75–85	94–95
Specificity – %	Occlusion	99	99	99
	Stenosis	84	93–96	92–93

* Data derived from Rojoa[91] and Wardlaw.[199]

subtraction angiography (DSA). Patients with ACS or SCS also benefit from functional CT/MRI imaging. In ACS patients, the presence of silent infarction confers a higher risk of stroke (section 3.6). In symptomatic patients, increasing acute infarction size predicts higher risks of stroke or intracranial haemorrhage after carotid revascularisation (section 4.7).

Recommendation 1 — **Changed**

For patients undergoing evaluation of the extent and severity of extracranial carotid stenoses, duplex ultrasound, computed tomographic angiography and/or magnetic resonance angiography are recommended.

Class	Level	References	ToE
I	B	Wardlaw *et al.* (2006)[199], Patel *et al.* (2002)[200]	

Recommendation 2 — **Changed**

For patients where 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.

Class	Level	References	ToE
I	B	Wardlaw *et al.* (2006)[199]	

Recommendation 3 — **Changed**

For a patient where carotid artery 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.

Class	Level	References	ToE
I	B	Wardlaw *et al.* (2006)[199]	

Recommendation 4 — **Unchanged**

In units which base management decisions in patients with atherosclerotic carotid disease on duplex ultrasound measurement, it is recommended that reports should state which measurement method is used.

Class	Level	References	ToE
I	C	Walker *et al.* (2006)[191]	

Recommendation 5 — **Changed**

For patients with atherosclerotic disease being considered for revascularisation, intra-arterial digital subtraction angiography is not recommended, unless there are significant discrepancies on non-invasive imaging.

Class	Level	References	ToE
III	B	Wardlaw *et al.* (2006)[199]	

2.6. Role of the multidisciplinary team

Where possible, decisions about carotid interventions should involve an MDT, which might include neurologists or stroke physicians, vascular surgeons, and interventional cardiologists or radiologists. This advice is supported by the 2021 ESO and German-Austrian guidelines.[2,3] MDTs increase the proportion undergoing urgent CEA (22% *vs.* 4%, $p < .001$).[201] Waiting for MDT meetings should not introduce unnecessary delay and urgent decisions can be made by at least two members. Procedural risks vary according to who assesses the patient. In a systematic review of 50 studies ($n = 15\,956$), 30 day death/stroke was 7.7% (95% CI 5.0 – 10.2) if the assessor was a neurologist *vs.* 2.3% (95% CI 1.8 – 2.7) where the surgeon adjudicated outcomes.[202] The German ProCAS Stent registry observed that neurologist assessment reported higher rates of transient (8.2% *vs.* 5.1%) or permanent neurological deficits (3.3% *vs.* 0.9%), *vs.* assessments undertaken by the operator performing CAS.[203]

Recommendation 6 — **Unchanged**

Multidisciplinary team review is recommended to reach consensus decisions regarding the indications for, and treatment of, patients with carotid stenosis regarding carotid endarterectomy, carotid stenting or optimal medical therapy.

Class	Level	References	ToE
I	C	Bazan *et al.* (2014)[201]	

Recommendation 7 — **Unchanged**

Independent neurological assessment before and after carotid interventions is recommended to audit peri-procedural risks.

Class	Level	References	ToE
I	C	Rothwell *et al.* (1995)[202], Theiss *et al.* (2004)[203]	

3. MANAGEMENT OF ASYMPTOMATIC CAROTID DISEASE

An asymptomatic carotid artery stenosis (ACS) refers to a stenosis detected in patients without any clinical history of ischaemic stroke, TIA, or other neurological symptoms which might be referable to the carotid arteries. These were the inclusion criteria adopted by ACAS,[195] while patients randomised within ACST-1 should not have reported any symptoms referable to the ipsilateral ACS within the preceding six months.[204]

3.1. Optimal medical therapy

Most primary prevention RCTs did not specifically recruit ACS patients, focussing primarily on stroke prevention in general. Some did include ACS patients or published subgroup analyses in ACS patients, and these have been highlighted where appropriate.

3.1.1. Lifestyle measures. Patients with ACS or symptomatic carotid stenoses (SCS) require lifestyle advice about diet, exercise, smoking cessation, and weight loss. Diets should be high in fruits, vegetables, whole grains, nuts, and legumes; moderate in low fat dairy and seafood; and low in processed meats, sugar sweetened drinks, refined grains, and sodium.[205] In a meta-analysis of four ACS screening cohorts, smoking increased the prevalence of > 70% ACS (odds ratio [OR] 3.0; 95% CI 2.1 — 4.4),[20] plaque progression,[207] and ischaemic stroke (relative risk increase [RRI] 1.9; 95% CI 1.7 — 2.2).[20] Moderate to high exercise conferred a 25% relative risk reduction (RRR) in stroke,[209] while obesity was associated with major increases in stroke (RRI 1.64; 95% CI 1.36 — 1.99).[210] The AHA recommended exercise intensity to prevent cardiovascular disease is 30 minutes, five times a week to reach at least 150 minutes per week of moderate exercise, or 25 minutes, three times a week to reach at least 75 minutes per week of vigorous activity.[211] A US Preventive Services Task Force (USPSTF) meta-analysis of nine RCTs (n = 12 551) evaluated behavioural counselling to promote healthy diets and physical activity. There was a reduced risk of cardiovascular events at 24 months (RRR 0.80; 95% CI 0.73 — 0.87) attributed to substantial reductions in BP, LDL-C, fasting glucose, and obesity.[85]

Recommendation 8			Changed
For patients with asymptomatic and symptomatic carotid disease, behavioural counselling to promote healthy diet, smoking cessation and physical activity is recommended.			
Class	**Level**	**References**	**ToE**
I	B	O'Connor *et al.* (2020)[85], Herder *et al.* (2012)[207], Shinton *et al.* (1989)[208], Lee *et al.* (2003)[209], Strazzullo *et al.* (2010)[210]	

3.1.2. Antiplatelet therapy

3.1.2.1. Monotherapy. Only one RCT (which did not show benefit) and one observational study (which did show benefit) evaluated APRx in patients with > 50% ACS on BMT (Table 4).

Two thirds of ACS patients have subclinical CAD.[214] In a systematic review of 17 observational studies in 11 391 patients with > 50% ACS, 63% of deaths were cardiac (average annual cardiac mortality 2.9%).[215] A meta-analysis of primary prevention trials reported that aspirin conferred a 12% reduction in serious vascular events, mainly through reduced non-fatal myocardial infarction (MI), 0.18% *vs.* 0.23% per year (HR 0.77; 95% CI 0.67 — 0.89, p < .001).[216] There are no large scale RCT data on the efficacy of clopidogrel, dipyridamole, ticagrelor, or prasugrel in ACS patients. If intolerant of aspirin, clopidogrel is a reasonable alternative, based on data extrapolation from ischaemic stroke patients.[81,217] If intolerant of, or allergic to, aspirin and clopidogrel, 200 mg dipyridamole twice daily is an alternative,[81] also based on data extrapolation from TIA/stroke patients.[218]

3.1.2.2. Combination. No RCT data support long term aspirin + clopidogrel or aspirin + dipyridamole in ACS patients, unless for other clinical indications.

3.1.2.3. In patients undergoing carotid endarterectomy. In the Aspirin and Carotid Endarterectomy Trial (ACE), 2 849 ACS/SCS patients undergoing CEA were randomised to four doses of aspirin (81 mg, 325 mg, 650 mg, 1 300 mg). In an efficacy analysis, which excluded patients on ≥ 650 mg aspirin before randomisation, the composite risk of 30 day stroke/MI/death was statistically significantly lower in patients randomised to 81 — 325 mg aspirin (3.7%) *vs.* 650 — 1 300 mg (8.2%; p < .001).[219] No RCTs have evaluated clopidogrel monotherapy or combination APRx in ACS patients undergoing CEA. If aspirin intolerant, it is reasonable to prescribe clopidogrel.[81] If intolerant or allergic to aspirin and clopidogrel, 200 mg dipyridamole monotherapy is an alternative.[81]

3.1.2.4. In patients undergoing carotid artery stenting. Table 5 summarises two RCTs evaluating APRx (and i.v. heparin) in patients undergoing CAS. In RCTs comparing CEA with CAS in ACS patients, aspirin + clopidogrel was recommended for > 24 hours[222,223] to three days pre-operatively,[224,225] and for two to four weeks[223,224] or at least six weeks[222,225] post-procedurally in CAS patients. The choice of three days pre-treatment with clopidogrel 75 mg daily (without a loading dose) is based on evidence that clopidogrel's maximum antiplatelet effect occurs after three to five days of therapy.[226] In CREST, aspirin 325 mg twice daily and clopidogrel 75 mg twice daily was recommended for ≥ 48 hours before CAS, followed by aspirin 325 mg daily for 30 days, combined with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily for at least four weeks.[227] Patients were not randomised to different APRx regimens in the larger RCTs and ticlopidine is no longer used because of unfavourable side effects.

3.1.3. Combination antiplatelet therapy and direct oral anticoagulants. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial randomised 27 395 patients with stable atherosclerotic disease, defined as CAD, peripheral arterial disease (PAD), or carotid disease (prior CEA/CAS or ≥ 50% ACS) to 100 mg enteric coated aspirin daily (n = 9 126), combination low dose rivaroxaban (2.5 mg twice daily) plus 100 mg aspirin daily (n = 9 152) or 5 mg twice daily rivaroxaban (n = 9 117).[15] After a mean follow up of 23 months, the composite endpoint of stroke, MI, or cardiovascular death was statistically significantly reduced from 5.4% in aspirin patients to 4.1% with low dose rivaroxaban + aspirin (HR 0.76; 95% CI 0.66 — 0.86, p < .001). There was, however, a statistically significantly higher rate of major bleeding complications with combination therapy (3.1% *vs.* 1.9%: HR 1.7, 95% CI 1.4 — 2.05, p < .001).[15]

Table 4. Studies evaluating antiplatelet therapy in asymptomatic carotid stenosis patients

Study name	Stenosis severity	Study method	Follow up time	Principle findings
Asymptomatic Cervical Bruit Study[212]	50–100%	RCT: 325 mg enteric coated aspirin daily ($n = 188$) *vs.* placebo ($n = 188$)	Median 2.3 y	No difference in composite endpoint of TIA, ischaemic stroke, unstable angina, MI and any cause death between groups (HR 0.99, 95% CI 0.67–1.46; $p = .61$)
Asymptomatic Carotid Emboli Study[213]	70–99%	Observational: APRx ($n = 419$) *vs.* no APRx ($n = 58$) at baseline	Mean 2 y	APRx significantly reduced risk of ipsilateral stroke or TIA (HR 0.45, 95% CI 0.31–0.66) and any stroke or cardiovascular death (HR 0.13, 95% CI 0.06–0.27) *vs.* no APRx

RCT = randomised controlled trial; APRx = antiplatelet therapy; TIA = transient ischaemic attack; MI = myocardial infarction; HR = hazard ratio; CI = confidence interval.

Within COMPASS, 1 919 had carotid disease,[9] but patients were excluded if they had a "non-lacunar" ischaemic stroke within one month of randomisation or had a history of lacunar or haemorrhagic stroke.[9,11] After a median follow up of 21 months, there was a non-statistically significant reduction in the composite endpoint from 6.1% (aspirin) to 3.9% with low dose rivaroxaban + aspirin (HR 0.63; 95% CI 0.38 – 1.05, $p = .07$).[9] The upper limit of the 95% CI was close to 1.0, suggesting the subgroup analysis was underpowered as a result of insufficient carotid patients being recruited. There was no statistically significant increase in major bleeding risks with low dose rivaroxaban + aspirin *vs.* aspirin alone (HR 1.18; 95% CI 0.55 – 2.51, $p = .6$).[9] Higher dose rivaroxaban did not reduce major vascular events in carotid patients (HR 1.01; 95% CI 0.65 – 1.56) but increased major bleeding risks (HR 2.34; 95% CI 1.21 – 4.52, $p = .009$). Despite forest plots showing similarly beneficial results in carotid patients and those with PAD and CAD, further trials are required before low dose rivaroxaban + aspirin can be recommended as routine antithrombotic treatment in well phenotyped ACS patients. No other guideline currently recommends low dose rivaroxaban + aspirin in ACS patients.[1–4]

Recommendation 9 — **Changed**

For patients with >50% asymptomatic carotid stenosis, lower dose aspirin (75–325 mg daily) should be considered, mainly for the prevention of late myocardial infarction and other cardiovascular events.

Class	Level	References	ToE
IIa	C	King *et al.* (2013)[213], Antithrombotic Trialists Collaboration *et al.* (2009)[216]	

Recommendation 10 — **New**

For patients with >50% asymptomatic carotid stenosis who are intolerant or allergic to aspirin, clopidogrel 75 mg daily should be considered. If intolerant or allergic to both aspirin and clopidogrel, dipyridamole monotherapy (200 mg twice daily) should be considered.

Class	Level	References	ToE
IIa	C	Murphy *et al.* (2019)[81]	

Table 5. Randomised controlled trials (RCTs) evaluating antiplatelet and intravenous heparin therapy in patients undergoing carotid artery stenting

Study	Stenosis severity	Method	Antithrombotic therapy	Main findings
Dalainas[220]	70–99%	RCT ($n = 100$; 88 with ACS)	325 mg aspirin daily for 7 d pre-CAS + 24 h i.v. heparin post-op, then 325 mg aspirin daily *vs.* 325 mg aspirin daily + 250 mg ticlopidine twice daily for 7 d pre-CAS and 30 d post-CAS, then 325 mg aspirin daily	Aspirin + heparin associated with significant increase in ipsilateral; ischaemic stroke/TIA (16%) *vs.* 2% ($p < .05$). No difference in bleeding complications (4 *vs.* 2%; $p > .05$)
McKevitt[221]	70–99%	RCT ($n = 47$; 9 with ACS)	75 mg aspirin daily + 24 h i.v. heparin (APTT ratio 1.5–2.5) *vs.*75 mg aspirin daily + clopidogrel (300 mg stat 6–12 h pre-op, 75 mg 2 h pre-op + 75 mg daily for days 1–28)	Aspirin + heparin associated with significant increase in 30 d ipsilateral amaurosis fugax, TIA, any stroke (25 *vs.* 0%, $p = .02$). No difference in incidence of groin haematoma (17 *vs.* 9%; $p = .35$)

ACS = asymptomatic carotid stenosis; TIA = transient ischaemic attack; APTT = activated partial thromboplastin clotting time.

Recommendation 11			New
For patients with asymptomatic carotid stenosis who are undergoing carotid endarterectomy, lower dose aspirin (75–325 mg daily) rather than higher dose aspirin (>325 mg daily) is recommended.			
Class	**Level**	**References**	**ToE**
I	B	Taylor *et al.* (1999)[219]	

Recommendation 12			Unchanged
For patients with asymptomatic carotid stenosis undergoing carotid stenting, combination antiplatelet therapy with aspirin (75–325 mg daily) and clopidogrel (75 mg daily) is recommended. Clopidogrel (75 mg daily) should be started at least three days before stenting or as a single 300 mg loading dose given in urgent cases. Aspirin and clopidogrel should be continued for at least four weeks after stenting and then antiplatelet monotherapy should be continued indefinitely.			
Class	**Level**	**References**	**ToE**
I	B	Murphy *et al.* (2019)[81], McKevitt *et al.* (2005)[221], Mannheim *et al.* (2017)[222], Gurm *et al.* (2008)[223], Rosenfield *et al.* (2016)[224], Eckstein *et al.* (2016)[225], Quinn *et al.* (1999)[226]	

3.1.4. Lipid lowering therapy. No RCTs have evaluated lipid lowering therapy in ACS patients. A post hoc analysis from the Asymptomatic Carotid Surgery Trial-1 (ACST-1) reported that patients taking statins had lower 10 year rates of non-peri-operative stroke *vs.* no statins (13.4% *vs.* 24.1%).[228] In a meta-analysis of 27 RCTs (n = 174 149), statins were associated with statistically significant reductions in stroke in people with a $\leq$ 10% five year predicted risk of major vascular events (RR 0.76, 95% CI 0.61 – 0.95, $p < .001$) per 1 mmol/L reduction in LDL-C.[229] Because of higher rates of cardiovascular events in ACS patients and low rates of serious adverse effects with treatment, statins (with or without ezetimibe[111]) are recommended as for SCS patients (section 4.2.7), independent of age and presence of hyperlipidaemia. At present, evidence is lacking to support specific LDL-C targets in ACS patients. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may stabilise plaques,[230] but no RCTs included large numbers of ACS patients.[95] However, in ACS patients with hyperlipidaemia who are intolerant of statins or ezetimibe, it is reasonable to consider PCSK9 inhibitors.[18]

Recommendation 13			Changed
For patients with asymptomatic carotid stenosis, lipid lowering therapy with statins (with or without ezetimibe) is recommended for the long-term prevention of stroke, myocardial infarction, and other cardiovascular events.			
Class	**Level**	**References**	**ToE**
I	B	Zhan *et al.* (2018)[111], Halliday *et al.* (2010)[228], Cholesterol Treatment Trialists Collaboration (2012)[229]	

Recommendation 14			New
For patients with asymptomatic carotid stenosis with dyslipidaemia who are intolerant of statins, with or without ezetimibe, lipid lowering therapy with PCSK9 inhibitors should be considered.			
Class	**Level**	**References**	**ToE**
IIa	C	Giugliano *et al.* (2020)[18], Schmidt *et al.* (2020)[95]	

3.1.5. Management of hypertension. Hypertension increases the likelihood of developing ACS,[231] and treatment in adults with ICA stenosis (*vs.* placebo) reduces stenosis progression (14% *vs.* 31%; p = .02).[232] No RCT has evaluated antihypertensive therapy for stroke prevention in ACS patients, but in a meta-analysis of 61 observational studies (1 million adults), there was a relationship between BP and stroke or death. Between 40 and 69 years of age, every 20 mmHg increase in systolic blood pressure (SBP), or 10 mmHg increase in diastolic blood pressure (DBP), was associated with a twofold increase in stroke/death. Differences in vascular morbidity/mortality were half as pronounced in patients aged 80 – 89 years. The influence of age was similar in men *vs.* women and for cerebral ischaemia *vs.* haemorrhage.[233] In another meta-analysis of 25 RCTs in patients with no vascular disease (standardised for 10 mmHg SBP and 5 mmHg DBP reduction), there was a reduction in late stroke (RR 0.54; 95% CI 0.45 – 0.65).[234] In another RCT, in hypertensive patients (n = 20 702) with no prior stroke/MI, enalapril + folic acid (*vs.* enalapril alone) reduced first ever stroke (HR 0.79; 95% CI 0.68 – 0.93).[235] The GWC advise adoption of ESC-European Society for Hypertension (ESC-ESH) recommendations, which the GWC consider reasonable for treating ACS and SCS patients.[236] The ESC-ESH guidelines recommend a target BP $<$ 130 mmHg/$<$ 80 mmHg in non-diabetic patients $<$ 65 years of age and $<$ 140 mmHg/$<$ 80 mmHg in non-diabetic patients $\geq$ 65 years old.[236] In diabetic patients, ESC-ESH advise a target SBP of 120 – 129 mmHg and a DBP of 70 – 79 mmHg in patients $<$ 65 years of age and a target SBP of 130 – 139 mmHg and a DBP of 70 – 79 mmHg in patients $>$ 65 years.[236]

Recommendation 15			Unchanged
For patients with asymptomatic or symptomatic carotid stenoses and hypertension, antihypertensive treatment is recommended.			
Class	**Level**	**References**	**ToE**
I	A	Williams *et al.* (2018)[236]	

3.1.6. Management of diabetes mellitus. Diabetes mellitus (DM) patients are more likely to develop stroke (*vs.* the general population without DM) and 20% of DM patients will die after a stroke.[237] DM is associated with a higher prevalence of ACS,[206] hypertension, and abnormal lipid profiles, but neither plaque burden nor plaque instability are increased in DM patients.[238] No RCTs have been performed in ACS patients, but in type II DM patients randomised to intensive *versus* conventional therapy, intensive intervention with multiple drug combinations and

behaviour modification was associated with a 60% RRR in cardiovascular events (HR 0.41; 95% CI 0.25 − 0.69, $p < .001$) and cardiovascular death (HR 0.43; 95% CI 0.19 − 0.94, $p = .04$).[239] In the Collaborative Atorvastatin Diabetes Study (2 838 type II DM patients without increased cholesterol levels), there was a reduction in stroke in patients treated (*vs.* not treated) with atorvastatin 10 mg/day (RRR 48%; 95% CI 11 − 69).[240] Meta-analyses found no evidence that optimal glycaemic control reduced stroke risk,[241] but it did reduce other DM related complications. The Prospective Pioglitazone Clinical Trial in macro−Vascular Events (PROACTIVE) trial ($n = 5\ 238$) reported that 45 mg pioglitazone (+ existing glucose lowering and cardiovascular medications), lowered stroke risks in type II DM patients.[242] Accordingly, it is important to aim for optimal glycaemic control in ACS patients, as per DM guidelines.[243−246]

Recommendation 16			Unchanged
For diabetic patients with asymptomatic carotid stenoses, optimal glycaemic control is recommended.			
Class	**Level**	**References**	**ToE**
I	B	NICE[243], NICE[244], ABCD[245], American Diabetes Association[246]	

3.1.7. Adherence to medications. In ACS patients, full adherence to medications is reduced with cognitive impairment, a patient's lack of insight regarding their illness, a lack of belief in the benefits of prescribed treatments, mental health issues, inadequate follow up or discharge planning, poor doctor patient relationships, barriers to accessing medications, missed appointments, treatment complexity, and drug costs.[247,248] In a simulation model in ACS patients, survival was significantly higher in patients who remained compliant, *vs.* non-compliant with BMT.[249]

3.2. Screening for asymptomatic carotid disease

The rationale for screening is 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, acceptable to the population in question; (iii) there is an accepted treatment for screen positive patients and an agreed policy for who to treat; and (iv) interventions should be cost effective.[250]

3.2.1. Is stroke prevention important? Section 2.2 summarises the burden and costs associated with stroke, which is also an important cause of long term disability.

3.2.2. Unheralded stroke and asymptomatic carotid stenoses. About 15% of ischaemic strokes are caused by an ipsilateral 50−99% carotid stenosis or occlusion.[185] Stroke in ACS patients has decreased over the last decade (section 2.3), attributed to BMT and risk factor control.[186,251]

3.2.3. Is duplex ultrasound reliable for diagnosing stenosis severity? The USPSTF noted that DUS was accessible and non-invasive, with 94% sensitivity and 92% specificity for diagnosing 60−99% ACS.[252] Accuracy varied (especially in inexperienced hands) and indiscriminate use in low prevalence populations resulted in low positive predictive values, as a result of high numbers of false positives. The USPSTF reported that screening 100 000 adults for 60−99% ACS with a predicted prevalence of 1% yielded 893 true positives plus 7 920 false positives. Even if all false positive tests underwent CEMRA, 792 with false positive scans might undergo CEA or CAS (almost as many as the 893 true positives).[252] If, however, the preferred therapy in screened patients was BMT, diagnosing stenosis severity becomes less important.[253]

3.2.4. Prevalence of asymptomatic carotid stenoses. The prevalence of > 50% and > 70% ACS in 23 706 people recruited from four general population based cohorts was 2% and 0.5%, respectively.[206] Table 6 details prevalences of > 50% and > 70% ACS, stratified for age and sex. The yield for finding > 70% ACS through unselected screening of patients aged < 80 years would be < 2%,[206] which is neither cost nor clinically effective. In a 2020 global meta-analysis, the prevalence of > 50% ACS in patients aged 30 − 79 years was 1.5% (95% CI 1.1 − 2.1), but this represented a 59% increase since 2000.[96]

3.2.5. Can a high risk of stenosis cohort be identified? Poorthuis validated a model to identify > 50% and > 70% ACS, involving 596 000 people attending screening clinics.[254,255] Notable predictors included increasing age, male sex, smoking, DM, prior stroke/TIA, CAD, PAD, high BP, and raised lipids. Using the highest risk decile in this model, one patient with > 50% ACS was detected for every 13 patients screened (while one patient with > 70% stenosis was found for every 58 patients screened). Screening of the highest decile might therefore identify 41% of people with > 50% stenosis and 51% with > 70% ACS.

3.2.6. Potential benefits of selective screening. Screening permits risk factor modification and BMT optimisation in screen detected patients, irrespective of stenosis severity. "Higher risk of stroke on BMT" patients may be candidates for CEA or CAS (section 3.6). In a study on compliance, 3 532 participants prescribed primary prevention therapy were randomised to undergo (or not) DUS. Patients randomised to

Table 6. Duplex ultrasound prevalence of >50% and >70% asymptomatic carotid stenosis in the general population*

Age − y	Stenosis − %	Stenosis prevalence − %	
		Men	Women
<50	>50	0.2	0.0
	>70	0.1	0.0
50−59	>50	0.7	0.5
	>70	0.2	0.1
60−69	>50	2.3	2.0
	>70	0.8	0.2
70−79	>50	6.0	3.6
	>70	2.1	1.0
≥80	>50	7.5	5.0
	>70	3.1	0.9

* Based on data from de Weerd *et al.*[206]

DUS and who had a carotid stenosis were shown their carotid lesions to reinforce the importance of compliance. In the DUS group, the Framingham Risk Score reduced at one year but increased in those not shown their atherosclerotic lesions.[34]

3.2.7. Potential harms with screening. Patients may undergo unnecessary interventions following a false positive screen, and some may suffer peri-operative stroke/death. Meta-analyses of RCTs comparing CEA with CAS report a 30 day death/stroke of 3.17% after CAS and 2.24% after CEA[94] (section 3.3.2). There may also be patient anxiety associated with screening.

3.2.8. Does screening prevent ipsilateral stroke? There is no evidence that screening the general population reduces stroke and no RCTs have evaluated the benefits of screening *vs.* non-screening for ACS.

3.2.9. Who advocates routine or selective screening? All published guidelines advise against routine screening. The 14-Society, ESC, SVS and German-Austrian guidelines recommend screening patients with multiple risk factors, provided they are willing to consider CEA or CAS if substantial stenosis is found.[3,4,256–258] SVS risk factors include PAD, age > 65 years with CAD, smoking, or hypercholesterolaemia[4], while 14-Society advice is to include those with no clinical evidence of atherosclerosis but with at least two of: hypertension, hyperlipidaemia, smoking, family history of stroke, or early onset atherosclerosis.[256] The 2021 USPSTF guidelines advise against any form of ACS screening.[105] ESO made no recommendation.[2]

Recommendation 17		Unchanged
Routine population screening for asymptomatic carotid stenosis is not recommended.		
Class	**Level**	**References**
III	C	Consensus

Recommendation 18		Unchanged
For patients with two or more vascular risk factors, selective screening for asymptomatic carotid stenosis may be considered in order to optimise risk factor control and medical therapy. The main purpose is to reduce late cardiovascular morbidity and mortality, rather than identifying candidates for carotid interventions.		
Class	**Level**	**References** **ToE**
IIb	B	AbuRahma *et al.* (2022)[4], Poorthuis *et al.* (2021)[254], Poorthuis *et al.* (2021)[255], Brott *et al.* (2011)[256], Cosentino *et al.* (2020)[257], Mach *et al.* (2019[258]

3.3. Randomised trials: endarterectomy versus best medical therapy

The Veteran's Affairs Co-operative Study (VACS), ACAS, and ACST-1 compared CEA plus BMT *vs.* BMT alone in 5 526 ACS patients.[195,204,259] Angiogram related stroke in patients randomised to CEA was included in intention to treat analyses.[195]

3.3.1. Medical therapy in the randomised trials. In VACS, 650 mg aspirin (daily) was taken by 55% of patients, while 27% took lower doses. Antihypertensive therapy was less commonly prescribed in VACS, and no patient received statins. In ACAS and ACST-1, BP, APRx, and lipid lowering therapy increased (13% of ACAS patients were on lipid lowering therapy at entry *vs.* 32% in ACST-1).[195,204,259]

3.3.2. Outcomes in the randomised trials. Table 7 details early and late outcomes in the three RCTs. In VACS and ACAS, half of all peri-operative strokes in CEA patients occurred after angiography.[195,259] VACS reported no difference in any or ipsilateral stroke at four years.[259] ACST found that CEA conferred notable reductions in any stroke at five and 10 years,[228] while ACAS reported that CEA conferred notable reductions in ipsilateral and any stroke at five years.[195]

3.4. Important subgroup analyses

3.4.1. Age. ACST-1 published outcomes stratified for age (< 65 years [$n = 912$]; 65 — 74 years [$n = 1\,558$], and > 75 years [$n = 650$]). Excluding peri-operative risks, CEA patients aged < 65 years had a five year risk of any stroke of 1.8% *vs.* 9.6% after BMT (ARR 7.8%; 95% CI 4.3 — 11.3). CEA patients aged 65 — 74 years had a five year risk of any stroke of 2.2% *vs.* 9.7% after BMT (ARR 7.5%; 95% CI 4.7 — 10.3), while CEA patients aged > 75 years had a 5.5% risk of any stroke at five years *vs.* 8.8% after BMT (ARR 3.3%; 95% CI 1.9 — 8.4).[228] Half of those aged > 75 who were randomised to CEA died in less than five years and once peri-operative risks (3.7%) were included, there was no evidence that CEA conferred benefit in patients aged > 75 years.[204] However, selected patients aged > 75 years with a predicted life expectancy of more than five years and at least one clinical/imaging feature that may make them "higher risk of stroke on BMT" might benefit from intervention (section 3.6).

3.4.2. Sex. A meta-analysis of ACAS and ACST-1 data at five years reported that men randomised to BMT were twice as likely to have a stroke *vs.* CEA (HR 2.04; 95% CI 1.5 — 2.8), while CEA did not appear to benefit women (OR 0.96; 95% CI 0.63 — 1.45).[260] At 10 years, however, ACST-1 reported that women gained benefit from CEA (ARR 5.8%; 95% CI 1.1 — 11.4), as did men (ARR 5.5%; 95% CI 0.9 — 10).[228] Reasons for the lack of early benefit in women may be that while procedural risks after CEA were similar to men, long term stroke risks on BMT were lower in women, so benefit took longer to accrue.

3.4.3. Stenosis severity. ACST-1 and ACAS reported that increasing stenosis severity was not associated with higher rates of stroke in BMT patients.[195,228] Meta-analyses of ACAS and ACST data showed that patients with 80—99% ACS were not more likely to suffer late stroke than < 80% ACS patients (OR 0.9; 95% CI 0.6 — 1.2).[62] The lack of a

Table 7. Five and 10 year outcomes after treatment of asymptomatic carotid stenoses with carotid endarterectomy (CEA) or best medical therapy (BMT) in Veterans Affairs Carotid Study (VACS), Asymptomatic Carotid Atherosclerosis Study (ACAS), and Asymptomatic Carotid Surgery Trial (ACST-1)

RCT (follow up time)	30 d D/S after CEA − %	Ipsilateral stroke including peri-op D/S*					Any stroke including peri-op D/S*				
		CEA − %	BMT − %	ARR − %	NNT	Stroke / 1 000	CEA − %	BMT − %	ARR − %	NNT	Stroke / 1 000
VACS (4 y)[259]	4.6	7.0	9.4	2.4	42	24 at 5 y	10.4	12.0	1.6	63	16 at 4 y
ACAS (5 y)[195]	2.3	5.1	11.0	5.9	17	59 at 5 y	12.4	17.8	5.4	19	53 at 5 y
ACST (5 y)[204]	2.8	No published data					6.4	11.8	5.4	19	53 at 5 y
ACST (10 y)[228]	2.8	No published data					13.4	17.9	4.5	22	45 at 10 y

RCT = randomised controlled trial; D/S = death/stroke; ARR = absolute risk reduction; NNT = number needed to treat to prevent one stroke; stroke / 1 000 = number of strokes prevented per 1 000 CEAs.
* Includes strokes occurring after diagnostic angiography.

relationship between stenosis severity and stroke risk was also reported in a meta-analysis of six RCTs and 35 observational studies, which observed that ipsilateral stroke rates were 1.9/100 person years (50—69% ACS,) *vs.* 2.1/100 person years for 70—99% ACS ($p = .43$).[251] The 2017 ESVS guidelines concluded that increasing stenosis severity was not associated with increased stroke risk.[165]

Since 2017, two meta-analyses have informed the debate. The first (five RCTs, 36 prospective observational cohort studies, and 15 retrospective cohort studies [$n = 13\,717$]) reported that ipsilateral stroke in cohort studies (but not in RCTs) was highly correlated with increasing stenosis severity.[62] It was hypothesised that the absence of increased stroke in 80—99% *vs.* < 80% ACS in the RCTs may have been a result of selection bias because trial investigators might have randomly assigned patients with severe stenosis whom they considered to be relatively low risk and enrolled patients with moderate ACS, whom they thought to be high risk.[62] If ACAS and ACST-1 data are excluded, patients in cohort studies with 80—99% ACS were more likely to experience late ipsilateral stroke *vs.* patients with < 80% ACS (OR 2.5; 95% CI 1.8 — 3.5).[62] However, six of the 11 cohort studies included ACS patients with a history of contralateral stroke/TIA, which is known to increase stroke risk.[62] Contralateral TIA/stroke was included in the 2017 ESVS guidelines as a higher risk of stroke on BMT criterion[165] when considering performing CEA or CAS in ACS patients (section 3.6).

In OXVASC, where contralateral ACS was diagnosed in patients presenting with stroke/TIA, all strokes ipsilateral to the ACS occurred in the first two years after the contralateral stroke/TIA[62] (rather than spread evenly over a five year period), suggesting a systemic vulnerability in this type of patient. When meta-analyses were restricted to the five cohort studies with no history of prior TIA/stroke, 80—99% ACS was still associated with higher rates of ipsilateral stroke compared with < 80% ACS (11.5% *vs.* 4.5%; OR 3.1, 95% CI 1.8 — 5.5).[62] However, four of the five cohort studies completed recruitment in the 1980s/early 1990s, when BMT was not comparable with the modern era and there were only 218 patients with 80—99% ACS in the five cohort studies.[62]

In the second meta-analysis (64 non-randomised cohort studies [$n = 20\,751$]), nine high risk features (HRFs) were defined in ACS patients.[67] These included AHA plaque type IV—V (MRI diagnosed lipid or necrotic core surrounded by fibrous tissue with possible calcification[262]); plaque type VI (MRI diagnosed complex plaque with surface defect, haemorrhage, or thrombus[262]); plaque echolucency; large lipid rich necrotic core; silent brain infarction; thin/ruptured fibrous cap; plaque ulceration; intraplaque haemorrhage (IPH); impaired CVR and spontaneous micro-embolisation (MES) on TCD.[67] Six of the nine HRFs were already high risk of stroke on BMT criteria in the 2017 guidelines.[165] The incidence of ipsilateral stroke was higher with ACS plus at least one HRF *vs.* no HRFs (OR 2.0; 95% CI 1.5 — 2.7).[67] HRFs increased late stroke/TIA as stenosis severity increased. In patients with 50—99% ACS, stroke/TIA was 4.3/100 patient years in patients with at least one HRF *vs.* 0.9/100 patient years with no HRFs (OR 4.5; 95% CI 1.8 — 10.9). In patients with 70—99% ACS, the risk of stroke/TIA increased to 7.3/100 patient years in patients with at least one HRF *vs.* 1.7/100 patient years in patients with no HRFs (OR 3.2; 95% CI 1.7 — 5.9).[67]

The second meta-analysis suggests that increasing stenosis severity was an important predictor for late ipsilateral stroke/TIA, but only with concurrent HRFs.[67] The impact of HRFs on late ipsilateral stroke was reported in more detail by the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study, where annual stroke rates varied from 0.2% to 8.7% with 50—79% ACS and from 0.5% to 10% in patients with 80—99% ACS, dependent on whether patients did (or did not) have a history of contralateral TIA/stroke or had low *vs.* high carotid plaque area or had low *vs.* high grey-scale median plaque scores on computerised plaque analysis.[263,264]

3.5. Controversy regarding modern medical therapy

ACAS, ACST-1, and VACS recruited between 1983 and 2003 when fewer patients took statins and a greater proportion smoked. Some now question whether the data remain relevant in the modern era.[265] A meta-analysis (six RCTs, 35 prospective cohort studies [$n = 16\,178$]) reported ipsilateral stroke rates of 2.3/100 person years in studies completing

recruitment before 2000 *vs.* 1.0/100 person years for 2000 − 2010 ($p < .001$).[251] The decline in stroke was attributed to BMT improvements and smoking cessation. In studies where fewer than 25% took statins, ipsilateral stroke was 1.2/100 person years *vs.* 2.3/100 person years where more than 25% took statins ($p = .009$).[251] Another systematic review (three RCTs, 17 cohort studies) reported declining annual stroke rates in BMT patients occurring across all grades of ACS severity (50−99%, 60−99%, and 70−99%), which was also apparent in ACAS and ACST, where annual rates of stroke may have declined by 60% between 1995 and 2010.[266]

3.6. Who is at high risk of stroke on medical therapy?

The 2021 SVS guidelines recommend CEA in "low surgical risk" patients with 70−99% ACS,[4] while AHA guidelines advise that only highly selected patients should undergo CEA,[267] without defining what "highly selected" means. In the 2021 ESC guidelines, coronary calcium score or carotid plaque/stenosis were recognised as being important "risk modifiers". ESC considered that the presence of ACS in people without clinical signs of cardiovascular disease, placed the patient in the same very high risk group as patients with CAD or PAD.[268] The 2021 ESO guidelines advise that CEA is recommended in patients with ≥ 60% ACS considered to be at increased risk of stroke on BMT alone, citing the higher risk criteria published in the 2017 ESVS guidelines to inform this aspect of the ESO guideline.[2] The 2017 ESVS guidelines and the 2017 ESC/ESVS PAD guidelines were the first to propose clinical/imaging criteria for identifying a higher risk of stroke on BMT cohort in whom CEA or CAS might be targeted.[165,269] Table 8 summarises these criteria, which were based on meta-analyses, multicentre studies, and RCT subgroup analyses (but not single centre data). Criteria include silent infarction on CT/MRI, ≥ 20% stenosis progression, large plaque area or large juxtaluminal black area (JBA) on computerised ultrasound plaque analysis (defined as an area of pixels with a greyscale value < 25 adjacent to the lumen without a visible echogenic cap after image normalisation[264]), plaque echolucency, IPH on MRI, impaired CVR (defined in section 3.10.1) and at least one spontaneous MES during ≥ 1 hour of transcranial Doppler (TCD) monitoring.

Corroboration of the ESVS criteria come from a 2020 meta-analysis of 64 cohort studies ($n = 20\ 751$), which evaluated stroke/TIA rates in ACS patients, stratified for whether they had HRFs or not.[67] Six of the nine HRFs were already adopted in the 2017 ESVS higher risk of stroke on BMT criteria (Table 8). The pooled prevalence of HRFs was 26.5% (i.e., a minority of ACS patients). The evidence for including plaque morphology features (within the ESVS criteria) is detailed in Table 8 and is supported by a recent study comparing computer based analyses of plaque morphology using CT with plaque biological processes, including transcriptomic analyses. Symptomatic and asymptomatic patients with a large lipid rich necrotic core, IPH, plaque matrix and increased plaque burden had molecular signatures associated with inflammation and extracellular matrix degradation (usually associated with plaque instability and a higher risk of symptoms). By contrast, highly calcified plaques exhibited a molecular signature indicative of plaque stability with increased profibrotic pathways and reduced inflammation.[279]

The GWC considered the evidence from the two new meta-analyses (section 3.4.3) regarding whether 80−99% ACS should now be included as a higher risk of stroke on BMT criterion in the 2023 guidelines. After reviewing the evidence, the GWC decided (by a vote of 11:3) against including 80−99% ACS for four reasons. Firstly, most patients in the cohort studies had a prior history of contralateral TIA/stroke, which increases stroke rates in ACS patients, and which would already make them candidates for CEA/CAS.[165] Secondly, even though there was statistical significance, four out of five cohort studies that included ACS patients without a history of stroke/TIA were published 25 − 35 years ago, raising questions about generalisability in the modern era of BMT. In addition, there were only 218 patients with 80−99% ACS in these five cohort studies with no prior stroke/TIA. Thirdly, the GWC felt it counterintuitive to simply dismiss RCT data (normally considered the highest level of evidence) on the basis there might have been selection biases 20 − 30 years ago (a hypothesis never raised before). There are many examples in carotid practice where RCT data appear discordant with observational studies (e.g., locoregional *vs.* general anaesthesia[60] and eversion *vs.* conventional CEA[86]). Finally, the Kamtchum-Tatuene meta-analysis and ACSRS demonstrated that increasing stenosis severity was an important predictor for late ipsilateral stroke, but only in the presence of concurrent HRFs.[67] The decision not to include 80−99% ACS as a "high risk of stroke on BMT" criterion in the 2023 guidelines will be reconsidered following publication of CREST-2, which will provide contemporaneous data on whether > 80% ACS is associated with higher stroke risks in the context of modern BMT.

The 2021 German-Austrian guidelines have adopted the ESVS "high risk of stroke on BMT" criteria, with the addition of males aged < 75 years, based on five year ACST-1 data which showed no major benefit for CEA in women.[3] However, because the ARR in 10 year stroke conferred by CEA in males < 75 years in ACST-1 (5.5%; 95% CI 0.9 − 10) was very similar to that of females (ARR 5.8%; 95% CI 1.1 − 11.4),[228] the ESVS GWC decided against including males aged < 75 years as a "high risk of stroke on BMT" criterion.

3.7. Duplex surveillance in asymptomatic patients

In patients with a 50−60% ACS who would consider a future CEA or CAS (if indicated), it is reasonable to offer annual DUS surveillance (plus assessment of plaque lucency, MES, etc.) as this allows monitoring of risk factors and BMT. Patients progressing to a 60−99% stenosis and who have at least one clinical or imaging feature making them higher risk of stroke on BMT, might then be considered for CEA or CAS.

Table 8. Clinical and imaging features associated with an increased risk of late stroke in patients with asymptomatic 50–99% carotid stenoses treated medically

Imaging / clinical parameter	Stenosis severity – %	Study type	Annual rate of ipsilateral stroke	OR/HR of increased stroke (95% CI)
Silent ipsilateral infarction on CT[270]	60–99	Multicentre, obs.	Yes: 3.6% No: 1.0%	Yes *vs.* No: 3.0 (1.46–6.29); $p = .002$
Stenosis progression >20%[271]	50–99	Multicentre, obs.	Regression: 0.0% Unchanged: 1.1% Progression: 2.0%	Progression *vs.* unchanged: 1.92 (1.14–3.25); p = .05
Stenosis progression[272]	70–99	Multicentre, RCT		Regression: 0.7 (0.4–1.3) No change, comparator: Prog 1 sten grade 1.6 (1.1–2.4) Prog 2 sten grades 4.7 (2.3–9.6)
Plaque area on computerised ultrasound plaque analysis[273]	70–99	Multicentre, obs.	<40 mm^2: 1.0% 40–80 mm^2: 1.4% >80 mm^2: 4.6%	<40 mm^2: comparator 40–80 mm^2: 2.08 (1.05–4.12) >80 mm^2: 5.81 (2.67–12.67)
JBA on computerised ultrasound plaque analysis[264]	50–99	Multicentre, obs.	<4 mm^2: 0.4% 4–8 mm^2: 1.4% 8–10 mm^2: 3.2% >10 mm^2: 5.0%	Trend, $p < .001$
Intraplaque haemorrhage on MRI[274]	50–99	Meta-analysis		Yes *vs.* No: OR 3.66 (2.77–4.95); $p < .01$
Impaired CVR[275]	70–99	Meta-analysis		Yes *vs.* No: OR 6.14 (1.27–29.5); $p = .02$
Plaque lucency on DUS[276]	50–99	Meta-analysis	Predominantly echolucent: 4.2% Predominantly echogenic: 1.6%	Echolucent *vs.* echogenic: OR 2.61 (1.47–4.63); $p = .001$
≥1 spontaneous MES during ≥1 h TCD monitoring[277]	50–99	Meta-analysis		Yes *vs.* No: OR 7.46 (2.24–24.89); $p = .001$
Spontaneous embolisation plus uniformly or predominantly echolucent plaque[278]	70–99	Multicentre, obs.	Yes: 8.9% No: 0.8%	Yes *vs.* No: OR 10.61 (2.98–37.82); $p < .001$
Contralateral TIA/stroke[261]	50–99	Multicentre, obs.	Yes: 3.4% No: 1.2%	Yes *vs.* No: OR 3.0 (1.9–4.73); $p < .001$

OR/HR = odds ratio/hazard ratio; CI = confidence interval; CT = computed tomography; RCT = randomised controlled trial; JBA = juxtaluminal black area; MRI = magnetic resonance imaging; CVR = cerebral vascular reserve; DUS = duplex ultrasound; MES = microembolic signals; TCD = transcranial Doppler; TIA = transient ischaemic attack; obs. = observational.

The 2021 German-Austrian guidelines give similar advice.[3] There is no consensus about how long surveillance should continue, but the patient's wishes should be considered. If a patient would not consent to any future carotid intervention, surveillance is not indicated, but the patient should be advised to seek urgent medical advice if symptoms occur.

3.8. Randomised trials: endarterectomy versus stenting

3.8.1. Thirty day outcomes in average risk patients. Table 9 details 30 day outcomes in meta-analyses of six RCTs comparing CEA *vs.* CAS in 7 030 ACS patients (excluding carotid angioplasty [CA]).[94] CAS (mostly TFCAS) incurred higher rates of 30 day any stroke and death/any stroke. Compared with CEA, CAS had lower 30 day MI.[94] There was no major difference in any other endpoint.

Table 10 details 30 day outcomes for 6 659 patients in four RCTs randomising > 500 patients, including the Carotid Revascularisation Endarterectomy *vs.* Stenting Trial (CREST-1), the Stent Protected percutaneous Angioplasty of the Carotid artery *vs.* Endarterectomy trial-2 (SPACE-2), the Asymptomatic Carotid Trial-1 (ACT-1), and ACST-2.[224,225,280] Thirty day any stroke and death/any stroke was higher after CAS, while 30 day MI was higher after CEA.[94] There was no major difference in other endpoints.

ACST-2 have commented that contemporary procedural risks may be better evaluated in large representative registries (rather than from meta-analyses of RCT data), on the basis that this may better reflect routine clinical practice.[20] This is despite the fact that registry outcome data are often self reported rather than independently assessed (as occurs in RCTs). In this respect, the German mandatory registry of in hospital procedural risks after CEA ($n = 86\,000$) and CAS ($n = 18\,000$) in asymptomatic patients, reported no major difference in the risks of disabling stroke or death (0.7% CAS; 0.7% CEA) and any stroke or death (1.8% CAS; 1.4% CEA). About half of the German registry patients had pre- and post-operative independent neurological assessment. Outcome data were also unaffected by gender or age.[143]

3.8.2. Long term outcomes in average risk of surgery patients. Table 11 details rates of late ipsilateral and any stroke (excluding 30 day stroke/death), showing that late stroke rates after CAS were similar to CEA, that is, CAS was as durable as CEA.

Table 9. Thirty day outcomes in six randomised controlled trials (RCTs) comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA) in patients with asymptomatic carotid stenosis*

	Death	Stroke	Death / stroke	Disabling stroke	Death / disabling stroke	MI	Death / stroke / MI
RCTs / patients − *n*	3 / 5 313	6 / 7 030	6 / 7 030	3 / 6 257	2 / 5 076	3 / 6 257	4 / 6 393
RCTs included	ACT-1, SAPPHIRE, ACST-2	CREST-1, ACT-1, Mannheim, SPACE-2, SAPPHIRE, ACST-2	CREST-1, ACT-1, Mannheim, SPACE-2, SAPPHIRE, ACST-2	CREST-1, ACT-1, ACST-2	ACT-1, ACST-2	CREST-1, ACT-1, ACST-2	CREST-1, ACT-1, Mannheim, ACST-2
CAS − *n* (%)	5 / 3 017 (0.16)	119 / 3 876 (3.07)	123 / 3 876 (3.17)	21 / 3 494 (0.60)	21 / 2 900 (0.72)	17 / 3 494 (0.49)	125 / 3 562 (3.5)
CEA − *n* (%)	8 / 2 298 (0.35)	63 / 3 156 (2.00)	71 / 3 156 (2.24)	15 / 2 765 (0.54)	20 / 2 178 (0.92)	28 / 2 765 (1.01)	86 / 2 833 (3.03)
OR (95% CI)	0.53 (0.17–1.65)	1.61 (1.18–2.21)	1.47 (1.09–1.99)	1.19 (0.61–2.35)	0.86 (0.46–1.61)	0.49 (0.26–0.90)	1.19 (0.89–1.59)
p value	.27	.003	.011	.61	.63	.024	

Red shade: significant benefit favouring CEA; green shade: significant benefit favouring CAS. MI = myocardial infarction; OR = odds ratio; CI = confidence interval.
* Reproduced with permission from Saratzis.[94]

An algorithm for managing average risk ACS and SCS patients is presented in Figure 2.

3.8.3. High risk for carotid endarterectomy patients. SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) randomised 334 high risk for CEA patients to CEA *vs.* CAS.[282] High risk criteria were 70—99% ACS plus at least one of: significant cardiac disease (congestive cardiac failure [CCF], abnormal stress test, awaiting cardiac surgery); severe pulmonary disease; contralateral occlusion; contralateral recurrent laryngeal nerve (RLN) palsy; prior radical neck surgery, cervical irradiation; re-stenosis after CEA; and age > 80 years.[282] The majority (70%) were asymptomatic, in whom 30 day death/stroke was 5.8% (CAS) *vs.* 6.1% (CEA).[282] At these levels of risk, most would gain no benefit (regarding late stroke prevention), suggesting they would be better treated medically.

3.9. Should the 3% risk threshold for carotid interventions be modified?

Guidelines since 1998 advise that CEA should be performed with a 30 day stroke/death rate ≤ 3%,[283] and that this should be independently audited (section 2.6). However, there is debate about whether the 3% threshold should be reduced. The 2021 German-Austrian and ESO guidelines advise that in hospital death/stroke should be ≤ 2%.[2,3] However, this does not mean that the 30 day 3% threshold is being reduced. It is

Table 10. Thirty day outcomes in four randomised controlled trials (RCTs) comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA), which randomised >500 patients with asymptomatic carotid stenosis*

	Death	Stroke	Death / stroke	Disabling stroke	Death / disabling stroke	MI	Death / stroke / MI
RCTs / patients − *n*	2 / 5 078	4 / 6 659	4 / 6 659	3 / 6 259	2 / 5 078	3 / 6 259	3 / 6 259
RCTs included	ACT-1, ACST-2	CREST-1, ACT-1, SPACE-2, ACST-2	CREST-1, ACT-1, SPACE-2, ACST-2	CREST-1, ACT-1, ACST-2	ACT-1, ACST-2	CREST-1, ACT-1, ACST-2	CREST-1, ACT-1, ACST-2
CAS − *n* (%)	3 / 2 900 (0.10)	111 / 3 691 (3.00)	114 / 3 691 (3.08)	21 / 3 494 (0.60)	21 / 2 900 (0.72)	17 / 3 494 (0.49)	123 / 3 494 (3.52)
CEA − *n* (%)	7 / 2 178 (0.32)	58 / 2 968 (1.95)	65 / 2 968 (2.19)	15 / 2 765 (0.54)	20 / 2 178 (0.92)	28 / 2 765 (1.01)	85 / 2 765 (3.07)
OR (95% CI)	0.33 (0.08–1.34)	1.61 (1.16–2.23)	1.47 (1.07–2.01)	1.19 (0.61–2.36)	0.86 (0.42–1.66)	0.49 (0.26–0.91)	1.18 (0.89–1.58)
p value	.12	.005	.017	.60	.63	.023	.25

Red shade: significant benefit favouring CEA; green shade: significant benefit favouring CAS. MI = myocardial infarction; OR = odds ratio; CI = confidence interval.
* Reproduced with permission from Saratzis.[94]

Table 11. Late "ipsilateral" and "any" stroke after carotid endarterectomy (CEA) and carotid artery stenting (CAS) excluding 30 day outcomes

Trial	Follow up time	Ipsilateral stroke (average per annum) − %		Any stroke (average per annum) − %	
		CAS	CEA	CAS	CEA
Lexington[281]	4 y	0 (0)	0 (0)	0 (0)	0 (0)
Mannheim[222]	26 mo	0 (0)	0 (0)	0 (0)	0 (0)
ACT-1[224]	5 y	2.2 (0.44)	2.7 (0.54)	6.9 (1.38)	5.3 (1.01)
CREST-1[227,280]	5 y	2.5 (0.50)	2.7 (0.54)	7.1 (1.42)	6.8 (1.36)
CREST-1[227,280]	10 y	6.9 (0.69)	5.6 (0.56)	13.4 (1.34)	12.5 (1.25)
ACST-2[20]	5 y	2.1 (0.42)	1.0 (0.20)	5.2 (1.04)	4.5 (0.90)

more an attempt to define acceptable risk thresholds while the patient remains in hospital (i.e., easier to audit). RCTs suggest that 19—24% of peri-operative strokes and deaths occur after the eighth post-operative day,[284] which effectively means that the 3% 30 day death/stroke threshold continues to be retained by these two guidelines.

Given the apparent reduction in stroke on modern BMT,[251] plus a meta-analysis of six RCTs and 47 community registries (n = 259 053) reporting that by 2013, 30 day death/stroke after CEA in ACS patients had fallen to 1.2%,[80] the GWC debated whether the 30 day 3% threshold should be reduced. After reviewing the evidence, the GWC concluded that it would not be appropriate to do so at present. This was based on recognition that some authors do not accept that the risk of stroke on BMT has decreased,[285,286] while meta-analyses of four large RCTs comparing CEA with CAS (n = 6 659) showed that the 30 day death/stroke rate was 2.19% (CEA) *vs.* 3.08% (CAS) (section 3.8.1), which differs from meta-analyses suggesting a decline in risks to < 2%.[80] CREST-2 is currently randomising ACS patients to CEA or CAS *vs.* BMT, and this debate will not be resolved until it reports whether there has been a decline in stroke rates on modern BMT, compared with when ACAS/ACST were recruiting.

Recommendation 19 **Unchanged**

For average surgical risk patients with an asymptomatic 60—99% stenosis, carotid endarterectomy should be considered in the presence of one or more imaging or clinical characteristics that may be associated with an increased risk of late stroke*, provided 30 day stroke/death rates are ≤3% and patient life expectancy exceeds five years.

Class	Level	References	ToE
IIa	B	Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (1995)[195], MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group (2004)[204], Halliday *et al.* (2010)[228], Nicolaides *et al.* (2005)[261], Kakkos *et al.* (2013)[264], Kakkos *et al.* (2009)[270], Kakkos *et al.* (2014)[271], Hirt *et al.* (2014)[272], Nicolaides *et al.* (2010)[273], Gupta *et al.* (2013)[274], King *et al.* (2011)[275], Gupta *et al.* (2015)[276], Markus *et al.* (2010)[277], Topakian *et al.* (2011)[278]	

* See Table 8 for imaging/clinical criteria conferring an increased risk of stroke on BMT in ACS patients.

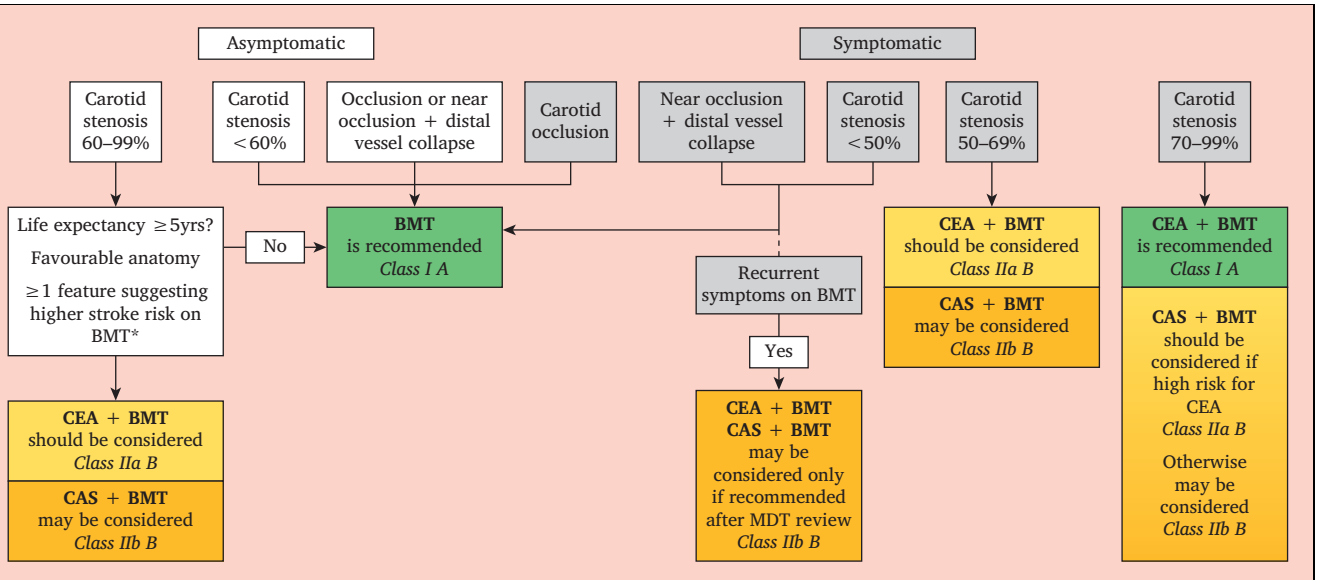


Figure 2. Management of "average risk" patients with asymptomatic and symptomatic carotid stenoses with best medical therapy (BMT), carotid endarterectomy (CEA), and/or carotid artery stenting (CAS). *See Table 8 for imaging/clinical criteria that confer an increased risk of stroke on BMT.

Recommendation 20			Unchanged
For average surgical risk patients with an asymptomatic 60–99% stenosis in the presence of one or more imaging or clinical characteristics that may be associated with an increased risk of late stroke*, carotid stenting may be an alternative to carotid endarterectomy, provided 30 day stroke/death rates are ≤3% and patient life expectancy exceeds five years.			
Class	**Level**	**References**	**ToE**
IIb	B	Mannheim *et al.* (2017)[222], Rosenfield *et al.* (2016)[224], Eckstein *et al.* (2016)[225], Nicolaides *et al.* (2005)[261], Kakkos *et al.* (2013)[264], Kakkos *et al.* (2009)[270], Kakkos *et al.* (2014)[271], Hirt *et al.* (2014)[272], Nicolaides *et al.* (2010)[273], Gupta *et al.* (2013)[274], King *et al.* (2011)[275], Gupta *et al.* (2015)[276], Markus *et al.* (2010)[277], Topakian *et al.* (2011)[278], Silver *et al.* (2011)[280]	

* See Table 8 for imaging/clinical criteria conferring an increased risk of stroke on BMT in ACS patients.

Recommendation 21			Unchanged
For asymptomatic patients 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/clinical characteristics that may be associated with an increased risk of late stroke on best medical therapy, carotid stenting may be considered provided anatomy is favourable, 30 day death/stroke rates are ≤3% and patient life expectancy exceeds five years*.			
Class	**Level**	**References**	**ToE**
IIb	B	Gurm *et al.* (2008)[223], Nicolaides *et al.* (2005)[261], Kakkos *et al.* (2013)[264], Kakkos *et al.* (2009)[270], Kakkos *et al.* (2014)[271], Hirt *et al.* (2014)[272], Nicolaides *et al.* (2010)[273], Gupta *et al.* (2013)[274], King *et al.* (2011)[275], Gupta *et al.* (2015)[276], Markus *et al.* (2010)[277], Topakian *et al.* (2011)[278], Yadav *et al.* (2004)[282]	

* See Table 8 for imaging/clinical criteria conferring an increased risk of stroke on BMT in ACS patients.

3.10. Carotid revascularisation and cognitive impairment

Five per cent of patients aged > 60 have dementia. Globally, the annual cost of treating dementia exceeds $US 1 trillion (€ 816 billion) and may reach $US 2 trillion (€ 1.6 trillion) by 2030.[287] In 20% of dementia patients, atherosclerosis or other occlusive diseases affecting cerebral vessels is responsible (vascular dementia), while 20–30% have vascular dementia and Alzheimer's.

3.10.1. Do asymptomatic carotid stenoses cause cognitive impairment? There is speculation that ACS may be responsible for cognitive decline. In a 2013 systematic review, nine out of 10 observational studies reported an association between ACS and cognitive impairment,[50] but there was no further scrutiny as to whether this translated into a causal association. In a larger systematic review (35 observational studies; 3 626 ACS patients, 10 936 controls), 33/35 studies (94%) reported an association between ACS and cognitive impairment.[87] However, such association does not necessarily mean ACS has an aetiological role *versus* being a marker for something else. The systematic review examined the evidence and was unable to unequivocally demonstrate that ACS was causally associated with cognitive dysfunction via involvement in the pathophysiology of white matter hyperintensities on MRI, lacunar infarction or via an embolic mechanism.[87] Surprisingly few studies have evaluated the relationship between ACS, ipsilateral cortical infarction, and cognitive impairment. An alternative mechanism whereby ACS might cause cognitive impairment is haemodynamic. As the ACS becomes more severe, patients with a non-functioning CoW and poor collateralisation compensate by vasodilation of ipsilateral intracranial arterioles. This maintains cerebral blood flow, but a point arises where arterioles cannot dilate further. The patient then enters a state of impaired then exhausted cerebral vascular reserve (CVR) with limited (or no) capacity to vasodilate further and blood flow then starts to decline. CVR can be measured using single photon emission tomography, positron emission tomography, or TCD monitoring of ipsilateral mean middle cerebral artery (MCA) velocities during CO_2 inhalation or breath holding (which raises blood CO_2 levels), which causes vasodilatation and increased MCA velocities, but only if CVR is not exhausted.

Ten studies have evaluated the relationship between impaired CVR and cognitive impairment, with 90% reporting at least one test of impaired cognition.[87] There was a stepwise increase in severity of cognitive impairment from normal in patients with severe ACS plus normal CVR (bilaterally), through unilateral impaired CVR (increased cognitive impairment), with maximum cognitive dysfunction in patients with bilateral impaired CVR.[288] Patients with severe ACS (unilateral or bilateral) and normal CVR had cognitive scores similar to controls.[289,290] Finally, patients with severe ACS and impaired CVR were more likely to suffer further cognitive decline over time *versus* patients with severe ACS and normal CVR.[288,291–293]

3.10.2. Do carotid interventions improve cognition function? A second systematic review (31 observational studies) evaluated the effect of carotid interventions on early and late post-operative cognition in ACS patients.[46] Assessment of early cognitive function was defined as re-assessment within three months after CEA or CAS (*vs.* baseline). Assessment of late cognitive function involved assessment at least five months after CEA or CAS. In 13/21 cohorts, late reassessment was at least one year after baseline.[46] Table 12 details the effect of carotid interventions on early post-operative cognition in 24 patient cohorts (11 CEA; 10 CAS; 3 CEA + CAS), and late cognitive function in 21 patient cohorts (12 CEA; 7 CAS; 2 CEA + CAS).[46]

Table 12. Effect of carotid interventions on cognitive function*

Effect	Early outcome, baseline *vs.* <3 mo		Late outcome, baseline *vs.* >5 mo	
	Cohorts	Patients	Cohorts	Patients
All domains / tests significantly improved	2 / 24	91 / 2 059 (4.4)	1 / 21	24 / 1 554 (1.5)
Most domains unchanged, one to two tests significantly improved	7 / 24	250 / 2 059 (12.1)	11 / 21	386 / 1 554 (24.8)
Mixed findings, some tests improved; similar proportion worse	3 / 24	257 / 2 059 (12.5)	1 / 21	19 / 1 554 (1.2)
No change in cognitive function	9 / 24	1 086 / 2 059 (52.7)	6 / 21	1 073 / 1 554 (69.0)
Most domains unchanged, one to two significantly worse	2 / 24	347 / 2 059 (16.8)	1 / 21	24 / 1 554 (1.5)
All domains / tests significantly worse	1 / 14	28 / 2 059 (1.4)	1 / 21	28 / 1 554 (1.8)

Data are presented as *n* or *n* (%).
* Reproduced with permission from Ancetti.[46]

At late follow up (Table 12), 69% reported no major change in cognitive function, while in 25%, cognitive scores were mostly unchanged, but one to two individual tests were substantially improved. Few patients had substantial improvement in late cognitive function (one cohort; 1.5% of study population) and only one cohort (1.8% of the overall study population) had substantial late cognitive impairment.

Only one study has evaluated whether haemodynamic status influenced post-operative cognitive function in three groups of ACS patients.[294] Patients with 80—99% ACS plus normal CVR undergoing CAS had no change in post-operative cognition. Controls with 80—99% ACS plus impaired CVR who did not undergo CAS had no change in cognition at follow up assessment. However, patients with 80—99% ACS plus impaired CVR who underwent CAS showed improvements across all cognitive domains after CAS.[294]

Not included in the systematic review was a post hoc analysis of 1 601 UK and Swedish patients, randomised within ACST-1. Using trial data, electronic health records and (in the UK) telephone and postal review, there was no difference in 10 year rates of recorded dementia between CEA and BMT patients (6.7% *vs.* 6.6%) or in 20 year rates (14.3% *vs.* 15.5%), that is, CEA was not associated with reductions in late dementia *versus* BMT (HR 0.98; 95% CI 0.75 — 1.28, $p = .89$).[21]

Until new research clearly identifies at risk ACS subgroups for developing cognitive impairment which is then improved by carotid interventions or provides direct evidence that silent embolisation from ACS causes cognitive impairment, indications for CEA and CAS in ACS patients (to prevent or reverse cognitive decline) are lacking. Impaired CVR is a criterion for being higher risk of stroke on BMT, in ACS patients in whom CEA or CAS may be considered (section 3.6). No other guideline has made any recommendations regarding a role for CEA/CAS in preventing or reversing cognitive impairment in ACS patients.[1—4]

Recommendation 22			Unchanged
For patients with a 70—99% asymptomatic carotid stenosis, carotid interventions are not recommended for the prevention of cognitive impairment until a causal association between severe asymptomatic carotid stenoses and cognitive decline has been established.			
Class	**Level**	**References**	**ToE**
III	B	Halliday *et al.* (2022)[21], Paraskevas *et al.* (2021)[87]	

4. MANAGEMENT OF SYMPTOMATIC CAROTID DISEASE

4.1. Symptoms attributable to carotid and vertebral artery disease

Being classed as recently symptomatic includes patients with symptoms in the past six months, which was the inclusion criterion in ECST/NASCET (Table 13). Most TIA/stroke symptoms are negative (e.g., loss/impairment of power, sensation, coordination) *versus* positive (e.g., paraesthesia). Occasional patients with carotid embolism can develop ischaemia or infarction in the posterior cerebral artery (PCA) territory, due to a persisting foetal PCA origin from the ICA via the posterior communicating artery. The severity of symptoms can be scored using the modified Rankin Score (mRS) or National Institutes of Health Stroke Score (NIHSS).[295,296]

The term "non-hemispheric symptoms" is applied to patients with isolated syncope (blackout, drop attack), pre-syncope (faintness), isolated dizziness, isolated double vision (diplopia), tinnitus, and isolated vertigo. There is no evidence that patients with non-hemispheric symptoms benefit from carotid (or vertebral) interventions, unless they co-exist with the more focal symptoms listed in Table 13.

4.2. Optimal medical therapy

Most secondary prevention RCTs (APRx, hypertension, lipid lowering, DM) did not specifically recruit SCS patients, focussing primarily on the prevention of stroke in general. Some did publish subgroup analyses in SCS patients, and these have been highlighted.

4.2.1. Lifestyle measures. Management of risk factors and lifestyle is the same as for ACS (section 3.1.1).

4.2.2. Antiplatelet therapy

4.2.2.1. Monotherapy. No adequately powered RCTs have evaluated monotherapy *versus* combination APRx in SCS patients. However, older RCTs suggest aspirin monotherapy should be started urgently in APRx I TIA/ischaemic stroke patients, to reduce recurrent ischaemic stroke, death, or dependency.[297,298] If monotherapy is adopted, 300 mg aspirin may be prescribed for days 1 — 14 to maximally inhibit thromboxane biosynthesis,[299,300] followed by 75 — 325 mg daily.

Table 13. Carotid and vertebrobasilar territory symptoms

Carotid territory symptoms	Vertebrobasilar territory symptoms
Higher cortical dysfunction (aphasia, dysgraphia, apraxia, visuospatial problems, visual field deficits)	Complete visual loss blurring, hemianopia
Amaurosis fugax / transient monocular blindness blurring	Diplopia, ptosis
Chronic ocular ischaemia syndrome	Vertigo; usually with other brain stem symptoms
Weakness and/or sensory impairment of face/arm/leg (one or all areas may be affected)	Acute sensorineural hearing loss
Upper/lower limb clumsiness	Dysarthria (also occurs with carotid territory ischaemia)
"Limb-shaking TIAs" (haemodynamic events in patients with severe SCS and exhausted CVR)	Dysphagia (also occurs with carotid territory ischaemia)
	Dysphonia
	Bilateral facial or limb weakness/numbness
	Ataxia

TIA = transient ischaemic attack; SCS = symptomatic carotid stenosis; CVR = cerebral vascular reserve.

4.2.2.2. Combination. There is increasing interest in the role of combination or dual antiplatelet therapy (DAPT), over monotherapy, to optimise protection against recurrent vascular events in patients with TIA or ischaemic stroke, including those with SCS. Table 14 summarises data from three RCTs evaluating aspirin + dipyridamole, which randomised patients < 24 hours to six months after TIA/ischaemic stroke to aspirin + dipyridamole *versus* aspirin monotherapy or placebo.[301–303] Aspirin + dipyridamole was more effective than aspirin monotherapy in preventing recurrent stroke,[301] or recurrent ischaemic vascular events in patients with TIA or ischaemic stroke[302] and can be safely started < 24 hours after symptom onset.[303] Long term aspirin + dipyridamole has not been shown to be superior to clopidogrel monotherapy in patients with ischaemic stroke or neuro-imaging confirmed TIAs, although 28.3–28.8% of patients had symptoms attributed to "large artery atherosclerosis", the precise proportion with symptomatic extracranial ICA stenosis was not specified, and those scheduled for urgent CEA were excluded.[304]

Table 15 details studies evaluating aspirin + clopidogrel on rates of spontaneous MES in SCS patients, which is an

Table 14. Main findings of three randomised controlled trials (RCTs) comparing aspirin plus dipyridamole antiplatelet therapy with aspirin monotherapy after transient ischaemic attack or ischaemic stroke

RCT	Patients (% with SCS) – *n*	Cohort	Combination antiplatelet strategy	Main findings
ESPS-2[301]	6 602 (not clear)	TIA / ischaemic stroke <3 mo	Dipyridamole 200 mg twice daily *vs.* aspirin 25 mg twice daily *vs.* aspirin 25 mg plus dipyridamole 200 mg twice daily *vs.* placebo	RRR in stroke at 2 y: Dipyridamole *vs.* placebo: 16%, p <.050 Aspirin *vs.* placebo: 18%, p <.050 Aspirin and dipyridamole *vs.* placebo: 37%, p <.050 Aspirin and dipyridamole *vs.* dipyridamole: 25%, p <.050 Aspirin and dipyridamole *vs.* aspirin: 23%, p <.050
ESPRIT*[302]	2 739 (9–11% with >50% SCS)	TIA / ischaemic stroke <6 mo	Aspirin 30–325 mg daily *vs.* aspirin 30–325 mg daily plus dipyridamole 200 mg twice daily	Non-fatal stroke / MI / major bleed / vascular death at 3 y: Aspirin and dipyridamole *vs.* aspirin (HR 0.80, 95% CI 0.66–0.98) Non-fatal stroke or MI / vascular death at 3 y: Aspirin and dipyridamole *vs.* aspirin (HR 0.78, 95% CI 0.63–0.97)
EARLY[303]	543 (not clear)	Ischaemic stroke <24 h, NIHSS ≤20, not for thrombolysis	Aspirin 25 mg plus dipyridamole 200 mg MR twice daily days 1–90 ("Early") *vs.* aspirin 100 mg daily days 1–7, then aspirin 25 mg plus dipyridamole 200 mg MR twice daily days 8–90 ("Late")	Good functional outcome (mRS 0–1) at 90 d: Early *vs.* Late treatment (56.4 *vs.* 52.4%, p = .45) Non-fatal stroke / TIA / non-fatal MI / non-fatal major bleeding complication / vascular death: Early *vs.* Late treatment: 10 *vs.* 15% (HR 0.73, 95% CI 0.44–1.19; p = .20)

MR= modified release; RRR = relative risk reduction; MI = myocardial infarction; SCS = symptomatic carotid stenosis; mRS = modified Rankin Score.

Table 15. Effect of combination aspirin plus clopidogrel in reducing spontaneous embolisation in recently symptomatic patients with carotid stenosis (SCS) and in patients undergoing carotid endarterectomy (CEA)

Author or trial	Study type, patients − *n*	Cohort	Combination antiplatelet strategy	Principle findings
Payne[310]	RCT, 100	≥50% SCS or ≥70% ACS	Aspirin 150 mg daily for 4 w pre-op plus placebo *vs.* aspirin 150 mg daily for 4 w pre-op plus single 75 mg dose of clopidogrel 12 h pre-op	During 3 h of post-op TCD monitoring, aspirin plus clopidogrel was associated with a tenfold reduction in the proportion of patients with ≥20 emboli detected: (OR 0.1, 95% CI 0.01−0.80; $p = .010$)
CARESS[306]	RCT, 107	>50% SCS + ≥1 MES on TCD at baseline	Aspirin 75 mg daily plus clopidogrel 300 mg on day 1, followed by 75 mg clopidogrel daily until day 7 *vs.* aspirin 75 mg daily	At 7 d, aspirin plus clopidogrel was associated with a significant reduction in the proportion of patients with persistent embolisation on TCD: (43.8 *vs.* 72.7%; RRR 39.8%, 95% CI 13.8−58; $p = .005$)
AMBDAP[307]	RCT, 60	50% SCS	Aspirin 300 mg, then 75 mg daily plus dipyridamole 200 mg twice daily for 30 d *vs.* aspirin 300 mg, then 75 mg daily plus clopidogrel 300 mg, then 75 mg daily for 30 d	At 48 h, there was a similar reduction in the frequency of microembolisation for: Aspirin plus dipyridamole (75.5%) Aspirin plus clopidogrel (77.5%, $p = .77$)
Batchelder[308]	Obs., 100	SCS patients undergoing CEA <8 d of symptom onset	Aspirin 300 mg, then 75 mg daily plus 75 mg clopidogrel 12 h pre-op *vs.* aspirin 300 mg, then 75 mg daily plus 75 mg clopidogrel daily for 48−72 h pre-op	Starting aspirin plus clopidogrel 48−72 h pre-op was associated with significant reductions in: Recurrent TIA/stroke prior to CEA (3% *vs.* 13%) (OR 0.20, 95% CI 0.06−0.66; $p = .010$) and Spontaneous embolisation pre-op (5% *vs.* 21%) (OR 0.2, 95% CI 0.09−0.66; $p = .005$)

RCT = randomised controlled trial; Obs. = observational; TIA = transient ischaemic attack; SCS = symptomatic carotid stenosis; ACS = asymptomatic carotid stenosis; RRR = relative risk reduction; OR = odds ratio; CI = confidence interval.

important predictor of increased stroke risk.[309] The CARESS RCT reported reductions in ongoing micro-embolisation in patients with > 50% SCS who were MES positive at baseline randomised to seven days of aspirin + clopidogrel *versus* aspirin alone.[306] However, it was not powered to show differences in clinical outcome. The AMBDAP study revealed similar reductions in embolisation on aspirin + dipyridamole *versus* aspirin + clopidogrel in patients with > 50% SCS.[307] In a prospective audit, starting aspirin + clopidogrel in a rapid access TIA clinic after ICH was excluded on CT/MRI was associated with a reduction in recurrent TIA/stroke before expedited CEA, plus reductions in MES.[308] Sustained embolisation in the early time period after CEA is a predictor of post-operative thromboembolic stroke.[309] One study randomised 100 CEA patients established on 150 mg aspirin daily (84% SCS), to a single dose of 75 mg clopidogrel ($n = 46$) or placebo ($n = 54$) 12 hours before CEA.[310] In comparison with placebo, clopidogrel statistically significantly reduced the odds of having > 20 emboli on TCD in the first three post-operative hours ($p = .010$).

It is now accepted that the highest risk period for recurrent stroke is the first 7 − 14 days after symptom onset (section 4.5.1). Three RCTs have evaluated whether very early institution of aspirin + clopidogrel (within 24 hours of symptom onset) reduces the risk of early recurrent stroke *versus* aspirin alone.[25,311,312] A fourth RCT undertook a similar evaluation of aspirin + ticagrelor *versus* aspirin.[24] The methodology and results are summarised in Table 16. CHANCE, POINT, and THALES excluded SCS patients in whom urgent CEA/CAS was planned.

A meta-analysis of the three RCTs comparing aspirin + clopidogrel *versus* aspirin alone showed that starting aspirin + clopidogrel within 24 hours of the onset of a high risk TIA or minor stroke reduced (i) non-fatal recurrent ischaemic or haemorrhagic stroke at 90 days (ARR = 1.9%; RR 0.70, 95% CI 0.61 − 0.80); (ii) non-fatal ischaemic stroke (ARR = 2%; RR 0.69, 95% CI 0.60 − 0.79); (iii) moderate to severe functional disability (ARR 1.4%); and (iv) poor quality of life (ARR 1.3%). Combination APRx had no impact on all cause mortality or MI, but there was a small, but important increase in moderate to major extracranial bleeding (absolute risk increase [ARI] 0.2%; RR 1.71, 95% CI 0.92 − 3.2).[59] Although the risk of bleeding complications increased slowly over the first 90 days of combination APRx treatment, early recurrent stroke was highest in the first 10 − 21 days.[25,59] Accordingly, limiting combination APRx to 21 days after symptom onset would reduce early recurrent stroke, while minimising major bleeding complications.[59]

4.2.2.3. Prior to carotid artery stenting. Patients with 50−99% SCS undergoing CAS are routinely prescribed

Table 16. Randomised controlled trials (RCTs) evaluating the effect of aspirin plus clopidogrel or aspirin plus ticagrelor, *versus* aspirin monotherapy, in preventing early recurrent stroke

RCT	Patients − *n*	Cohort	Combination antiplatelet strategy	Main findings
FASTER[*] [311]	392	Acute minor ischaemic stroke or TIA with initiation of APRx <24 h of symptom onset[†]	All patients received aspirin 81 mg/d (162 mg × 1 dose if aspirin naïve) and were randomised to additional clopidogrel (300 mg × 1 dose and then 75 mg/d; clopidogrel plus simvastatin 40 mg/d; simvastatin 40 mg/d; or placebo	Aspirin plus clopidogrel did not significantly reduce 90 d risk of stroke *vs.* aspirin monotherapy (5.1 *vs.* 9.5%, $p > .050$) Symptomatic bleeding higher in the clopidogrel *vs.* no clopidogrel groups (3 *vs.* 0%; $p = .030$)
CHANCE [312]	5 170	Acute minor ischaemic stroke or "high risk" TIA patients in China, with initiation of APRx <24 h of symptom onset[‡]	75−300 mg aspirin × 1 d, plus 75 mg aspirin × 21 d, plus clopidogrel 300 mg stat plus clopidogrel 75 mg/d days 2−90 *vs.* 75−300 mg aspirin × 1 d plus aspirin 75 mg/d days 2−90	Compared with aspirin, aspirin plus clopidogrel was associated with significant reductions in 90 d: Stroke (8.2 *vs.* 11.7%; HR 0.68, 95% CI 0.57−0.81; $p < .001$) Fatal/disabling stroke (5.2 *vs.* 6.8%; HR 0.75, 95% CI 0.6−0.94; $p = .010$) Ischaemic stroke (7.9 *vs.* 11.4%; HR 0.67, 95% CI 0.56−0.81; $p < .001$) Compared with aspirin, aspirin plus clopidogrel was associated with no significant difference in 90 d: Moderate or severe bleeding (0.3 *vs.* 0.3%; $p = .73$)
POINT[§] [25]	4 881	Acute minor ischaemic stroke or "high risk" TIA, with initiation of APRx <12 h of symptom onset[‡]	Aspirin 50−325 mg/d plus clopidogrel 600 mg stat plus clopidogrel 75 mg/d days 2−90 *vs.* aspirin 50−325 mg/d × 90 d (162 mg aspirin/d for 5 d and then 81 mg/d recommended)	Compared with aspirin, aspirin plus clopidogrel was associated with significant reductions in 90 d: Stroke / MI / ischaemic vascular death (5 *vs.* 6.5%; HR 0.75, 95% CI 0.59−0.95; $p = .020$) Ischaemic stroke (4.6 *vs.* 6.3%; HR 0.72, 95% CI 0.56−0.92; $p = .010$) Compared with aspirin, aspirin plus clopidogrel was associated with significant increase in 90 d: Major bleeding (0.9 *vs.* 0.4%; HR 2.32, 95% CI 1.10−4.87; $p = .020$)
THALES [24,27]	11 016	Acute minor ischaemic stroke or "high risk" TIA, with initiation of APRx <24 h of symptom onset[‖]	Aspirin 300−325 mg stat and then 75−100 mg aspirin days 2−30 plus ticagrelor 180 mg stat + ticagrelor 90 mg twice daily days 2−30 *vs.* aspirin 300−325 mg stat and 75−100 mg aspirin daily days 2−30	Compared with aspirin, aspirin plus ticagrelor was associated with significant reductions in 30 d: Stroke / death (5.5 *vs.* 6.6%; HR 0.83, 95% CI 0.71−0.96; $p = .020$) Ischaemic stroke (5.0 vs. 6.3%; HR 0.79, 95% CI 0.68−0.93; $p = .004$) Compared with aspirin, aspirin plus ticagrelor was associated with significant increase in 30 d: Severe bleeding (0.5 *vs.* 0.1%; HR 3.9, 95% CI 1.74−9.14; $p = .001$)

TIA = transient ischaemic attack; APRx = antiplatelet therapy; RR = relative risk; HR = hazard ratio; CI = confidence interval; NIHSS = National Institute of Health Stroke Score.

* Trial stopped early because of slow enrolment.

† Acute minor ischaemic stroke (NIHSS score ≤3) or TIA.

‡ Acute minor ischaemic stroke (NIHSS score ≤3) or TIA with ABCD[2] score ≥4.

§ Trial stopped early because data and safety monitoring board determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischaemic events and a higher risk of major haemorrhage at 90 days.

‖ Acute minor ischaemic stroke (NIHSS score ≤5) or TIA with ABCD[2]score ≥6, or symptomatic intracranial or extracranial stenosis ≥50%.

combination APRx, based on two small RCTs (section 3.1.2.4). In most RCTs involving SCS patients, aspirin + clopidogrel[313−317] or aspirin + ticlopidine[314,316] were prescribed for 48 hours[316] to 72 hours[314,317] before CAS and for at least four to six weeks thereafter.[314,316,317] Ticlopidine is no longer prescribed, so aspirin + clopidogrel is preferred. It is reasonable to prescribe 300 − 325 mg aspirin daily for 14 days, followed by 75 − 81 mg daily (if aspirin naive), in combination with clopidogrel in CAS patients. Clopidogrel (75 mg daily) should start three days before CAS, to inhibit ADP induced platelet aggregation, or as a 300 mg loading dose in urgent cases. Aspirin + clopidogrel should continue for at least four weeks, after which patients should revert to monotherapy (usually clopidogrel 75 mg daily[318]), to protect against late cardiovascular events.[81,217] Long term aspirin + clopidogrel is not recommended, unless for other clinical indications, as the increased bleeding risk is not justified over the benefits conferred by APRx monotherapy

in TIA/stroke patients.[59,319,10,320] There are no large RCTs on aspirin + ticagrelor *versus* aspirin monotherapy in CAS patients with a ≥ 50% SCS.

4.2.2.4. Prior to carotid endarterectomy. No RCT has compared APRx monotherapy with combination therapy in CEA patients. However, international guidelines increasingly recommend a 21 day course of aspirin + clopidogrel in patients with minor ischaemic stroke or high risk TIA, starting as soon as possible after symptom onset once ICH has been excluded on CT/MRI, to prevent early recurrent stroke.[1,321–324] Although CHANCE, POINT, and THALES excluded SCS patients in whom CEA was planned, any patients with a TIA or minor ischaemic stroke and a 50–99% stenosis who are deemed to require CEA by the MDT should otherwise also be considered high risk.

4.2.2.4.1. Monotherapy

Aspirin: Only one RCT has evaluated aspirin *versus* placebo in CEA patients. Two hundred and thirty two patients (215 SCS) were randomised to placebo or aspirin 75 mg daily, starting the night before CEA and continuing for six months.[325] Aspirin reduced disabling stroke at seven days *versus* placebo (1.7% *vs.* 9.6%; $p = .010$), but there was no difference in recurrent TIA/stroke/death at six months. The ACE trial (section 3.1.2.3) showed that lower dose aspirin (81 − 325 mg) was preferable to higher dose (> 650 mg) in CEA patients.[219] Historically, surgeons have almost exclusively used aspirin monotherapy prior to CEA, although benefits may not be as good as combination APRx for preventing early recurrent stroke after symptom onset and before CEA (section 3.1.2.2).

Clopidogrel: No RCTs have compared clopidogrel with placebo or aspirin in SCS patients undergoing CEA. CAPRIE showed that 75 mg clopidogrel daily reduced the relative risk of ischaemic stroke, MI, or vascular death by 8.7% *versus* 325 mg aspirin daily in a vascular disease population ($p = .043$). However, the 7.3% RR in the ischaemic stroke subgroup did not reach statistical significance.[217] Moreover, no patients were included within one week of stroke onset and patients undergoing CEA were excluded. However, in a SCS patient who has had a TIA/stroke while on aspirin (or who is aspirin or dipyridamole intolerant), clopidogrel monotherapy (75 mg daily) is an alternative in the peri-operative period, if APRx monotherapy is preferred. In this situation, it is reasonable to prescribe a 300 mg loading dose followed by 75 mg clopidogrel daily to produce a more rapid and stable inhibitory effect than seen with 75 mg daily.[326] Clopidogrel monotherapy was equally effective as aspirin + dipyridamole at preventing recurrent stroke at 2.5 years.[304]

Dipyridamole: If intolerant of, or allergic to both aspirin and clopidogrel, 200 mg of dipyridamole MR monotherapy twice daily is an alternative peri-operative regimen.[81,218]

Ticagrelor: Ticagrelor reversibly inhibits the platelet $P2Y_{12}$ ADP receptor.[24] A secondary analysis of the SOCRATES trial compared outcomes on ticagrelor ($n = 1\,542$) *versus* aspirin ($n = 1\,539$) in patients randomised within 24 hours of a high risk TIA ($ABCD^2 \geq 4$) or ischaemic stroke (NIHSS ≤ 5) and who had ≥ 50% ipsilateral stenosis of an extracranial or intracranial artery, mobile thrombus in the aortic arch, or aortic arch plaques ≥ 4mm thick.[5] The risk of stroke, MI, or death at 90 days was statistically significantly lower in TIA/ischaemic stroke patients of atherosclerotic origin on ticagrelor *versus* aspirin (6.7% *vs.* 9.6%; HR 0.68, 95% CI 0.53 − 0.88, $p = .003$).[24] The number with extracranial ≥ 50% SCS was not specified and there were too few events in CEA patients to draw conclusions regarding the benefits of ticagrelor over aspirin. However, in SCS patients intolerant or allergic to aspirin, clopidogrel, and dipyridamole (in whom CEA is not planned), ticagrelor monotherapy is an option (180 mg loading dose, then 90 mg twice daily).[24]

4.2.2.4.2. Combination therapy. Historically, surgeons have been reluctant to perform CEA in patients on aspirin + clopidogrel, because of concerns about peri-operative bleeding complications. However, evidence suggests that attitudes may be changing. In 2007, an audit of UK vascular surgeons reported that if patients were taking aspirin + clopidogrel, 52% would discontinue clopidogrel before CEA.[327] By 2012, only 24% would discontinue clopidogrel.[158,159] In a SVS vascular quality initiative (VQI) between 2003 and 2014 ($n = 28\,683$), 25% of CEA patients were on aspirin + clopidogrel,[137] increasing to 31% between 2010 and 2018 ($n = 100\,432$).[150] In a recent Danish multicentre audit ($n = 1\,125$), the proportion of SCS patients undergoing CEA on aspirin + clopidogrel was 50%.[144]

The increase in the proportion of CEA patients prescribed aspirin + clopidogrel in the peri-operative period occurred before publication of CHANCE, POINT, and THALES. However, international guidelines have now changed clinical practice in high risk patients with TIA/minor ischaemic stroke without carotid stenosis, with aspirin + clopidogrel increasingly being recommended in the early time period after onset of symptoms (section 4.2.2.2). In THALES, a subgroup analysis of 2 351 patients with ≥ 30% stenosis of an ipsilateral extracranial or intracranial brain supplying artery, which might have accounted for their TIA/stroke (excluding those scheduled for urgent CEA with more severe stenoses), revealed that patients randomised to aspirin + ticagrelor had statistically significantly lower risks of stroke/death at 30 days (8.1% *vs.* 10.9%) with aspirin alone (HR 0.73; 95% CI 0.56 − 0.96, $p = .023$).[6] In the other 8 665 THALES patients without atherosclerotic stenosis, the 90 day risk of stroke/death was similar with aspirin + ticagrelor *versus* aspirin alone (4.8% *vs.* 5.4%; HR 0.89; 95% CI 0.74 − 1.08, $p = .23$).[6] In addition, the risk of stroke/death was not statistically significantly different between those randomised to aspirin + ticagrelor *vs.* aspirin in the subgroup with ≥ 30% extracranial arterial stenosis (7.6% *vs.* 8.9%; HR 0.84, 95% CI 0.6 − 1.17, $p = .31$) but was statistically significantly lower in patients with intracranial stenosis on aspirin + ticagrelor (HR 0.66; 95% CI 0.47 − 0.93, $p = .016$). Exploratory analyses showed that the risk of stroke/death in patients undergoing post-randomisation CEA or CAS was 8.7% (4/46) with aspirin + ticagrelor *versus* 23.7% (9/38) on aspirin ($p = .069$), with severe bleeding in one patient in each group. However, the small number of subjects undergoing revascularisation precludes any definitive comment. THALES has not yet published outcomes on aspirin + ticagrelor therapy *versus* aspirin alone in

patients with recent TIA/stroke and a 50—99% extracranial SCS.

The debate regarding peri-operative monotherapy *versus* combination APRx must take account of all potential benefits and not just focus on peri-operative bleeding risks. In addition to RCT evidence that aspirin + clopidogrel reduces early recurrent stroke,[25,311,312] evidence suggests it also reduces recurrent stroke in the 48 — 72 hour time period between SCS patients being seen in a TIA clinic and undergoing CEA,[308,328] as well as evidence from national registries that aspirin + clopidogrel reduces peri-operative stroke,[137] especially early post-operative thromboembolic stroke.[309] The most important bleeding complication after CEA is neck haematoma, which is associated with increased morbidity and mortality.[137] In a 2011 audit of practice between 2003 and 2009 ($n = 5$ 264), the Vascular Study Group of New England (VSGNE) registry found no evidence that aspirin + clopidogrel was associated with higher rates of re-exploration for neck haematoma (1.5%: no APRx; 1.2%: aspirin monotherapy; 0.7%: clopidogrel monotherapy; and 1.4%: aspirin + clopidogrel).[329] However, in a meta-analysis of one RCT and seven observational studies ($n = 36\ 881$), CEA patients on aspirin + clopidogrel ($n = 8\ 536$) had a small but statistically significantly higher rate of major bleeding complications (1.27% *vs.* 0.83%) than patients on APRx monotherapy (Risk Difference 0.005; 95% CI 0.00 — 0.01, $p = .003$).[47] Two prospective, observational studies which did not report increased risks of post-operative bleeding on aspirin + clopidogrel[308,330] were not included in this meta-analysis.

For the increasing proportion of physicians/surgeons prescribing combination APRx in the peri-operative period, there are three scenarios (each with different durations and dosages), making it essential that neurologists and stroke physicians liaise with vascular surgical colleagues to develop protocols specifying preferred APRx regimens (combination *vs.* monotherapy) before commencing treatment, so as not to delay CEA. This is important as the antiplatelet effects of aspirin, clopidogrel, and dipyridamole last the lifetime of the platelet (up to 10 days). The three scenarios include patients with: (1) 0—49% carotid stenosis with no other apparent cause for TIA/stroke on neurovascular work up in whom CEA/CAS is not indicated; (2) recent TIA/stroke with a 50—99% stenosis where CEA/CAS is not being considered (patient choice, comorbidities); and (3) recent TIA/stroke with a 50—99% stenosis where urgent CEA or CAS is planned. Figure 3 details choices of combination APRx for each scenario, including dosages and alternative antiplatelet strategies after neuro-imaging has excluded ICH. CEA should be performed with careful control of post-operative BP, as uncontrolled post-CEA hypertension increases the risk of hyperperfusion syndrome, ICH, and neck haematoma formation (section 7.1.4). If one opts for peri-operative aspirin + clopidogrel combination therapy, aspirin can be stopped on day one after CEA and clopidogrel 75 mg daily continued indefinitely, unless contraindicated (Figure 3).

The 2021 AHA guidelines made no recommendation regarding combination APRx prior to CEA.[1] The German-Austrian guidelines recommend combination APRx between

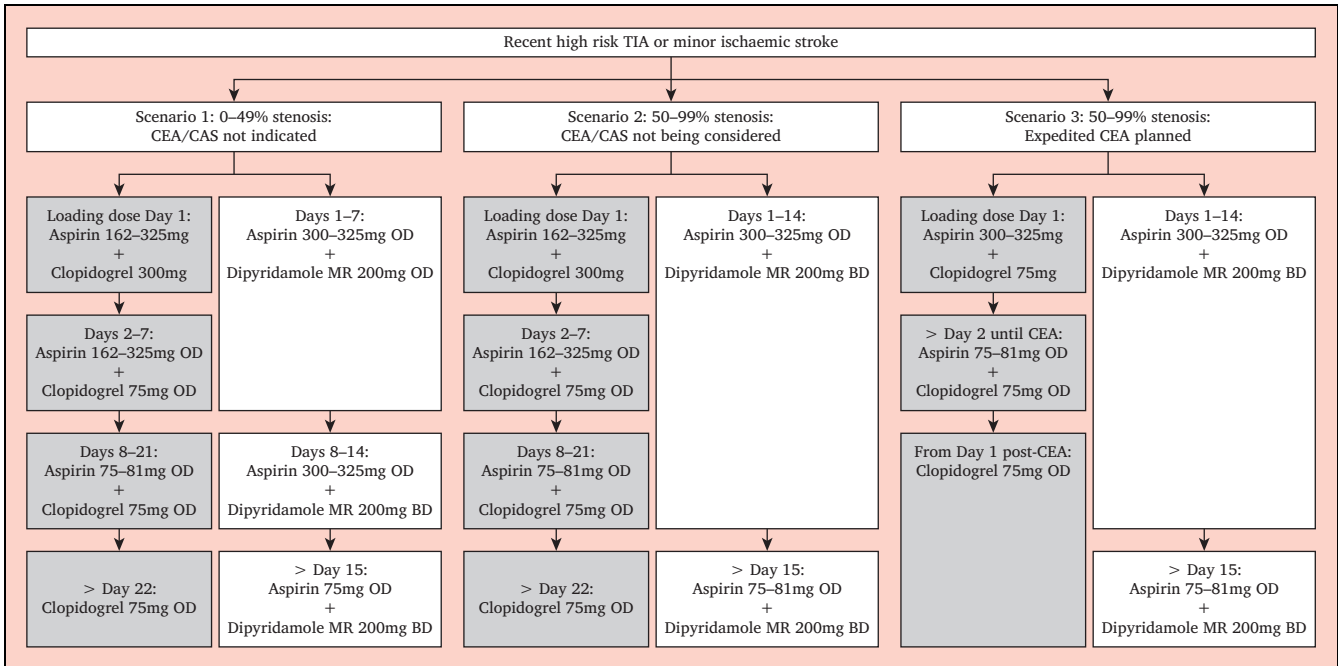


Figure 3. Timing, dose, and duration of combination antiplatelet therapy in the early phase after onset of transient ischaemic attack (TIA) or minor ischaemic stroke in patients with symptomatic carotid stenosis with or without planned treatment by carotid endarterectomy (CEA) or carotid artery stenting (CAS). MR = modified release; OD = once daily; BD = twice daily. Reproduced with permission from: Naylor AR, McCabe DJH. Cerebrovascular Disease: Decision making including optimal medical therapy. In: Eds: Sidawy A & Perler B. *Rutherford's Vascular Surgery and Endovascular Therapy*, 10th Edition. Philadelphia, Chapter 92, pages 1203—1219, Elsevier. 2021.[331]

symptom onset and CEA (to prevent early recurrent stroke) and that aspirin + clopidogrel may be considered to prevent peri-operative stroke after CEA.[3] The SVS guidelines advise that in patients with a TIA or minor stroke within 24 hours of onset, aspirin + clopidogrel is recommended over aspirin alone, or as an alternative to aspirin + dipyridamole. However, it was unclear what policy SVS applied to CEA patients, as they advised that decisions regarding DAPT should be individualised.[4]

4.2.3. When to prescribe gastric protection medications?

Prescribing proton pump inhibitors (PPI) may prevent gastrointestinal bleeding, but some (omeprazole, esomeprazole, lansoprazole) may interfere with clopidogrel's antiplatelet effects.[332] In the absence of risk factors, DAPT can be prescribed without a PPI. However, if the patient to be started on DAPT has a higher than average risk of gastrointestinal (GI) bleeding (prior GI ulcer or GI haemorrhage, anticoagulation or corticosteroid prescription) or more than two of: age > 65 years, dyspepsia, gastro-oesophageal reflux, *Helicobacter pylori* infection, and chronic alcohol use, gastric protection should be considered.[333] If a PPI is indicated, it is recommended to select a PPI which does not interact with clopidogrel (e.g., pantoprazole).[40,334] If the patient is PPI intolerant or they are ineffective, an H_2 receptor antagonist (e.g., famotidine) is an alternative.[335]

Recommendation 23 — New

For symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting following a transient ischaemic attack or minor ischaemic stroke, short term aspirin plus clopidogrel for 21 days followed by clopidogrel monotherapy, or long term aspirin plus modified release dipyridamole is recommended*.

Class	Level	References	ToE
I	A	Hao *et al.* (2018)[59], Diener *et al.* (1985)[301], ESPRIT Study Group *et al.* (2006)[302], Sacco *et al.* (2008)[304], King and Markus (2009)[305], King *et al.* (2011)[307]	

* Alternative antiplatelet strategies and dosages in the event of allergy or intolerance to aspirin or clopidogrel are detailed in section 4.2.2.4.

Recommendation 24 — New

For recently symptomatic carotid stenosis patients who are not being considered for carotid endarterectomy or stenting who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole monotherapy or ticagrelor monotherapy is recommended*.

Class	Level	References	ToE
I	B	Amarenco *et al.* (2017)[5], Diener *et al.* (1996)[218]	

* Alternative antiplatelet strategies and dosages in the event of allergy or intolerance to aspirin or clopidogrel are detailed in section 4.2.2.4.

Recommendation 25 — New

For recently symptomatic carotid stenosis patients in whom carotid endarterectomy is being considered, it is recommended that neurologists/stroke physicians and vascular surgeons develop local protocols to specify preferred antiplatelet regimens (combination therapy *vs.* monotherapy), so as not to delay urgent carotid surgery.

Class	Level	References
I	C	Consensus

Recommendation 26 — Unchanged

For recently symptomatic carotid stenosis patients scheduled to undergo carotid endarterectomy, it is recommended that all be prescribed antiplatelet therapy throughout the peri-operative period and in the long term.

Class	Level	References	ToE
I	A	Murphy *et al.* (2019)[81], Lindblad *et al.* (1993)[325], Taylor *et al.* (1999)[219]	

Recommendation 27 — New

For recently symptomatic patients with a 50–99% carotid stenosis who are to undergo carotid endarterectomy, peri-operative combination antiplatelet therapy should be considered, and should be started after imaging has excluded intracranial haemorrhage*.

Class	Level	References	ToE
IIa	C	Hao et al. (2018)[59], Markus et al. (2005)[306], Batchelder et al. (2015)[308], Payne et al. (2004)[310]	

* Alternative antiplatelet strategies and dosages in the event of allergy or intolerance to aspirin or clopidogrel are detailed in section 4.2.2.4.

Recommendation 28 — New

In recently symptomatic patients with a 50–99% carotid stenosis who are to undergo carotid endarterectomy where antiplatelet monotherapy is preferred to combination therapy, aspirin (300–325 mg daily for 14 days, followed by 75–162 mg daily) should be considered.

Class	Level	References	ToE
IIa	B	Taylor *et al.* (1999)[219]	

Recommendation 29 — New

For recently symptomatic patients undergoing carotid endarterectomy on aspirin monotherapy, lower dose aspirin (75–325 mg daily) rather than higher dose (>325 mg daily) is recommended.

Class	Level	References	ToE
I	B	Taylor *et al.* (1999)[219]	

Recommendation 30	New		
For recently symptomatic carotid stenosis patients undergoing carotid endarterectomy who are intolerant of, or allergic to, aspirin and clopidogrel, dipyridamole modified release monotherapy (200 mg twice daily) is recommended.			
Class	**Level**	**References**	**ToE**
I	C	Diener *et al.* (1996)[218]	

Recommendation 31	Changed		
For recently symptomatic patients undergoing carotid stenting, combination antiplatelet therapy with aspirin (75–325 mg daily) and clopidogrel is recommended. Clopidogrel (75 mg daily) should be started at least three days prior to stenting or as a single 300 mg loading dose in urgent cases. Aspirin and clopidogrel should be continued for at least four weeks after stenting and then long term antiplatelet monotherapy (preferably clopidogrel 75 mg daily) should be continued indefinitely.			
Class	**Level**	**References**	**ToE**
I	C	Murphy *et al.* (2019)[81], McKevitt *et al.* (2005)[221], Quinn *et al.* (1999)[226], NICE[318]	

Recommendation 32	Unchanged		
For patients who have undergone carotid endarterectomy or carotid stenting, long term aspirin + clopidogrel therapy is not recommended unless required for cardiac or other vascular disease indications.			
Class	**Level**	**References**	**ToE**
III	A	Hao *et al.* (2018)[59], Diener *et al.* (2004)[320]	

Recommendation 33	Unchanged		
For patients on antiplatelet therapy with a higher than average risk of gastrointestinal bleeding*, gastroprotective treatment or proton pump inhibition should be considered. If a proton pump inhibitor is indicated, it is recommended to select one which does not significantly influence the antiplatelet effects of clopidogrel (e.g. pantoprazole).			
Class	**Level**	**References**	**ToE**
IIa	B	Arbel *et al.* (2013)[40], Gaglia *et al.* (2010)[332], Collett *et al.* (2021)[333], Furuta *et al.* (2010)[334], Chan *et al.* (2017)[335]	

* Alternative antiplatelet strategies and dosages in the event of allergy or intolerance to aspirin or clopidogrel are detailed in section 4.2.2.4. Criteria for being considered higher risk of gastrointestinal bleeding are detailed in section 4.2.3.

4.2.4. Combination antiplatelet therapy and direct oral anticoagulants. COMPASS provided no data on SCS patients,[15] and patients were excluded if they reported a "non-lacunar" ischaemic stroke within one month of randomisation.[9,11] The 2021 AHA guidelines highlighted the absence of evidence regarding the effectiveness of direct oral anticoagulants (DOACs) plus low dose aspirin for secondary stroke prevention as being a knowledge gap to be addressed.[1] No guideline currently recommends low dose rivaroxaban + aspirin in SCS patients.[1–4]

4.2.5. Antiplatelet "high on treatment platelet reactivity". In patients with > 50% SCS, the prevalence of antiplatelet "high on treatment platelet reactivity" (HTPR, previously termed antiplatelet resistance) can vary between 9% and 64% for aspirin and 0–83% for clopidogrel.[99] In ACS patients, aspirin HTPR has been reported in 23–57% of patients, with clopidogrel HTPR in 25–100%.[99,336,337] Reasons for the wide variability are that prescribed doses and timing of assessment of antiplatelet HTPR status after starting treatment varied between studies,[99] while the prevalence of antiplatelet HTPR is heavily influenced by shear stress levels to which platelets are exposed in the platelet function/reactivity testing platforms.[20,338] Because of the wide prevalence ranges observed both within and between studies, it is not clear which (if any) of the currently available platelet function/reactivity assays are likely to inform treatment decisions in ACS/SCS patients who may have "antiplatelet HTPR" on their prescribed APRx regimen.[99] This is clinically important because a meta-analysis of 20 observational studies ($n = 4\,989$) evaluating platelet function/reactivity testing showed a higher risk of recurrent TIA/stroke, MI, or vascular death in TIA/ischaemic stroke patients with *versus* without antiplatelet HTPR on any antiplatelet regimen (OR 2.93; 95% CI 1.90 − 4.51).[76] However, no studies were adequately powered to determine whether *ex vivo* antiplatelet HTPR status can predict risks of ischaemic or haemorrhagic events in SCS or ACS patients in the peri-operative or non-peri-operative periods.[99,336]

The available evidence does not currently support the routine use of *ex vivo* HTPR testing to tailor APRx in individual patients with carotid stenosis unless they are included within research studies or clinical trials. These studies are vitally important and should include more than one type of testing platform to assess HTPR status, because no single device has been shown to be superior at predicting outcomes in patients with carotid stenosis.[99] No guidelines currently recommend routine antiplatelet HTPR testing to tailor APRx in individual patients. The SVS noted that routine testing for platelet reactivity is not yet supported by evidence.[4]

4.2.6. Carotid interventions in patients on anticoagulants. No guideline has specifically addressed how to manage patients undergoing carotid interventions who are taking anticoagulants pre-operatively. The aim is to minimise peri-operative thromboembolic and bleeding complications. The decision about whether CEA or CAS is preferred should be based on which is considered the best intervention for each individual patient. This section offers pragmatic advice on the management of patients awaiting a carotid intervention who are currently prescribed anticoagulants, based on a consensus of the GWC. Other guidelines have advised on when to stop

and restart anticoagulation in patients requiring a surgical or endovascular intervention,[339] but not when to prescribe adjunctive antiplatelet therapy during the peri-operative period.

Planning appropriate antithrombotic strategies requires careful assessment of thrombotic and bleeding risks in individual patients, as well as the bleeding risk associated with the procedure. Conditions associated with high thrombotic risk include mechanical heart valves (aortic tilting disc, any mitral prosthesis), thrombophilias, and a venous thromboembolic event within three months or which occurred on therapeutic anticoagulation.[339,340,341] Conditions associated with high bleeding risks include a HAS-BLED score $>$ 3,[342] bleeding episode less than three months, thrombocytopenia ($< 50 \times 10^9$/L) and previous bleeding after a similar procedure or with bridging therapy. Peri-operative antithrombotic management should be discussed within an MDT whenever thrombotic and/or bleeding risks are deemed high (ideally including specialists in coagulation), and an agreed strategy should be documented in the case notes. Whichever anticoagulation strategies are selected, careful control of post-operative BP after CEA and CAS is essential to reduce the risk of neck haematoma and ICH (section 7.1.3.3).

4.2.6.1. Assessing peri-operative bleeding risks: carotid endarterectomy. In an SVS-VQI audit ($n = 28\,683$), CEA patients undergoing re-exploration for neck haematoma incurred significantly higher in hospital risks *versus* patients not re-explored, including; stroke: 3.7% *vs.* 0.8%, ($p < .001$); MI: 6.2% *vs.* 0.8%, ($p < .001$); death: 2.5% *vs.* 0.2%, ($p < .001$); stroke/death: 5.0% *vs.* 0.9%, ($p < .001$).[137] Accordingly, CEA is classified as a "high risk of bleeding" operation.[343]

4.2.6.2. Assessing peri-operative bleeding risks: carotid artery stenting. Bleeding complications after CAS are mostly access related and the incidence of re-intervening for bleeding complications in RCTs was $\leq$ 1%.[48] Care should be taken to minimise access complications in patients on anticoagulants, including using smaller sheaths ($\leq$ 6 Fr) and ultrasound guided CFA puncture, which reduces bleeding complications by 50—60%.[97] CAS is classified as a low risk of bleeding intervention.[343,344]

4.2.6.3. Peri-operative antiplatelet and anticoagulation strategies. This depends on the procedure (CEA, CAS), thromboembolic risk, bleeding risk, type of anticoagulant (vitamin K antagonist [VKA] or DOAC), renal function, and whether bridging anticoagulation is required.

4.2.6.3.1. Carotid endarterectomy. Because CEA is a high risk of bleeding procedure, the anticoagulants need to be stopped routinely and for longer durations than for low risk of bleeding procedures. Figure 4 details suggested timings for stopping and restarting VKAs and DOACs. Decisions regarding restarting VKAs/DOACs must take account of post-operative bleeding complications, as well as the patient's ability to swallow. Aspirin 300 mg daily should be prescribed as indicated in Figure 4.

The need for pre-operative bridging anticoagulation requires careful discussion within an MDT as an RCT involving patients with atrial fibrillation undergoing elective surgery showed that bridging was associated with higher risks of major bleeding and did not reduce thromboembolic events.[14] The Dresden Registry reported similar findings.[117] Accordingly, pre-operative bridging with therapeutic dose low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is only indicated in a very small cohort of CEA patients considered at high risk of thromboembolism after cessation of VKAs, which would include patients with a recent (within three months) deep vein thrombosis or pulmonary embolism, or those who suffered a thromboembolic event during previous interruption of oral anticoagulation.[343] If pre-operative bridging is indicated in VKA patients (Figure 5), the last dose of LMWH should be $\geq$ 24 hours pre-operatively. Intravenous UFH can be stopped four to six hours before CEA.

Post-operative bridging is reasonable in CEA patients who have stopped their VKAs and who are considered high risk of thromboembolism. Pre-operative bridging is not, however, recommended in patients on DOACs, as their predictable short half life allows for proper timing of DOAC cessation just before surgery.[343]

In CEA patients whose VKAs have been stopped and who are classed as low thromboembolic risk, VKAs can be restarted on day 3. Aspirin (300 mg daily) should be continued until either a last dose on day 5 or when the International Normalised Ratio is therapeutic (Figure 5). In CEA patients whose VKAs have been stopped and who are considered high thromboembolic risk, prophylactic subcutaneous LMWH can be prescribed for the first 48 hours after CEA, with VKAs restarted on day 3, when the LMWH is increased to therapeutic doses and continued until the International Normalised Ratio has reached therapeutic levels. In the latter patients, the last dose of aspirin should be on day 3 (Figure 5).

DOAC patients usually do not require post-operative bridging because they achieve full anticoagulation within eight hours of restarting DOACs. Patients at low thromboembolic risk can, therefore, restart DOACs on post-operative day 3, with the last dose of aspirin (300 mg) being taken on day 3 (Figure 5). In DOAC patients considered at high thromboembolic risk, the potential for increased bleeding complications needs to be considered. Prophylactic dose LMWH can be started 6 — 24 hours post-operatively and continued until day 3 when the DOAC is restarted. In these patients, the last dose of aspirin is taken on day 3.

4.2.6.3.2. Carotid artery stenting. Decisions about anticoagulation and antiplatelet strategies during CAS depend upon whether unit policy is to (i) stent patients while on anticoagulation with the addition of a single antiplatelet agent during the peri-operative period, (ii) stent patients after anticoagulation is stopped with a single antiplatelet agent prescribed during the peri-operative period, or (iii) stent patients after anticoagulation is stopped with combination antiplatelet therapy prescribed during the peri-operative period. Much of the debate is driven by concerns about post-operative bleeding complications (especially ICH) if anticoagulation is continued, *versus* worries about higher rates of peri-operative ischaemic stroke if

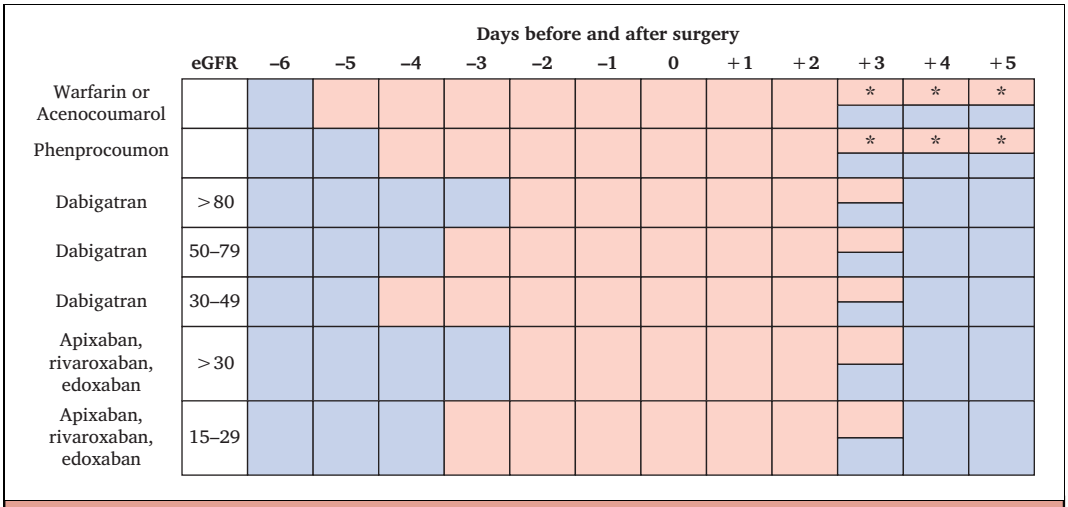


Figure 4. Stopping and restarting anticoagulation prior to carotid endarterectomy (CEA). Blue boxes represent days for taking anticoagulant, red boxes represent days to take 300 mg aspirin daily. If intolerant of, or allergic to aspirin, 75 mg of clopidogrel daily or 200 mg of dipyridamole modified release monotherapy twice daily are alternatives. eGFR = estimated glomerular filtration rate, measured as mL/min/1.73m.[2] *In patients taking vitamin K antagonists (VKA), post-operative aspirin is continued until the International Normalised Ratio is therapeutic (after VKA restarted) or until the patient is started on therapeutic dose low molecular weight heparin or intravenous unfractionated heparin.

antiplatelet therapy is not co-prescribed. Accordingly, individual units will benefit from MDT review, which should ideally include a specialist in coagulation (especially if bridging is being considered) and agreed treatment strategies should be documented in the case notes.

Historically, most CAS procedures were performed with anticoagulation stopped pre-operatively. However, the 2019 Society of Interventional Radiology guidelines advise that anticoagulants do not need to be stopped routinely, unless there are additional high risk of bleeding features.[344] This advice has probably not, however, translated into clinical practice in many CAS centres. Although there have been no RCTs in CAS patients, evidence from observational studies suggest that CAS can be performed safely while the patient is taking anticoagulants plus antiplatelet therapy during the peri-operative period, without increasing bleeding complications,[345,346] especially if smaller sheaths and ultrasound guided punctures are used.[97] Extrapolation of data from

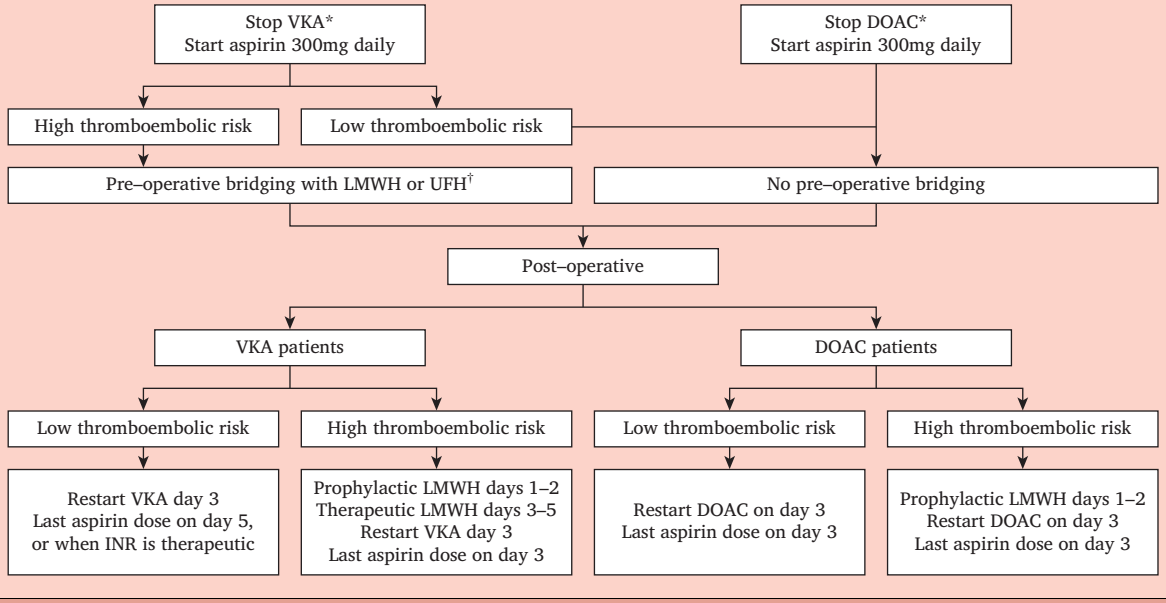


Figure 5. Anticoagulation, antiplatelet, and bridging strategies in patients undergoing carotid endarterectomy (CEA). If intolerant of, or allergic to aspirin, 75 mg of clopidogrel monotherapy daily or 200 mg of dipyridamole modified release monotherapy twice daily are alternatives. *Vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) should be stopped according to timings in Figure 4. †If pre-operative bridging is being considered, this decision should involve multidisciplinary team discussion (preferably involving a specialist in coagulation) and the benefits and risks of bridging must be clearly explained to the patient and documented in the case notes. LMWH = low molecular weight heparin; UFH = unfractionated heparin.

RCTs in AF patients undergoing percutaneous coronary interventions suggest that dual antithrombotic therapy (anticoagulant plus a single antiplatelet agent) appears to be superior to triple therapy (anticoagulant plus aspirin and clopidogrel) in reducing bleeding events, while being non-inferior regarding the associated risks of thromboembolic events.[341] Figure 6 provides a pragmatic algorithm for anticoagulation and single agent antiplatelet strategies in CAS patients.

In CAS patients where VKAs and DOACs are to be stopped, the timing is the same as for CEA (Figure 4). If bridging is being considered in VKA patients, this decision should involve MDT review (ideally involving a specialist in coagulation) and the benefits *versus* risks of bridging must be clearly explained to the patient and documented in the case notes. In the patient algorithm (Figure 6), antiplatelet monotherapy (aspirin 300 mg the day before CAS, then 75 — 100 mg daily until 30 days) is appropriate, given that these patients will also receive intra-operative heparin. If the patient is intolerant of, or allergic to aspirin, 75 mg of clopidogrel monotherapy daily or 200 mg of dipyridamole modified release monotherapy twice daily are alternatives. After 30 days, antiplatelet therapy is stopped, and anticoagulation continued long term.

In some centres, CAS practitioners prefer to stop anticoagulation therapy pre-operatively and then prescribe combination antiplatelet therapy throughout the peri-procedural period, to minimise the risks of embolic stroke from the CAS site. If this is the preferred management strategy, combination antiplatelet therapy should be started on the day after VKA/DOAC cessation (see section 4.2.2.3 for choice and dosages of combination APRx). However, it is important that the MDT determine exactly when post-operative combination antiplatelet therapy should cease and when anticoagulation should be restarted.

4.2.7. Lipid lowering therapy

4.2.7.1. Statins as secondary prevention. RCTs have evaluated lipid lowering therapy in TIA or minor ischaemic stroke patients (Table 17), but only one subgroup analysis included patients with carotid disease.[347]

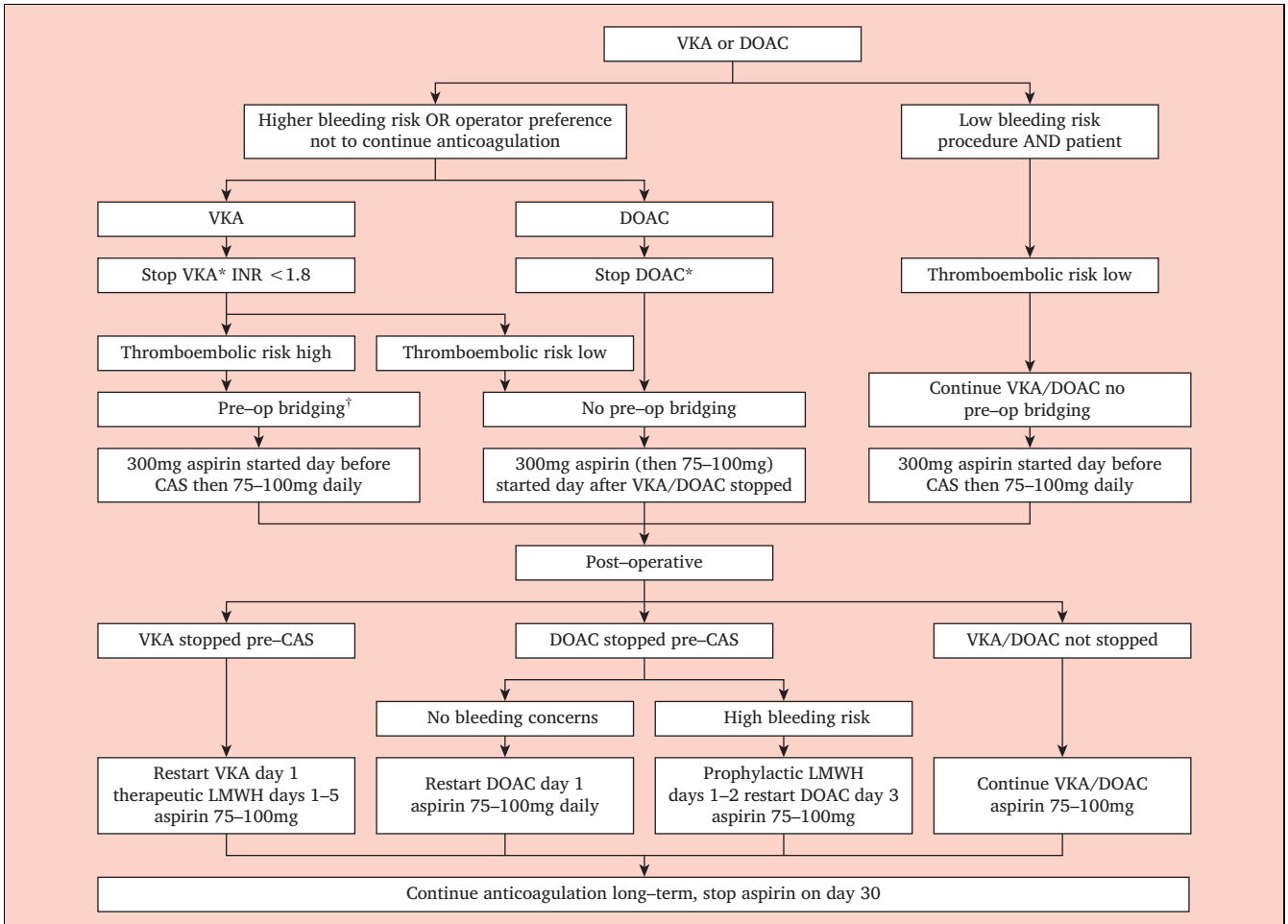


Figure 6. Anticoagulation and antiplatelet strategies in patients undergoing carotid artery stenting (CAS) who are taking anticoagulants pre-operatively. If intolerant of, or allergic to aspirin, 75 mg clopidogrel monotherapy daily or 200 mg dipyridamole modified release monotherapy twice daily are alternatives. *Vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) should be stopped according to timings in Figure 4. †If bridging is being considered, this decision should involve multidisciplinary team discussion (preferably involving a specialist in coagulation) and the benefits and risks of bridging must be clearly explained to the patient and documented in the case notes. LMWH = low molecular weight heparin.

Table 17. Randomised controlled trials (RCTs) evaluating lipid lowering therapy in transient ischaemic attack (TIA) or minor ischaemic stroke patients

RCT	Inclusion criteria	Treatment strategy	Main findings
HPS[348]	3 280 patients with prior TIA (46%), minor ischaemic stroke (63%), prior carotid revascularisation (10%) plus cholesterol >3.5 mmol/L. Mean interval from symptom onset to randomisation: 4y	40 mg simvastatin daily *vs.* placebo	Simvastatin conferred 20% RR in stroke, non-fatal MI, death from coronary artery disease and/or coronary or non-coronary revascularisation in patients with prior cerebrovascular disease ($p = .001$). 19% RR in ischaemic stroke with simvastatin (6.1%) *vs.* placebo (7.5%) was not significant ($p = .10$) with no statistically significant increase in haemorrhagic stroke with simvastatin (1.3% *vs.* 0.7%)
FASTER[311]	392 patients randomised <24 h of TIA or minor ischaemic stroke using factorial design	All received aspirin plus either clopidogrel *vs.* placebo and simvastatin *vs.* placebo	No significant differences in 90 d endpoint of any stroke between those who were *vs.* not taking simvastatin
SPARC[349]	4 731 patients with ischaemic stroke / TIA <6 mo with baseline LDL-C 2.6–4.9 mmol/L and no known CAD	80 mg atorvastatin *vs.* placebo	80 mg atorvastatin conferred significantly lower fatal / non-fatal stroke at 5y (11.2% *vs.* 13.1%; HR 0.84, 95% CI 0.71–0.99; $p = .030$). Significant increase in haemorrhagic stroke with atorvastatin *vs.* placebo (2.3% *vs.* 1.4%; HR 1.66, 95% CI 1.08–2.55; $p = .020$) which did not negate benefit of atorvastatin
SPARCL[347]	1 007 SPARCL patients with carotid stenosis (mean 51%) not undergoing CEA or CAS <30 d of randomisation	80 mg atorvastatin *vs.* placebo	80 mg atorvastatin associated with significant reductions in any stroke (HR 0.67, 95% CI 0.47–0.94; $p = .020$); late carotid revascularisation (HR 0.44, 95% CI 0.24–0.79; $p = .006$), and major coronary events (HR 0.57, 95% CI 0.32–1.0; $p = .050$)
TST Trial[7]	2 860 patients <3 mo of ischaemic stroke (mRS 0–3) or <15 d of TIA (patients randomised within median of 6 d after TIA / stroke). Outcomes in SCS patients not reported	Aggressive lipid lowering with statins ± ezetimbe to achieve lower LDL-C target of <1.8 mmol/L *vs.* higher LDL-C target of 2.3–2.8 mmol/L	66% in lower LDL-C and 94% in higher LDL-C groups received statins only with 33.8% and 5.8%, respectively, also receiving ezetimibe (10 mg daily). Lower LDL-C target (*vs.* higher target) associated with significant reduction in composite endpoint of any cardiovascular death, stroke, MI, hospitalisation for unstable angina requiring urgent CABG or PCI or TIA treated by urgent CEA / CAS at 3.5 y. (8.5 *vs.* 10.9%; HR 0.78, 95% CI 0.61–0.98; $p = .040$)
STARS[30]	98 patients randomised <12 h of ischaemic stroke	40 mg simvastatin *vs.* placebo (only 4% of simvastatin patients and 15% of placebo patients had LAA)	Independence at 90 d (mRS ≤2): simvastatin 69% *vs.* 70% placebo (OR 0.99, 95% CI 0.35–2.78; $p = .98$) No difference in safety (haemorrhagic transformation, haemorrhagic events, death, infections, serious adverse events)
ASSORT[37]	257 with acute ischaemic stroke plus dyslipidaemia or LDL-C >2.6 mmol/L randomised to early statin therapy *vs.* delayed statin therapy	131 started statin therapy <24 h (for 12 w) *vs.* 126 starting statins on day 7 (for 11 w); atorvastatin 20 mg/d, pitavastatin 4 mg/d or rosuvastatin 5 mg/d)	At 90 d, mRS distribution not different between patients receiving early statin therapy vs delayed (OR 1.1, 95% CI 0.79–1.4) LAA responsible for 43% of strokes at presentation (but no data regarding extracranial *vs.* intracranial disease or whether they were carotid *vs.* VA)
EUREKA[22]	316 statin naïve patients randomised <48 h of acute ischaemic stroke. 33–37% had a 50–99% stenosis of a brain supplying artery, but number with extracranial SCS not reported	Rosuvastatin 20 mg (n=137) *vs.* placebo (n=152) over 14 days	No difference in NIBLs at 5 or 14 d on DW-MRI (19.7% rosuvastatin *vs.* 23.6% placebo; RR 0.83, 95% CI 0.53–1.3). Rosuvastatin group had a lower risk of new or worsening haemorrhagic transformation of an infarct (4.4%) *vs.* 14.5% with placebo ($p = .007$)

CEA = carotid endarterectomy; CAS = carotid artery stenting; CAD = coronary artery disease; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; RR = relative risk LDL-C = low density lipoprotein cholesterol; OR = odds ratio; CI = confidence interval; SCS= symptomatic carotid stenosis; mRS = modified Rankin score; NIBLs = new ischaemic brain lesions; DW-MRI = diffusion weighted magnetic resonance imaging; LAA = large artery atherosclerosis.

In most RCTs in patients presenting with TIA/stroke (including those with carotid disease), lipid lowering therapy reduced late cardiovascular events (including stroke). Lower LDL-C targets (< 1.8 mmol/L) were associated with lower stroke rates and greater regression of carotid atherosclerosis, compared with higher LDL-C targets (2.3 — 2.8 mmol/L).[8]

4.2.7.2. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Acute ischaemic stroke patients were excluded from many RCTs involving PCSK9 inhibitors. A secondary analysis of FOURIER assessed outcomes in patients with prior ischaemic stroke who had an LDL-C ≥ 1.8 mmol/L or non-high density lipoprotein cholesterol ≥ 2.6 mmol/L after at least two weeks stabilisation on a moderate or high intensity statin (3.2—3.9% were also on ezetimibe).[18] Median delay between stroke onset and randomisation was 3.3 years, with only 23% randomised within one year of stroke onset and none at less than four weeks. The risk of stroke, MI, cardiovascular death, hospitalisation for unstable angina or coronary revascularisation over a median 2.1 year follow up was significantly lower in 2 686 patients randomised to evolocumab (140 mg every two weeks or 420 mg every four weeks) *versus* 2 651 patients on placebo (HR 0.85; 95% CI 0.72 — 1.00, $p = .047$). However, the risks of any stroke and ischaemic stroke were no different. Evolocumab did not increase haemorrhagic stroke, despite median LDL-C levels of 0.7 — 0.8 mmol/L.[18] The authors suggested that patients with ischaemic stroke and additional atherosclerotic risk factors may benefit from LDL-C levels below current targets.

4.2.7.3. Lipid targets in stroke/transient ischaemic attack patients. There is sufficient high quality evidence to conclude that patients presenting with TIA or minor ischaemic stroke should be prescribed lipid lowering therapy, unless not tolerated. Both the 2021 AHA and the 2019 ESC-EAS guidelines recommend high dose atorvastatin 80 mg or rosuvastatin 20 mg, unless not tolerated.[1,258] As no RCTs have specifically evaluated lipid lowering targets in SCS or ACS patients, the GWC have mainly adopted targets recommended in the 2021 AHA[1] and the 2019 ESC-EAS guidelines.[258] The aim is for a total cholesterol < 3.5 mmol/L (< 135 mg/dL),[348] LDL-C < 1.8 mmol/L (< 70 mg/dL),[7,347,348] or a 50% reduction in LDL-C *versus* baseline.[1] It is reasonable to add ezetimibe (10 mg daily) in SCS patients who fail to achieve lipid targets on maximum doses or maximum tolerated statin doses.[1,7] The GWC acknowledges that the ESC-EAS guidelines recommend a lower target for LDL-C (< 1.4 mmol/L [< 54 mg/dL]) in very high risk patients with atherosclerotic cardiovascular disease, which includes TIA/stroke patients, as well as significant ACS, but ESC-EAS did not define what significant ACS meant.[258] However, due to a statistically significant increase in haemorrhagic stroke with atorvastatin *versus* placebo in SPARCL (2.3% *vs.* 1.4%; HR 1.66, 95% CI 1.08 — 2.55, $p = .020$)[349] and the exclusion of patients with TIA/acute stroke from PCSK9 inhibitor trials, the GWC based their recommended LDL-C target of < 1.8 mmol/L on RCTs involving stroke/TIA patients. However, in SCS or ACS patients with additional very high risk factors (e.g., CAD, PAD; type II DM with target organ damage, longstanding type I DM), a target LDL-C < 1.4 mmol/L (< 54 mg/dL) should be considered.[258] Pending RCT data, in SCS patients who are intolerant of, or not achieving LDL-C targets on statins (with or without ezetimibe), additional or alternative treatment with PCSK9 inhibitors should be considered.[18]

Recommendation 34			Unchanged
For patients with a symptomatic carotid stenosis, statin therapy is recommended for the long term prevention of stroke, myocardial infarction and other cardiovascular events.			
Class	**Level**	**References**	**ToE**
I	B	Sillesen *et al.* (2008)[347]	

Recommendation 35			New
For symptomatic carotid stenosis patients who do not reach their lipid targets on maximum doses or maximum tolerated doses of statins, ezetimibe (10 mg daily) is recommended.			
Class	**Level**	**References**	**ToE**
I	B	Amarenco *et al.* (2020)[7]	

Recommendation 36			New
For symptomatic carotid stenosis patients who are intolerant of, or not achieving target low density lipoprotein levels on statins, with or without ezetimibe, additional or alternative treatment with PCSK9 inhibitors should be considered.			
Class	**Level**	**References**	**ToE**
IIa	B	Giugliano *et al.* (2020)[18]	

4.2.7.4. Statins during carotid interventions. In a meta-analysis (seven observational studies; $n = 610$), statin pre-treatment in patients with > 50% SCS was associated with a lower incidence of MES during TCD monitoring *versus* statin naive patients (RR = 0.67; 95% CI 0.45 — 0.98).[93] In another meta-analysis (six observational studies; $n = 7\,503$), patients taking statins prior to CEA had lower peri-operative mortality (0.2% *vs.* 1.3%) than statin naive patients (OR 0.26; 95% CI 0.1—0.61), plus a non-significant reduction in peri-operative stroke (1.4% *vs.* 3.0%) over statin naive patients (OR 0.4; 95% CI 0.15—1.09).[100] In a third meta-analysis (11 observational studies; $n = 4\,088$), patients taking statins prior to CAS had lower mortality (OR 0.30; 95% CI 0.10 — 0.96) and procedural stroke (OR 0.39; 95% CI 0.27 — 0.58) than statin naive patients.[101] Stroke patients prescribed statins should not have this medication withdrawn acutely, because RCTs suggest that stopping statins for three days after acute stroke onset (*vs.* continuing atorvastatin 20 mg daily) was associated with increased rates of death or dependency at 90 days (OR 4.66; 95% CI 1.46 — 14.91, $p = .043$), after adjusting for age and baseline stroke severity.[41]

Recommendation 37			Unchanged
For patients scheduled to undergo endarterectomy or stenting, it is recommended to commence statin therapy pre-operatively.			
Class	**Level**	**References**	**ToE**
I	A	Safouris *et al.* (2018)[93], Texakalidis *et al.* (2018)[100], Texakalidis *et al.* (2018)[101]	

4.2.8. Management of hypertension

4.2.8.1. Secondary prevention in patients with stroke/transient ischaemia attack. A Cochrane review (11 RCTs; $n = 38\ 742$) reported that antihypertensive therapy reduced the relative risk of recurrent stroke by 24% in patients with a prior ischaemic stroke (RR 0.76; 95% CI 0.64 — 0.89).[114] A meta-analysis of secondary stroke prevention (14 RCTs; $n = 42\ 736$) showed that the extent of SBP and DBP reduction was linearly associated with the magnitude of reduction in recurrent cerebrovascular and cardiovascular events,[68] emphasising the importance of strict BP control in patients with prior cerebrovascular events. As with ACS patients, the GWC advises readers to refer to ESC-ESH thresholds for treating hypertension (section 3.1.5).[236]

4.2.8.2. Blood pressure management during carotid endarterectomy. Because SBP > 180 mmHg is an independent risk factor for stroke after CEA,[350] it is reasonable to perform urgent CEA when pre-operative BP is < 180 mmHg. There are no published data for CAS patients, but a similar approach seems reasonable. Symptomatic patients with SBP > 180 mmHg should receive urgent, titrated antihypertensive treatment before undergoing CEA, while acknowledging that very rapid BP lowering before CEA and CAS may be inadvisable in patients with severe bilateral stenoses.[351] Persisting or worsening hypertension after CEA should be treated actively to prevent hyperperfusion syndrome, ICH, bleeding complications, and cardiac events in the early post-operative period[309] (section 7.1.3.3).

Recommendation 38			Unchanged
For patients presenting with a transient ischaemic attack or minor ischaemic stroke with hypertension, antihypertensive treatment is recommended.			
Class	**Level**	**References**	**ToE**
I	A	Williams *et al.* (2018)[236]	

Recommendation 39			Unchanged
For symptomatic carotid stenosis patients awaiting endarterectomy or stenting, caution should be considered when rapidly lowering blood pressure in the early time period after onset of symptoms, but uncontrolled hypertension (>180/90 mmHg) should be treated.			
Class	**Level**	**References**	**ToE**
IIa	C	Bond *et al.* (2002)[350], Rothwell *et al.* (2003)[351]	

4.2.9. Management of diabetes mellitus. Principles underpinning the management of DM patients with SCS are similar to those with ACS (section 3.1.6). The Prospective Pioglitazone Clinical Trial in macroVascular Events (PROACTIVE) ($n = 5\ 238$) investigators reported that pioglitazone (in addition to existing glucose lowering and cardiovascular medications), lowered the risk of stroke in type II DM patients.[242] Treatment of DM is important in the acute stroke setting, but it is reasonable to aim for normoglycaemia because intensive blood glucose control has not been shown to be beneficial.[23,352,353] Thereafter, it is reasonable to aim for optimal glycaemic control as per updated guidelines from committees with expertise in treating patients with diabetes.[243,344]

4.2.10. Adherence to medications. Adherence was analysed in 114 TIA/ischaemic stroke patients who were followed for a median of 1.7 years.[354] Letters describing clinical details and a goal directed treatment plan were sent to the patient and referring doctor. The proportion continuing to take prescribed medications was 94% for aspirin, 73% for dipyridamole, 81% for clopidogrel, 88% for statins, and 90% for antihypertensive therapy. Overall, 99% reported full adherence the preceding day, while 11% reported missing at least one medication over the preceding 14 days. Half reported that they never forgot to take their medications.[354] The widest variation in adherence involved statins, possibly because of perceived side effects.[355] Non-adherence contributes towards patients not achieving LDL-C targets, which increases the risk of recurrent vascular events. The same may apply to aspirin plus dipyridamole therapy (usually dipyridamole induced headache), but this can be reduced by slow dose escalation in the first week of treatment.

4.3. Randomised trials: endarterectomy versus medical therapy

4.3.1. Thirty day and five year outcomes in the randomised trials. Three RCTs (NASCET, ECST, and the Symptomatic Veterans Affairs Co-operative Study [SVACS]) compared CEA with BMT in SCS patients reporting carotid territory symptoms within six months.[188,189,356] The Carotid Endarterectomy Trialists Collaboration (CETC) performed an individual patient meta-analysis of 6 092 patients in the three RCTs, with pre-randomisation angiograms re-measured using the NASCET method (Table 18).[357—359] CEA (plus BMT) conferred no benefit in patients with < 50% stenoses (see section 4.10 for management of patients developing recurrent symptoms despite BMT). CEA conferred benefit in patients with moderate (50—69%) and severe (70—99%) stenoses (Table 18). The benefit conferred by CEA increased with stenosis severity, with the exclusion of CNO. CETC concluded that CNO patients gained no benefit from CEA,[357,358] and the controversy is discussed further in section 4.12.

4.3.2. Who is at higher risk of stroke on medical therapy? Clinical/imaging predictors of increased stroke risk on BMT in the RCTs are detailed in Table 19.

4.4. Randomised trials: endarterectomy versus stenting

4.4.1. Thirty day outcomes. Ten RCTs compared CEA with CAS (not CA) in 5 797 SCS patients. A meta-analysis of 30

Table 18. Individual patient meta-analysis of five year risks of any stroke, including peri-operative stroke or death, from European Carotid Surgery Trial (ESCT), North American Symptomatic Carotid Endarterectomy Trial (NASCET), and Symptomatic Veterans Affairs Carotid Study (SVACS) randomised controlled trials*

Stenosis severity, NASCET − %	Patients − *n*	5 y risk of any stroke (including peri-op stroke) − %		ARR at 5 y − %	RRR at 5 y − %	NNT to prevent one stroke at 5 y	Strokes prevented per 1 000 CEAs at 5 y
		CEA + BMT	BMT				
0−30	1 746	18.4	15.7	-2.7	N/b	N/b	None
30−49	1 429	22.8	25.5	+2.7	N/b	N/b	27
50−69	1 549	20.0	27.8	+7.8	28	13	78
70−99	1 095	17.1	32.7	+15.6	48	6	156
CNO	262	22.4	22.3	-0.1	N/b	N/b	None

CEA = carotid endarterectomy; BMT = best medical therapy; ARR = absolute risk reduction in stroke; RRR = relative risk reduction in stroke; NNT = number needed to treat to prevent one stroke at five years; N/b = no benefit; CNO = chronic near occlusion.
* Data derived from the Carotid Endarterectomy Trialists Collaboration.[357−359]

Table 19. Clinical and imaging features that were predictive of a significant increase in late stroke in patients with 50−99% carotid stenoses randomised within European Carotid Surgery Trial (ESCT) and North American Symptomatic Carotid Endarterectomy Trial (NASCET)

Feature	Monitored risk	Risk reduction
Clinical features		
Increasing age[357,358,360]	5 y ARR in ipsilateral stroke conferred by CEA	<65 y: 5.6% (NNT18); 65−75 y: 8.6% (NNT 12); >75 y: 19.2% (NNT 5)
Recency of symptoms[358]	5 y ARR in ipsilateral stroke conferred by CEA	<2 w: 18.5% (NNT 5); 2−4 w: 9.8% (NNT 10); 4−12 w: 5.5% (NNT 18); >12: 0.8% (NNT 125)
Men *vs.* women[359]	5 y ARR in ipsilateral stroke conferred by CEA	Males: 11% (NNT 9); females: 2.8% (NNT 36)
Hemispheric *vs.* ocular symptoms[358]	5 y ARR in ipsilateral stroke conferred by CEA	Ocular: 5% (NNT 20); TIA: 15% (NNT 7); stroke: 18% (NNT 6)
Cortical vs. lacunar stroke[361]	3 y ARR in ipsilateral stroke conferred by CEA	Non-lacunar stroke: 15% (NNT 7); lacunar stroke: 9% (NNT 11)
Increasing medical comorbidities[189]	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%
Imaging features		
Irregular *vs.* smooth plaques[358]	5 y ARR in ipsilateral stroke conferred by CEA	Smooth: 8% (NNT 13); irregular: 17% (NNT 6)
Increasing stenosis severity[357]	5 y ARR in ipsilateral stroke conferred by CEA	50−69%: 4% (NNT 25); 60−69%: 5.9% (NNT 17); 70−79%: 15.8% (NNT 6); 80−99%: 17.7% (NNT 6); 90−99%: 32.4% (NNT 3);
Contralateral occlusion[358]	5 y ARR in ipsilateral stroke conferred by CEA	Contralateral occlusion: 24% (NNT 4); no occlusion: 13% (NNT 8)
Tandem intracranial disease[362]	3 y risk of ipsilateral stroke in medically treated patients with tandem intracranial disease increased with extracranial ICA stenosis severity	50−69%: 19% (NNT 5); 70−84%: 29% (NNT 3); 85−99%: 45% (NNT 2)
No recruitment of collaterals[363]	2 y ARR in ipsilateral stroke conferred by CEA collaterals recruited: 5% (NNT 20); no recruitment: 19% (NNT 5)	

CEA = carotid endarterectomy; BMT = best medical therapy; TIA = transient ischaemic attack; ICA = internal carotid artery; ARR = absolute risk reduction; NNT = number needed to treat to prevent one stroke; y = years; w = weeks.

day outcomes is detailed in Table 20. CAS (almost exclusively TFCAS) was associated with higher rates of any stroke, death/any stroke, death/disabling stroke, and death/any stroke/MI *versus* CEA.[48]

Table 21 details a meta-analysis of 30 day outcome data in 4 754 patients from four large multicentre RCTs that randomised > 500 patients including the Endarterectomy versus Stenting in patients with Symptomatic Severe carotid Stenosis (EVA-3S), the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, the International Carotid Stenting Study (ICSS) and the Carotid Revascularisation Endarterectomy *vs.* Stenting (CREST) Trial.[314,316,317,364] CAS (almost exclusively TFCAS) was associated with higher rates of 30 day stroke, death/stroke, and death/stroke/MI *versus* CEA.[48] All other endpoints were similar.

4.4.1.2. Thirty day outcomes stratified by age. The Carotid Stenting Trialists Collaboration (CSTC) performed an individual patient meta-analysis of 4 289 SCS patients in ICSS, CREST, EVA-3S, and SPACE. There was a strong association

Table 20. Meta-analysis of 30 day outcomes in 10 randomised controlled trials (RCTs)* on patients with symptomatic carotid artery disease comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA)†

	Death	Stroke	Death / stroke	Disabling stroke	Death / disabling stroke	MI	Death / stroke / MI
RCTs / patients − *n*	9 / 4 257	9 / 5 535	10 / 5 797	6 / 4 855	5 / 3 534	6 / 3 980	6 / 3 719
CAS (95% CI) − %	1.9 (1.4−2.6)	8.5 (5.9−12.1)	9.3 (6.8−12.6)	3.3 (1.6−6.7)	5.2 (3.0−8.9)	0.8 (0.5−1.4)	8.4 (5.0−13.8)
CEA (95% CI) − %	1.4 (0.9−2.0)	4.6 (3.3−6.4)	5.1 (3.7−6.9)	1.8 (1.1−3.1)	3.2 (2.5−4.1)	1.6 (1.0−2.3)	5.1 (4.1−6.3)
OR (95% CI)	1.38 (0.8−2.3)	1.73 (1.4−2.1)	1.71 (1.4−2.1)	1.35 (0.9−2.0)	1.42 (1.0−2.0)	0.50 (0.2−1.0)	1.61 (1.2−2.1)

Red shading indicate a statistically significant result favouring CEA. MI = myocardial infarction; OR = odds ratio; CI = confidence intervals.
* CREST-1; EVA-3S; ICSS; Kuliha; Naylor; Brooks; Steinbauer; SPACE-1; SAPPHIRE; Wallstent.
† Reproduced with permission from Batchelder A, Saratzis A, Naylor AR. Overview of Primary and Secondary Analyses from 20 randomised controlled trials comparing carotid artery stenting with carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2019;**58**:479−93.

Table 21. Meta-analysis of 30 day outcomes after carotid artery stenting (CAS) *versus* carotid endarterectomy (CEA) in four randomised controlled trials (RCTs) which randomised more than 500 patients with symptomatic carotid artery disease*,†

	Death	Stroke	Death / stroke	Disabling stroke	Death / disabling stroke	MI	Death / stroke / MI
RCTs / patients − *n*	3 / 3 413	4 / 4 754	4 / 4 754	4 / 4 754	3 / 3 413	3 / 3 551	2 / 3 031
CAS (95% CI) − %	1.2 (0.5−2.9)	7.8 (6.8−9.0)	8.7 (7.6−9.9)	3.3 (2.6−4.1)	4.3 (3.4−5.4)	0.7 (0.4−1.3)	8.0 (5.9−10.7)
CEA (95% CI) − %	0.9 (0.5−1.5)	4.8 (4.0−5.7)	5.5 (4.7−6.5)	2.4 (1.8−3.1)	3.2 (2.5−4.2)	1.0 (0.3−3.1)	5.2 (4.2−6.5)
OR (95% CI)	1.67 (0.9−3.2)	1.66 (1.3−2.1)	1.61 (1.3−2.0)	1.39 (0.9−2.0)	1.38 (0.9−2.0)	0.51 (0.3−1.0)	1.60 (1.2−2.1)

Red shade: statistically significant result favouring CEA. MI = myocardial infarction; OR = odds ratio; CI = confidence interval.
* Carotid Revascularization versus Stenting Trial (CREST) -1; Endarterectomy versus Stenting in patients with Symptomatic Severe carotid Stenosis (EVA-3S); The International Carotid Stenting Study (ICSS); Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE) -1.
† Reproduced with permission from Batchelder A, Saratzis A, Naylor AR. Overview of Primary and Secondary Analyses from 20 randomised controlled trials comparing carotid artery stenting with carotid endarterectomy. *Eur J Vasc Endovasc Surg* 2019;**58**:479−93.

between increasing age and higher 30 day death/stroke after CAS, but not CEA (Table 22).[169] Compared with CEA (Table 22), CAS patients aged > 70 years incurred higher rates of death/stroke. Below 70 years, CAS had similar outcomes to CEA.

4.4.2. Long term outcomes

4.4.2.1. Late ipsilateral stroke. Excluding peri-operative risks, a CSTC meta-analysis of four RCTs showed that five year rates of ipsilateral stroke were 3.1% after CEA *versus* 3.2% after CAS (HR 1.06; 95% CI 0.73 − 1.54), giving an average annual ipsilateral stroke rate of 0.62% (CEA) and 0.64% (CAS). Nine year rates of ipsilateral stroke were 3.9% after CEA *versus* 4.5% after CAS, giving an average annual ipsilateral stroke rate of 0.43% after CEA and 0.5% after CAS.[12] These data indicate that, as with ACS (section 3.8.2), CAS was as durable as CEA once the peri-operative period had elapsed. Accordingly, the decision to perform CEA or

Table 22. Age and 30 day rates of death or stroke after carotid endarterectomy (CEA) and carotid artery stenting (CAS) in patients with symptomatic carotid artery disease randomised within The International Carotid Stenting Study (ICSS), Carotid Revascularization versus Stenting Trial (CREST), Endarterectomy versus Stenting in patients with Symptomatic Severe carotid Stenosis (EVA-3S), Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE)*

Age − y	CAS		CEA		CAS *vs.* CEA
	30 d death or stroke	HR (95% CI)	30 d death or stroke	HR (95% CI)	HR (95% CI)†
<60	13 / 407 (3.2)	1.0‡	21 / 407 (5.2)	1.0‡	0.62 (0.31−1.23)
60−64	20 / 351 (5.7)	1.79 (0.89−3.60)	18 / 341 (5.3)	1.01 (0.34−1.9)	1.07 (0.56−2.01)
65−69	31 / 462 (6.7)	2.16 (1.13−4.13)	18 / 422 (4.3)	0.81 (0.43−1.52)	1.61 (0.90−2.88)
70−74	58 / 480 (12.1)	4.01 (2.19−7.32)	26 / 436 (6.0)	1.20 (0.68−2.13)	2.09 (1.32−2.32)
75−79	48 / 403 (11.9)	3.94 (2.14−7.28)	30 / 461 (6.5)	1.29 (0.74−2.25)	1.91 (1.21−3.01)
≥80	36 / 290 (12.4)	4.15 (2.20−7.84)	16 / 291 (5.5)	1.09 (0.57−2.10)	2.43 (1.35−4.38)

Data are presented as *n* (%) unless stated otherwise. HR = hazard ratio; CI = confidence interval.
* Data derived from Howard.[169]
† Age based HR calculation for CAS compared with CEA. If HR is < 1.0, CAS is associated with lower peri-operative death/stroke. If HR is > 1.0, CAS is associated with higher rates of peri-operative stroke or death.
‡ All HR age based calculations compared against age < 60 years.

CAS will be largely determined by factors associated with increases in peri-operative stroke/death after CEA or CAS in individual patients (sections 7.1.1.3 and 7.1.2.1).

4.4.2.2. Quality of life. Health Related Quality of life was assessed in CREST.[365] CAS patients had better quality of life in the post-operative period, especially physical limitation and pain ($p = .010$), but not at one year. Using disease specific scales, CAS patients reported fewer problems with driving, eating, swallowing, neck pain, and headache, but greater difficulty with walking and leg pain ($p < .050$). However, at one year, there was no difference. Peri-operative stroke was associated with poorer one year quality of life across all SF-36 domains, while peri-procedural MI and CNI were not.

4.4.2.3. Survival following peri-operative stroke or myocardial infarction. The relevance of peri-operative MI (especially non-ST elevation MI with troponin elevation) has been a source of controversy since its inclusion as a primary endpoint in SAPPHIRE and CREST.[282,316] The rationale was that peri-operative MI and/or troponin elevation were associated with poorer long term survival after non-cardiac surgery.[366] At 10 years, CREST patients having a peri-operative stroke had statistically significantly higher mortality compared with patients without peri-operative stroke (HR 1.74; 95% CI 1.21 − 2.5, $p < .003$).[28] Compared with CREST patients who did not have a peri-operative stroke, reduced long term survival was mainly a result of deaths occurring in the first 90 days (HR 14.41; 95% CI 5.33 − 38.94, $p < .001$). Thereafter, there was a non-significant trend towards increased mortality between 91 days and 10 years (HR 1.40; 95% CI 0.93 − 2.10). CREST patients with a peri-operative MI had statistically significantly higher mortality at 10 years compared with patients without peri-operative MI (HR 3.61; 95% CI 2.28 − 5.73, $p = .006$).[28] Increased mortality in CREST patients with a peri-operative MI continued through the first 90 days (HR 8.2; 95% CI 1.86 − 36.2, $p < .001$) and from day 91 to 10 years (HR 3.4; 95% CI 2.09 − 5.53, $p < .001$).[28]

Accordingly, peri-operative stroke and MI are associated with poorer long term survival, emphasising the importance of careful patient selection and optimisation of pre-operative BMT. ESC/European Society of Anaesthesiology guidelines currently do not recommend routine pre- and post-operative troponin measurement in patients undergoing CEA or CAS.[367] However, patients with post-operative MI or stroke should be evaluated carefully before discharge. Cardiology review is necessary after a documented MI or where troponin levels have been requested (on clinical grounds) and found to be elevated, as intensification of BMT before discharge (defined as compliance with ESC recommendations for the management of chronic coronary syndromes[368]) prevents major recurrent cardiac events. Patients with troponin elevation and no post-operative intensification of BMT are statistically significantly more likely to suffer major cardiac events at 12 months *versus* patients receiving intensified BMT (HR 2.8; 95% CI 1.05 − 24.2, $p = .040$).[369]

4.5. Timing of carotid interventions after onset of symptoms

4.5.1. Risk of recurrent stroke over time. CEA is sometimes delayed in SCS patients because it was believed that this may reduce procedural risks,[370] although deferral is advised in patients with disabling stroke (section 4.7). However, there is good evidence that CEA confers maximum benefit if performed within 14 days of symptom onset.[357–359] There is also evidence that the risk of early, recurrent stroke after TIA may be higher than previously thought. Natural history studies suggest the incidence of recurrent stroke after a TIA range from 5% to 8% at 48 hours, 4% to 17% at 72 hours, 8% to 22% at seven days, and 11% to 25% at 14 days (Table 23). Recurrent stroke rates at 14 days in the natural history studies are much higher than was reported at five years in BMT patients in ECST, NASCET, and SVACS, suggesting that many SCS patients who were destined to suffer an early recurrent stroke were never randomised within the RCTs (which tended to recruit patients somewhat later).

However, early recurrent stroke in a CSTC meta-analysis of four RCTs (4 754 SCS patients randomised to and then

Table 23. Risk of stroke in the early time-period after transient ischaemic attack (TIA) onset in patients with 50–99% symptomatic carotid stenosis

Study	Patients − *n*	Stroke risk after TIA − %				
		48 h	72 h	7 d	14 d	5 y
ECST+NASCET+VA 'BMT' patients*,[358]	1 227					21
Fairhead†,[371]	85				20	
Purroy†,[372]	90			10		
Ois†,[373]	163		17	22	25	
Bonifati†,[374]	36	8				
Johansson†,[375]	230	5		8	11	
Mono†,[376]	94		4			
Merwick†,[377]	387			8		
Marnane†,[378]	44	5	9	16		

NASCET = North American Symptomatic Carotid Endarterectomy Trial; VA = Symptomatic Veterans Affairs Carotid Study; ECST = European Carotid Surgery Trial; BMT = best medical therapy; SCS = symptomatic carotid stenosis.

* Timing relates to time from randomisation.

† Timing relates to time from TIA onset.

awaiting CEA/CAS) were compared with early recurrent stroke in three older RCTs which randomised patients to CEA or BMT.[16] Recurrent stroke in the more recent RCTs was only 2% at 120 days, which is much lower than in the older RCTs (Table 19) and in observational studies (Table 23). CSTC observed that while improvements in BMT, risk factor control, and lifestyle may have contributed to reduced early stroke risks in the modern era, RCTs may include patient populations with lower risks of stroke compared with observational cohorts. Accordingly, CSTC concluded that it remained advisable to adhere to recommendations supporting early revascularisation in SCS patients.[16] Other potential reasons for the apparent decline in early stroke after TIA/stroke onset in more recent RCTs include the absence of data on consecutive cases (all of the RCTs in Fisch's meta-analysis included patients already scheduled for CEA or CAS[16]) and early neurological deterioration after the index TIA being missed and, therefore, not reported.[379] Natural history studies suggest that rapid institution of BMT after TIA/minor stroke reduces early recurrent stroke, suggesting that emergency carotid interventions are probably unnecessary unless the patient reports crescendo TIAs or stroke in evolution (section 4.7).[144,308,328]

4.5.2. Timing of carotid endarterectomy in national registries and meta-analyses. Five national registries have published median delays from symptom onset to CEA. In the Netherlands, Norway, and UK, median delay is 11 days,[140,142,380] compared with nine days in Germany[381] and eight in Sweden.[382] Three European countries have published more detailed registry data regarding delays between symptom onset and undergoing CEA (Table 24).

Table 25 details 30 day rates of death/stroke, stratified for delays from symptom onset to CEA. The 2012 Swedvasc registry attracted the most controversy because when CEA was performed within 48 hours of symptom onset, the 30 day death/stroke rate was 11.5%.[382] This increase in risk was not, however, observed in the much larger German or UK registries.[380,381] After 48 hours has elapsed, all three registries showed that CEA could be performed with low procedural risks.[380–382]

A 2021 meta-analysis (three RCTs, 68 observational cohorts [$n = 232\,952$]) reported that when CEA was performed within two days of symptom onset (*vs.* days 3 – 14), there were higher rates of 30 day stroke (OR 1.57; 95% CI 1.3 – 1.9) and death (OR 5.19; 95% CI 4.1 – 6.6).[52] When CEA was performed within seven days (*vs.* days 8–14), there was a non-significant trend towards increased 30 day stroke (OR 1.2; 95% CI 0.96 – 1.50) and death/stroke (OR 1.22; 95% CI 0.99 – 1.45), but no difference in MI (OR 1.33; 95% CI 0.11 – 15.43) or mortality (OR 1.29; 95% CI (0.88 – 1.88).

4.5.3. Timing of carotid stenting in national registries and meta-analyses. Two European countries have published registry data on delays between symptom onset and CAS. Table 26 details the proportion undergoing CAS within each time period, while Table 27 details 30 day death/stroke after CAS, stratified for delays from symptom onset to CAS.

In the German Statutory Quality Assurance database, performing CAS three to seven days after symptom onset was not associated with reduced in hospital death/stroke *versus* when CAS was performed within two days. Performing CAS 8 – 14 days after symptom onset was associated with lower in hospital death/stroke *versus* patients undergoing CAS within two days of symptom onset (OR 0.36; 0.20 – 0.67, $p = .001$).[156] In a 2021 meta-analysis (three RCTs, 68 observational cohorts [$n = 232\,952$]), two studies evaluated outcomes when CAS was performed within two days *versus* 3 – 14 days of the index symptom.[52] Compared with CAS interventions at 3 – 14 days, CAS

Table 24. Proportion of patients undergoing carotid endarterectomy (CEA) in national audits within 0 – 2, 3 – 7, 8 – 14, and > 15 days after onset of symptoms caused by symptomatic carotid stenosis (SCS)

National audit	Patients – *n*	Patients undergoing CEA after SCS			
		0–2 d	3–7 d	8–14 d	≥15 d
Sweden[382]	2 596	148 (6)	804 (31)	677 (26)	967 (37)
UK[380]	23 235	780 (3)	5 126 (22)	6 292 (27)	11 037 (48)
Germany[381]	56 279	5 198 (9)	19 117 (34)	16 205 (29)	15 759 (28)

Data are presented as *n* (%) unless stated otherwise.

Table 25. Thirty day death or stroke after carotid endarterectomy (CEA), stratified for delay from onset of symptoms caused by symptomatic carotid stenosis (SCS)

National audit	Patients – *n*	30 d death or stroke after CEA for SCS			
		0–2 d	3–7 d	8–14 d	≥15 d
Sweden[382]	2 596	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[380]	23 235	29 / 780 (3.7) [2.5–5.3]	128 / 5 126 (2.5) [2.1–3.0]	132 / 6 292 (2.1) [1.8–2.5]	254 / 11 037 (2.3) [2.0–2.6]
Germany[381]	56 279	157 / 5 198 (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]

Data are presented as *n* (%) [95% confidence interval].

Table 26. Proportion of patients undergoing carotid artery stenting (CAS) in national audits within 0 − 2, 3 − 7, 8 − 14, and ≥ 15 days after onset of symptoms caused by symptomatic carotid stenosis (SCS)

National audit	Patients − *n*	Patients undergoing CAS after SCS			
		0–2 d	3–7 d	8–14 d	≥15 d
Sweden[383]	323	13 (4.0)	85 (26.3)	80 (24.8)	145 (44.9)
Germany[156]	4 717	550 (11.6)	1 579 (33.4)	1 244 (26.3)	1 344 (28.4)

Data are presented as *n* (%).

Table 27. Procedural death or stroke rates after carotid artery stenting (CAS) for symptomatic carotid stenosis (SCS), stratified for delay from symptom onset to CAS in national audits of practice

National audit	Procedural death or stroke after CAS for SCS			
	0–2 d	3–7 d	8–14 d	≥15 d
Sweden*,[383]	0 / 13 (0.0)	4 / 85 (4.7)	5 / 80 (6.3)	6 / 145 (4.1)
Germany†,[156]	33 / 550 (6.0)	70 / 1 579 (4.4)	30 / 1 244 (2.4)	40 / 1 344 (3.0)

Data are presented as *n* (%).
* Thirty day death/stroke.
† In hospital death/stroke.

within two days was not associated with increases in 30 day stroke (OR 1.36; 95% CI 0.84 − 2.04), but there was a substantially higher risk of death (OR 2.77; 95% CI 1.39 − 5.52). Two studies compared outcomes when CAS was performed within seven days *versus* 8−14 days.[52] CAS was associated with higher rates of 30 day stroke (OR 1.8; 95% CI 1.14 − 2.84) if performed within seven days (*vs.* 8−14 days) after the index event, with no difference in mortality rate (OR 1.70; 95% CI 0.78 − 3.73).[52]

4.5.4. Comparison of carotid endarterectomy with carotid artery stenting in the early time period after symptom onset. In a CSTC meta-analysis involving 4 138 SCS patients randomised in CREST, ICSS, EVA-3S, and SPACE, only 11% underwent CEA or CAS within 48 hours of symptom onset.[170] Among patients treated within seven days of symptom onset, patients undergoing TFCAS were more likely to suffer an adverse 30 day outcome, compared with patients undergoing CEA (Table 28).

CSTC concluded that for patients undergoing carotid interventions within seven days of symptom onset, CEA was safer than TFCAS.[170] In another CSTC meta-analysis, patients undergoing TFCAS within 8 − 14 days of their most recent symptom also had statistically significantly higher rates of 30 day death/stroke, at 8.1% compared with 3.4% after CEA (OR 2.42; 95% CI 1.0 − 5.7, $p = .040$).[384]

4.5.5. Transcarotid artery revascularisation outcomes stratified for timing after symptom onset. There has been considerable interest in whether TCAR confers lower procedural risks when performed < 14 days after symptom onset, *versus* TFCAS. Only one registry has reported procedural risks after TCAR, stratified for timing after symptom onset.[118] In an SVS-VQI audit involving 2 608 SCS patients

Table 28. Thirty day outcomes following carotid artery stenting (CAS) *versus* carotid endarterectomy (CEA), stratified for timing after symptom onset in a meta-analysis of symptomatic patients randomised in Carotid Revascularization versus Stenting Trial (CREST), The International Carotid Stenting Study (ICSS), Endarterectomy versus Stenting in patients with Symptomatic Severe carotid Stenosis (EVA-3S), and Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE)*

	30 day outcomes		OR (95% CI)	*p* value
	CEA	CAS		
Any stroke or death				
≤7 days	3 / 226 (1.3)	24 / 287 (8.4)	6.51 (2.00–21.21)	.002
>7 days	65 / 1 819 (3.6)	129 / 1 806 (7.1)	2.00 (1.49–2.67)	<.001
Any stroke				
≤7 days	3 / 226 (1.3)	23 / 287 (8.0)	6.27 (1.92–20.44)	.002
>7days	62 / 1 819 (3.4)	122 / 1 806 (6.8)	1.98 (1.47–2.67)	<.001
Fatal or disabling stroke				
≤7 days	1 / 226 (0.4)	9 / 287 (3.1)	8.29 (1.07–64.28)	.04
>7 days	26 / 1 819 (1.4)	46 / 1 806 (2.5)	1.77 (1.10–2.85)	.02

Data are presented as *n* (%). CEA = carotid endarterectomy; CAS = carotid artery stenting; OR = odds ratio; CI = confidence interval.
* Based on data from Rantner *et al.*[170]

treated by TCAR, 5.5% were performed within two days of the most recent symptom, 35% at 3 — 14 days, while 59% were performed after > 14 days had elapsed. In hospital outcomes are detailed in Table 29. These suggest that in hospital stroke and death/stroke were higher when TCAR was performed within two days of the most recent symptom, while TCAR performed 3 — 14 days after the most recent symptom incurred procedural risks similar to when performed after > 15 days had elapsed. The only statistically significant difference was that patients undergoing TCAR within 14 days were more likely to be discharged to a non-home destination (22% *vs.* 6.6%; OR 4.2, 95% CI 3.2 — 5.5, $p < .001$).[118] These findings are, however, similar to in hospital outcomes reported after TFCAS in the German Statutory Quality Assurance database (Table 27).[156]

More prospective audits are required to corroborate the SVS-VQI data which are otherwise encouraging. However, 1 169 SCS patients (31%) undergoing TCAR in the SVS-VQI audit did not meet the inclusion criteria, including an unknown proportion with no timing data available. In addition, in hospital endpoints underestimate 30 day procedural risks by 20—25%,[385,386] making direct comparison with 30 day outcomes after TFCAS or CEA less robust.

4.6. Should the 6% risk threshold for carotid interventions be reduced?

Guidelines since 1998 advise that the 30 day risk of stroke/death when performing CEA in patients reporting ipsilateral carotid territory symptoms of less than six months should be 6% or less,[283] and that this should be independently audited (section 2.6). Recent German-Austrian and ESO guidelines advise that in hospital death/stroke following CEA/CAS in SCS patients should be 4% or less.[2,3] However, this does not mean that the 30 day 6% threshold in SCS patients is being reduced. As with ACS patients (section 3.9), it is more an attempt to define acceptable risk thresholds while the patient is still in hospital (i.e., easier to audit). RCTs suggest that 19—24% of peri-operative strokes and deaths occur after the eighth post-operative day,[386] which effectively means the 6% 30 day death/stroke threshold has still been retained by the two guidelines.

One important change in practice over the last 15 years has been awareness that the highest risk period for recurrent stroke is the first 7 — 14 days after symptom onset (section 4.5.1). Previously, provided CEA was performed within six months of symptom onset, a 6% procedural risk was considered appropriate.[283] However, there have been concerns that intervening early in SCS patients might increase peri-procedural risks,[370] which could potentially negate any benefits regarding prevention of early recurrent stroke. However, a re-analysis of data from NASCET, ECST, and SVACS revealed that even if a surgeon performed CEA within 14 days with a 10% peri-operative risk, more strokes would probably be prevented at five years, compared with delaying CEA for four weeks and then by operating with a theoretical risk of 0%.[387] Many countries have reconfigured their services to deliver CEA as soon as possible after symptom onset (section 4.5.2). The GWC recognised the importance of promoting early interventions and that most CEAs in Europe are now performed within 7 — 14 days of symptom onset. The GWC concluded that the 30 day risk of stroke/death after CEA or CAS in recently symptomatic patients should be retained at 6% or less, mainly to minimise risk aversion, where surgeons or interventionists might delay interventions to achieve lower complication rates. Such delays could, in turn, lead to increased rates of early recurrent stroke in SCS patients.

Recommendation 40			Unchanged
For patients reporting carotid territory symptoms within the preceding six months and who have a 70—99% carotid stenosis, carotid endarterectomy is recommended provided the 30 day risk of death/stroke rate is <6%.			
Class	**Level**	**References**	**ToE**
I	A	Rothwell *et al.* (2003)[357], Rothwell *et al.* (2004)[358], Rothwell *et al.* (2004)[359]	

Recommendation 41			Unchanged
For patients reporting carotid territory symptoms within the preceding six months and who have a 50—69% carotid stenosis, carotid endarterectomy should be considered provided the documented 30 day risk of death/stroke rate is <6%.			
Class	**Level**	**References**	**ToE**
IIa	A	Rothwell *et al.* (2003)[357], Rothwell *et al.* (2004)[358], Rothwell *et al.* (2004)[359]	

Table 29. In hospital rates of stroke and death/stroke in 2 608 patients undergoing transcarotid artery revascularisation (TCAR), stratified for timing after most recent neurological event caused by symptomatic carotid stenosis*

	<2 days (n = 144)	3—14 days (n = 928)	>14 days (n = 1 536)
In hospital stroke — %	5.6	2.5	2.0
OR (95% CI)	2.8 (1.3—6.2)	1.3 (1.3—6.4)	Reference
p value	.01	.40	
In hospital stroke or death — %	6.5	2.9	2.3†
OR (95% CI)	2.9 (1.3—6.4)	1.2 (0.7—2.1)	Reference
p value	.01	.48	

OR = odds ratio; CI = confidence interval; TCAR = transcarotid artery revascularisation.
* Based on data from Cui *et al.*[118]
† OR (95% CI) calculated by comparing outcomes against those performed >14 days.

Recommendation 42			Unchanged
For patients aged ≥70 years who have experienced a carotid territory transient ischaemic attack or ischaemic stroke within the preceding 6 months in association with a 50–99% carotid stenosis, it is recommended that they should be treated by carotid endarterectomy, rather than carotid stenting.			
Class	**Level**	**References**	**ToE**
I	A	Howard *et al.* (2016)[169]	

Recommendation 43			Unchanged
For patients aged <70 years who have experienced a carotid territory transient ischaemic attack or ischaemic stroke within the preceding 6 months in association with a 50–99% carotid stenosis, carotid artery stenting may be considered an alternative to endarterectomy, provided the documented 30 day risk of death/stroke is <6%.			
Class	**Level**	**References**	**ToE**
IIb	A	Howard *et al.* (2016)[169]	

Recommendation 44			Unchanged
For symptomatic patients with a 50–99% stenosis in whom a carotid intervention is considered appropriate, it is recommended that this be performed as soon as possible, preferably within 14 days of symptom onset.			
Class	**Level**	**References**	**ToE**
I	A	Rothwell *et al.* (2004)[358], Rothwell *et al.* (2004)[359]	

Recommendation 45			Unchanged
For patients who are undergoing revascularisation within the first 14 days after onset of symptoms, it is recommended that they should undergo carotid endarterectomy, rather than carotid stenting.			
Class	**Level**	**References**	**ToE**
I	A	Rantner *et al.* (2017)[170], Rantner *et al.* (2013)[384]	

4.7. Intervening in neurologically unstable patients

Patients with a disabling stroke (mRS ≥ 3), or where the area of infarction exceeds one third of the MCA territory and those with altered consciousness should not undergo CEA/CAS until neurological improvement has occurred, because of higher risks of haemorrhagic transformation of an infarct or ICH.[388,389] Larger areas of acute cerebral infarction (pre-operatively) are recognised as being an important predictor of post-operative neurological complications. In a series of 646 recently symptomatic patients, 101 (15.6%) had a large area of recent infarction on pre-operative CT/MRI (defined as a maximum axial infarct size > 4 cm^2). Post-operative non-ischaemic cerebral complications (hyperperfusion syndrome, ICH) were independently associated with large infarcts (adjusted OR 6.839; 95% CI 1.699 – 27.534, $p = .001$).[390] Multivariable binary logistic regression showed that infarct size was an independent predictor of post-operative ICH and encephalopathy (infarct size per cm^2, adjusted OR 1.169; 95% CI 1.067 – 1.128, $p = .001$).[390] A similar finding was reported by Pini *et al.*[391] In a series of 489 recently symptomatic patients undergoing CEA, an acute cerebral ischaemic lesion volume ≥ 4 000 mm^3 on pre-operative CT was predictive of post-operative stroke (OR 4.6; 95% CI 1.1 – 19.1, $p = .03$), with a sensitivity of 75% and a specificity of 63%.[391]

In a meta-analysis of 13 observational studies ($n = 208$), 30 day stroke/death after CEA was 20% (95% CI 12.0 – 28.4) in patients with stroke in evolution and 11% (95% CI 6.1 – 16.7) in patients with crescendo TIAs.[392] However, in selected patients with smaller infarcts, emergency CEA can be performed with 2–8% rates of death/stroke for stroke in evolution and 0–2% for crescendo TIAs. These results compare favourably with the otherwise poor prognosis of these conditions. ESVS recommendations in patients with crescendo TIAs or stroke in evolution are the same as the 2021 SVS and German-Austrian guidelines.[3,4] There are no RCT data to advise whether i.v. heparin is superior to APRx in preventing early recurrent stroke in patients with stroke in evolution or crescendo TIAs. In a series of 144 patients with non-disabling stroke, a 50–99% stenosis, and TCD evidence of MES, spontaneous MES rates were reduced in patients on APRx, but not heparin.[395] In two RCTs comparing LMWH with aspirin monotherapy in acute stroke patients where APRx or antithrombotic therapy were commenced < 48 hours after stroke onset, there was no evidence that LMWH conferred additional benefits over aspirin.[396,397] In the absence of quality evidence, it would seem reasonable to consider heparin (plus aspirin) or combination APRx in patients with recurrent TIAs or crescendo TIAs prior to urgent CEA.

Recommendation 46			Unchanged
For patients with 50–99% stenoses who experience a disabling stroke (modified Rankin score ≥3), or whose area of infarction exceeds one third of the ipsilateral middle cerebral artery territory, or who have altered consciousness/drowsiness, it is recommended to defer carotid interventions to minimise the risks of post-operative parenchymal haemorrhage.			
Class	**Level**	**References**	**ToE**
I	C	Rantner *et al.* (2006)[388], Wolfle *et al.* (2004)[389]	

Recommendation 47			Unchanged
For patients with 50–99% stenoses who present with stroke in evolution or crescendo transient ischaemic attacks, urgent carotid endarterectomy should be considered, preferably within 24 hours.			
Class	**Level**	**References**	**ToE**
IIa	C	Munster *et al.* (2015)[80], Rerkasem *et al.* (2009)[392], Capoccia *et al.* (2012)[393], Gajin *et al.* (2014)[394]	

4.8. Timing of carotid endarterectomy and carotid artery stenting after intravenous thrombolytic therapy

In the absence of advanced imaging techniques, i.v. thrombolytic therapy (TT) is recommended in selected patients with acute ischaemic stroke, provided it is started within 4.5 hours of stroke onset in patients awake at symptom onset.[398,399] About 10—20% of TT patients will have an underlying 50—99% ICA stenosis and may be candidates for CEA or CAS. There are concerns, however, that performing CEA or CAS too soon after TT may increase the likelihood of haemorrhagic transformation of an infarct or neck haematoma formation, with consequent harm to the patient. To balance the risks of early recurrent stroke prevention with the higher risks of ICH, general criteria for selecting patients for early CEA after TT include (1) rapid neurological recovery (mRS 0 − 2); (2) infarction area less than one third the MCA territory; (3) recanalisation of a previously occluded MCA mainstem on repeat CTA; (4) ipsilateral 50—99% stenosis; and (5) no evidence of parenchymal haemorrhage or significant brain oedema.[400,401] Contraindications include (1) severe persistent neurological deficit (modified Rankin score $\geq$ 3); (2) anticipated high surgical risk; (3) parenchymal haemorrhage on CT; and (4) previous radical neck dissection or radiotherapy.[402] A systematic review identified 25 observational studies (n = 147 810 patients), including 2 557 who underwent CEA (n = 2 076) or CAS (n = 481) after TT. Table 30 details peri-operative outcomes in pooled series.[66]

Table 31 details meta-analysed case controlled data comparing peri-operative outcomes in CEA and CAS patients who did (did not) receive TT. TT was associated with higher rates of ICH and neck haematoma in patients undergoing CEA (*vs.* no TT), while TT was associated with higher stroke/death and ICH in patients undergoing CAS (*vs.* no TT).[66]

Thrombolysis is associated with complex haematological changes that may make CEA and CAS patients prone to ICH or neck haematoma formation. The half life of i.v. recombinant tissue plasminogen activator (rtPA) is five minutes (Tenecteplase 24 minutes), but fibrinogen and plasminogen levels only revert to $>$ 80% of pre-TT levels $\geq$ 24 hours after rtPA treatment.[403] Recombinant tPA increases circulating fibrin degradation products and levels $>$ 200 mg/L may be associated with a fivefold increase in parenchymal haemorrhage,[404] as well as increased permeability across the blood brain barrier (which increases parenchymal haemorrhage).[405] Vulnerability to haemorrhagic complications after TT will also be compounded by peri-operative APRx and heparin therapy. Guidelines advise that heparin and APRx should be withheld for 24 hours after TT completion and only restarted once a 24 hour CT scan shows no haemorrhagic transformation, after which appropriate APRx can be (re-)commenced before CEA or CAS.[399] The optimal timing of carotid interventions after TT remains controversial. A US National Inpatient Sample reported higher rates of post-operative stroke and ICH if CEA was performed early after TT, which then declined to levels comparable with those in non-TT patients by seven days after TT completion.[157] By contrast, the UK National Vascular Registry reported no association between CEA timing after TT and procedural risks.[136] Meta-regression analyses of published data demonstrated an inverse relationship between the time interval between TT and CEA and the risk of peri-operative stroke/death (p = .020); that is, performing CEA early after TT was associated with higher risks of peri-procedural stroke/death.[66]

Using meta-regression analysis (Figure 7), peri-operative stroke/death was 13% when CEA was performed three days after TT completion and 10.6% after four days. The risk was predicted to reduce to within the currently accepted 6% threshold after six days had elapsed,[66] suggesting that CEA should probably be deferred until six days after TT. Unfortunately, there were insufficient case control studies to permit similar analyses in CAS patients, but given the data in Tables 30 and 31, a similar deferral would seem reasonable.[66]

A short deferral permits repeat DUS/CTA imaging to ensure criteria for expedited CEA or CAS have been met (see earlier), and for heparin and APRx to be withheld for 24 hours, before restarting prior to any intervention. However, one potentially adverse consequence of deferring CEA (even for a short time) is recurrent thromboembolic stroke, which is rarely reported in the literature. In a Finnish study (n = 128), the risk of recurrent stroke between TT and undergoing CEA was 5.5% when performed a median of four days after TT (range 0 − 8).[406] This is lower than the predicted 10.6% risk associated with performing CEA four days after TT in the meta-regression analysis.[66] Recurrent stroke before deferred CEA in TT patients should be the subject of future audit, which should also include whether the presence/absence of acute infarction influences rates of ICH, to better stratify advice regarding deferral in individual patients as some vascular surgeons and physicians may still opt to proceed to CEA in selected patients less than six days after TT. It is also essential to actively treat post-CEA/CAS hypertension (section 7.1.3.3) as poorly controlled BP is a risk factor for ICH and neck haematoma formation. To date, no other guideline has made any recommendation regarding the optimal timing of carotid interventions after thrombolysis.[1—3]

Table 30. Peri-operative outcomes in pooled series undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS) after intravenous thrombolysis therapy for patients with acute ischaemic stroke*

Outcome	CEA (n = 2 076)	CAS (n = 481)
Stroke or death (95% CI) − %	5.2 (3.3–7.5)	14.9 (11.9–18.2)
ICH (95% CI) − %	3.4 (1.7–5.6)	5.5 (3.7–7.7)
Haemorrhage (95% CI) − %	Neck: 3.8 (2.9–4.9)	Local: 4.9 (0.09–16.2)

CI = confidence interval; ICH = intracranial haemorrhage.
* Data derived from Kakkos.[66]

Table 31. Peri-operative outcomes for case control studies in carotid endarterectomy (CEA) and carotid artery stenting (CAS) patients who did or did not have intravenous thrombolysis therapy for acute ischaemic stroke

Outcome	CEA			CAS		
	TT − %	No TT − %	OR (95% CI)	TT − %	No TT − %	OR (95% CI)
Stroke	4.1	1.2	2.74 (0.62–12.07)			
Death	2.1	0.7	2.84 (0.85–17.3)			
Stroke / death	4.3	1.5	2.34 (0.74–7.47)	5.2	1.5	8.49 (2.12–33.95)
Intracranial haemorrhage	2.2	0.1	7.82 (4.07–15.2)	5.4	0.7	7.48 (4.69–11.92)
Neck haematoma	3.6	2.3	1.65 (1.17–2.33)			

Data derived from Kakkos et al.[66] OR = odds ratio; CI = confidence interval.

Recommendation 48 — Unchanged

For symptomatic patients undergoing thrombolysis, it is recommended that intravenous heparin and antiplatelet therapy be withheld for 24 hours after completion of thrombolysis, but antiplatelet therapy should then be commenced before any carotid intervention is undertaken.

Class	Level	References	ToE
I	C	Berge *et al.* (2021)[399]	

Recommendation 49 — New

For patients with acute ischaemic stroke due to a symptomatic 50–99% carotid stenosis who have received intravenous thrombolysis, delaying carotid endarterectomy or carotid stenting by six days following completion of thrombolysis should be considered.

Class	Level	References	ToE
IIa	B	Kakkos *et al.* (2021)[66], Vellimana *et al.* (2018)[157]	

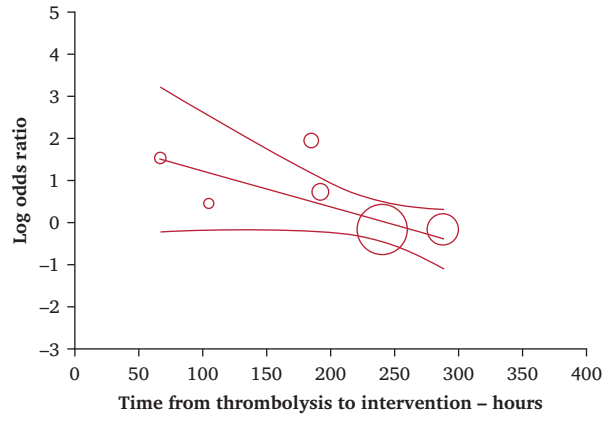


Figure 7. Regression of log odds ratio on time (hours) for peri-operative death/stroke in patients with stroke undergoing carotid endarterectomy after thrombolysis or without thrombolysis. Reproduced with permission from: Kakkos S, Vega de Ceniga, Naylor AR. A systematic review and meta-analysis of periprocedural outcomes in patients undergoing carotid interventions following thrombolysis. *Eur J Vasc Endovasc Surg* 2021;**62**:340–9.

Recommendation 50 — Unchanged

For patients undergoing early carotid interventions after thrombolysis, active treatment of post-interventional hypertension is recommended to reduce the risks of parenchymal haemorrhage.

Class	Level	References	ToE
I	C	Naylor (2015)[402]	

4.9. Carotid endarterectomy and carotid artery stenting after mechanical thrombectomy

Based on a meta-analysis of five RCTs (n = 1 287), which showed that MT conferred a twofold improvement in functional outcome,[407] guidelines recommend emergency MT in selected patients with acute ischaemic stroke.[398] About 10–20% of MT patients will have embolic MCA occlusion with tandem ICA thrombosis or severe stenosis.[61] Treatment options include (i) synchronous MT + CAS with APRx; (ii) synchronous MT + CAS with no APRx; (iii) synchronous MT + angioplasty (no stent, no APRx); and (iv) MT +/- deferred CEA/CAS. The TITAN registry evaluated all four treatment strategies in 482 patients.[163] After adjusting for confounding variables, CAS + MT + APRx was independently associated with higher rates of recanalisation, although rates of symptomatic ICH and mortality were similar across all four strategies.[164,408] The German Stroke Registry recently reported outcomes in 874 MT patients with tandem carotid stenosis or thrombosis, including 607 (69.5%) who underwent synchronous treatment of the extracranial carotid lesion. Synchronous MT + CAS was associated with a higher probability of successful reperfusion *versus* MT alone (OR 40.63; 95% CI 30.3 − 70.06), as well as statistically significantly better clinical outcomes (39.5% *vs.* 29.3%; $p < .001$) and lower mortality rates (17.1% *vs.* 27.1%; $p < .001$). MT + CAS was associated with similar complication rates to those in patients undergoing MT alone (23.9% *vs.* 18.1%, p = ns).[124]

There is, however, no consensus and a survey of clinicians treating acute stroke patients reported that 59% would perform MT + CAS, while 41% would not.[409] While awaiting data from the TITAN RCT (ClinicalTrials.gov Identifier: NCT03978988), imaging features that might support performing synchronous MT + CAS include poor antegrade ICA

flow after MT; poor collateralisation via the CoW after MT and patients with small volume infarcts and lower bleeding risks. Imaging features suggesting that emergency CAS is probably unnecessary (could be deferred) include poor intracranial revascularisation after MT, good filling of ipsilateral intracranial vessels via the VAs and/or contralateral ICA after MT, large volume infarcts and patients at increased bleeding risk.

If synchronous CAS + MT is being considered, should the intervention be intracranial first or extracranial first?[410] Advantages of extracranial first include (i) early flow restoration to the CoW (simply crossing an occluded or stenosed ICA with a large bore catheter can permit sufficient inflow to avoid CAS[411]); (ii) optimisation of endogenous fibrinolysis by increased intracranial flow; (iii) elimination of a proximal embolic source; (iv) avoiding blind navigation in occluded vessels; and (v) reduced risk of re-occluding intracranial vessels.[412] Disadvantages include embolisation during CAS, worsening of any neurological deficit and delay in recanalising intracranial occlusions.[410,411] A meta-analysis found no difference in either approach regarding mRS scores, procedural complications, symptomatic ICH, revascularisation rates, or procedure times,[107] although the German Stroke Registry reported statistically significantly shorter flow restoration times with an intracranial first strategy (53 minutes *vs.* 72 minutes, $p < .001$).[124] Few registries have reported outcomes following staged CEA after MT. In an audit of 63 consecutive cases from Sweden and Finland, 30 day death/stroke was 0.0%. Carotid endarterectomy was performed a median of seven days after presentation and 75% of patients underwent CEA in < 14 days.[138]

Similarly, there is no consensus regarding optimal APRx and antithrombotic therapy during MT + CAS. CAS mandates peri-procedural APRx (usually combination), which increases the risk of ICH, especially if the patient has also been thrombolysed (common). Conversely, CAS without APRx increases in stent thrombosis, while CA (without stenting) risks secondary embolisation of atherothrombotic debris. Combination APRx usually starts after a post-operative CT scan excludes parenchymal haemorrhage. Combining glycoprotein IIb/IIIa inhibitors and combination APRx provides better stent patency, but with increased ICH risks.[461,412] A Delphi consensus reported a preference for aspirin monotherapy (or IIb/IIIa receptor inhibitor) during CAS, with combination aspirin plus a P2Y12 inhibitor started post-operatively,[413] although this has not been tested in RCTs. Another study showed that heparin doses > 3 000 IU were only associated with higher bleeding risks when the ASPECTS score was ≤ 7 (indicating a large ischaemic core) and with more than one passage of the MT catheter.[414]

Although knowledge has increased since 2017, there is no consensus regarding the optimal strategy for treating acute stroke patients undergoing MT who have tandem extracranial stenoses, and few contemporary guidelines have published any recommendations. The 2021 German-Austrian guidelines, however, advise that endovascular treatment with emergency stenting and thrombectomy is indicated.[3]

Recommendation 51			New
For a patient with acute ischaemic stroke undergoing intracranial mechanical thrombectomy with a tandem 50–99% carotid stenosis and a small area of ipsilateral infarction, synchronous carotid stenting may be considered in the presence of poor antegrade internal carotid artery flow or poor collateralisation via the circle of Willis after mechanical thrombectomy.			
Class	**Level**	**References**	
IIb	**C**	Consensus	

4.10. Patients with < 50% stenoses who may benefit from interventions

In a CETC meta-analysis, CEA conferred no benefit over BMT in patients with < 50% stenoses (Table 19).[357] However, the risk of recurrent ipsilateral stroke in patients with 20–49% stenoses at baseline (and treated medically) is about 7.4% at three years.[415] In previously symptomatic patients with < 50% stenosis who experience recurrent TIA/stroke (despite BMT), it is essential to exclude other causes of recurrent symptoms (e.g., paroxysmal AF, antiphospholipid syndrome) that would warrant different secondary preventive therapy. If symptoms recur despite optimisation of BMT, it may be reasonable to consider CEA,[416,417] but only following detailed neurovascular work up and MDT review.

Recommendation 52			Unchanged
For patients presenting with carotid territory symptoms in the preceding six months and who have a <50% stenosis, a carotid intervention is not recommended.			
Class	**Level**	**References**	**ToE**
III	**A**	Rothwell *et al.* (2003)[357]	

Recommendation 53			Unchanged
For selected patients experiencing recurrent transient ischaemic attacks or minor stroke, despite best medical therapy and who have a <50% stenosis, carotid endarterectomy or carotid artery stenting may be considered but only following neurovascular work up and multidisciplinary team review.			
Class	**Level**	**References**	**ToE**
IIb	**C**	Karlsson *et al.* (2016)[415], Yoshida *et al.* (2019)[416], Kashiwazaki *et al.* (2019)[417]	

4.11. 'High risk for surgery' symptomatic patients

Certain clinical or anatomical features may be associated with poorer outcomes after CEA and are described as as 'high risk for CEA' criteria. However, being high risk for CEA does not mean that superior outcomes are achieved by CAS as, sometimes, procedural risks may be higher. The concept of being 'high risk for CEA' is also misinterpreted as being high risk of stroke, which is rarely the case. As will be seen, many studies regarding 'high risk for CEA' criteria are conflicting.

4.11.1. SAPPHIRE defined high risk criteria. In SAPPHIRE, 'high risk for CEA' criteria included carotid territory symptoms within 180 days and a 50—99% stenosis plus more than one of: major cardiac disease (CHF, abnormal stress test, awaiting cardiac surgery); severe COPD; contralateral occlusion; contralateral RLN palsy; previous radical neck surgery, cervical irradiation; re-stenosis after CEA; and age > 80 years.[282] In an SVS Registry, SAPPHIRE 'high risk for CEA' patients had similar rates of death/stroke/MI after CAS and CEA (9.1% *vs.* 7.3%; $p = .11$). No anatomical criteria were associated with poorer outcomes after CEA and there was only a trend towards lower rates of major adverse events after CAS in patients with re-stenosis after CEA (3.5% *vs.* 7.1%; $p = .10$).[418] VSGNE reported independent risk factors for increased stroke/MI/death one year after CEA as increasing age, pre-admission residence in a nursing home, CHF, DM, COPD, previous stroke/TIA, and contralateral occlusion. Three SAPPHIRE criteria (abnormal stress test, re-stenosis, and cervical irradiation) were not associated with increased morbidity/mortality.[419] Another retrospective study compared 424 'high risk for CEA' patients (173 with at least one physiological high risk criterion; 293 with at least one anatomical risk criterion) with 424 propensity matched patients with no high risk criteria. There were no notable differences in 30 day death/stroke/MI after CE.[420]

4.11.2. Increasing age. CSTC[169] reported that age ≥ 70 years was associated with higher peri-operative stroke rates after CAS, but not CEA (Table 22, section 4.4.1.1), possibly because of increased atherosclerotic burden, aortic arch calcification, changes in vascular anatomy, and increasing plaque vulnerability.[421]

4.11.3. Cervical irradiation. Cervical irradiation is cited as conferring poorer outcomes after CEA. However, in a systematic review of 27 observational studies (533 CAS or CEA patients), the risk of "any cerebrovascular event" was 3.9% with CAS *versus* 3.5% after CEA ($p = .77$).[422] CNI after CEA was 9.2% *versus* 0% after CAS, although few were permanent. After the peri-operative period, recurrent TIA/stroke was more common after CAS than after CEA (4.9/100 *vs.* 2.8/100 person years; $p = .014$).[422]

4.11.4. Re-stenosis after carotid endarterectomy. In an SVS-VQI registry involving 2 863 patients (33% ACS) undergoing redo CEA ($n = 1\,047$) or CAS ($n = 1\,816$) for re-stenosis after CEA, redo-CEA was associated with a higher mortality rate at 30 days (OR 2.83; 95% CI 1.13 — 7.14, $p = .027$) and at one year (HR 2.17; 95% CI 1.03 — 4.58, $p = .042$). However, there were no differences in peri-operative stroke (OR 0.54; 95% CI 0.20 — 1.45, $p = .22$) or MI (OR 0.98; 95% CI 0.31 — 3.10, $p = .97$).[15] A 2018 meta-analysis involving 13 observational studies (redo CEA = 1 678; CAS = 2 485) reported no difference in 30 day MI (OR 1.32; 95% CI 0.71 — 2.44), mortality (OR 1.82; 95% CI 0.94 — 3.53), or stroke (OR 1.28; 95% CI 0.82 — 2.00). CNIs were higher after redo CEA (OR 13.61; 95% CI 5.43 — 34.16).[102]

4.11.5. Contralateral carotid occlusion. Contralateral occlusion is another frequently cited 'high risk for CEA' criterion,[282,316] although data are conflicting. A meta-analysis of 43 RCTs or observational studies ($n = 96\,658$) observed that contralateral occlusion was associated with a statistically significant increase in peri-operative stroke/death after CEA (OR 1.8; 95% CI 1.55 — 2.1, $p < .001$) but not after CAS (OR 1.52; 95% CI 0.95 — 2.44).[72] By contrast, an SVS-VQI registry of patients with contralateral occlusion treated by CEA ($n = 3\,278$) or CAS ($n = 1\,048$) found that in ACS patients, 30 day death/stroke and two year ipsilateral stroke rates did not differ statistically significantly between CAS and CEA, but the adjusted risk of any stroke/death over two years was statistically significantly higher after CAS (adjusted HR 1.42; 95% CI 1.08 — 1.86, $p = .011$). In SCS patients, CAS was associated with statistically significantly higher 30 day risks of stroke (OR 2.90; 95% CI 1.06 — 7.94, $p = .038$) and death (OR 6.10; 95% CI 2.20 — 16.92, $p = .001$). The two year risk of stroke after intervening in SCS patients was also statistically significantly higher after CAS *versus* CEA (adjusted HR 1.94; 95% CI 1.18 — 3.19, $p = .009$).[151]

Recommendation 54 — **New**

For recently symptomatic patients with 50—99% stenoses and contralateral carotid occlusion or previous cervical radiation therapy, the choice of carotid endarterectomy or carotid artery stenting should be considered on an individual basis.

Class	Level	References	ToE
IIa	B	Kokkinidis *et al.* (2020)[72], Nejim *et al.* (2017)[151], Fokkema *et al.* (2012)[422]	

Recommendation 55 — **Unchanged**

For recently symptomatic patients with 50—99% stenoses with anatomical features or co-morbidities that are considered by the multidisciplinary team to be higher risk for carotid endarterectomy, carotid stenting should be considered as an alternative to endarterectomy, providing the documented 30 day risk of death/stroke is <6%.

Class	Level	References	ToE
IIa	B	Gurm *et al.* (2008)[223], Yadav *et al.* (2004)[282], Bonati *et al.* (2014)[315], Brott *et al.* (2010)[316]	

4.12. Managing patients with carotid "near occlusion"

The definition of CNO is covered in section 2.5. Of the 262 ECST and NASCET patients with CNO, 16 had total distal vessel collapse, while 246 had partial collapse. A CETC meta-analysis concluded that CEA conferred no notable reduction in stroke at five and eight years (Table 18, section 4.3.1), largely because of low rates of ipsilateral stroke in

BMT patients.[357] CETC data influenced the 2017 ESVS carotid guidelines, which advised against CEA in CNO patients.[165] However (in NASCET), 33/114 CNO patients (29%) randomised to BMT subsequently underwent CEA but were analysed as BMT on intention to treat analyses. This high rate of crossover may have confounded meaningful data interpretation, leading to a possible underestimation of benefit conferred by CEA. CETC data and ESVS recommendations also led to CNO patients being excluded from RCTs of carotid interventions.

A meta-analysis (32 observational studies) included 703 patients with CNO.[78] Thirty day death/stroke was 1.8% after CEA, 2.2% after CAS, and 4.9% with BMT. BMT was associated with higher 30 day death/stroke *versus* CEA (OR 5.63; 95% CI 1.3 — 24.45, $p = .021$). No differences were observed between CEA and CAS. One year freedom from stroke/death was 96% following CEA, 94% after CAS, and 81% with BMT. However, the number of adverse events was small, precluding robust statistical conclusions.[78] A subsequent meta-analysis (26 studies, $n = 1\ 506$ patients) reported that the late risk of ipsilateral stroke, neurological/cardiac death, or MI was 4.26/100 patient years (95% CI 2.92 — 6.2) in CNO patients treated by CEA or CAS, and 13.3/100 patient years (95% CI 5.54 — 31.95) in patients treated medically ($p < .001$).[110] However, only five studies directly compared outcomes in CNO patients undergoing CEA or CAS with BMT and found no statistically significant difference (HR 2.37; 95% CI 0.97 — 9.75, $p = .23$).[110] Xue's meta-analysis did not, however, report data regarding early or late ipsilateral stroke. There is also debate about the relevance of full or partial vessel collapse with CNO. CETC concluded that full collapse was associated with low stroke risks in BMT patients.[357] However, a pooled analysis of two studies ($n = 430$) observed that 116 patients (27%) had evidence of CNO, with 47/116 having full distal vessel collapse, while 69 had partial collapse.[194] The 28 day rate of ipsilateral stroke or central retinal artery occlusion was 27% in CNO patients with full collapse *versus* 11% in patients with partial collapse ($p = .047$).[194] By contrast, a Spanish multicentre registry reported no outcome differences between full or partial collapse.[126] In addition, while some centres have reported increased rates of post-operative ICH following CEA in patients with CNO and full distal vessel collapse,[424] others have reported no substantial increase.[423] In a single centre study involving 17 CNO patients with full vessel collapse and recurrent carotid territory symptoms (despite BMT), CEA was performed in 15, while two underwent carotid ligation and ECA endarterectomy. Postoperatively, 1/17 (5.8%) died from haemorrhagic stroke. During a median follow up of 23 months, one died of unknown causes at 90 days, but none of the remainder had recurrent TIA/stroke, suggesting that in selected CNO patients with full vessel collapse in whom BMT has failed, CEA may confer benefit.[423] The 2021 SVS and AHA guidelines made no specific recommendations regarding the management of CNO. ESVS recommendations are similar to the 2021 German-Austrian guidelines.[3]

Recommendation 56			Unchanged
For symptomatic patients with carotid near occlusion and distal vessel collapse, carotid endarterectomy and carotid stenting are not recommended, unless as part of a randomised controlled trial.			
Class	**Level**	**References**	**ToE**
III	**B**	Rothwell *et al.* (2003)[357]	

Recommendation 57			New
For patients with carotid near occlusion and distal vessel collapse with recurrent carotid territory symptoms (despite best medical therapy), carotid endarterectomy or carotid artery stenting may be considered only after multidisciplinary team review.			
Class	**Level**	**References**	**ToE**
IIb	**C**	Meershoek *et al.* (2019)[78], Xue *et al.* (2020)[110], García-Pastor *et al.* (2017)[126], Meershoek *et al.* (2018)[423]	

4.13. Management of free floating thrombus

Free floating thrombus (FFT) is defined as elongated thrombus attached to the arterial wall with circumferential blood flow distally.[49] It is reported in 1.3% of ischaemic stroke patients[54] and usually occurs on the surface of atherosclerotic plaques.[54] FFT is more common in men (ratio 2 : 1, $p < .001$)[49] and a substantial proportion (47%) are hypercoagulable because of thrombophilia, pregnancy, inflammatory, or infectious disease or cancer.[49,54] Optimal management is unclear, with no RCTs to guide practice. In a meta-analysis of 58 case series and 83 case reports ($n = 525$), 345 patients were treated with "antithrombotic" or "interventional" methods, in whom 30 day death, TIA/stroke, or silent ischaemia on MRI was 17.1% (95% CI 13.1 — 21.1), with a 30 day risk of stroke/death of 11.1% (95% CI 7.7 — 14.3).[54] These high event rates presumably reflect high rates of cerebral embolisation. In a Cox regression analysis of relatively poor data, neither anticoagulation *versus* no anticoagulation (HR 1.21; 95% CI 0.35 — 4.23, $p = .76$), nor interventions < 3 days *versus* > 3 days after symptom onset (HR 0.78; 95% CI 0.24 — 2.57), $p = .69$) were associated with different risks of silent ischaemia, TIA, or stroke/death at 30 days.[54] However, patients with FFT undergoing thrombolysis had higher rates of silent ischaemia, TIA, or stroke/death (HR 14.79; 95% CI 3.41 — 64.25) $p < .001$).[54] Endovascular thrombus aspiration and stent retriever thrombectomy with filter protection are alternatives to open surgery,[425] but evidence regarding their safety and efficacy is lacking.

In the absence of better quality evidence, decision making is influenced by (i) probable aetiology (e.g., thrombophilia requiring anticoagulation), (ii) whether patients had recurrent events on pre-existing APRx or anticoagulation, (iii) interval since TIA/stroke onset, (iv) size of infarct, and (v) whether FFT is located at the carotid bifurcation (accessible) or extends towards the skull base (less accessible). Serial DUS/CTA/MRA can inform clinicians of

responses to treatment. Selected patients with recurrent TIA/stroke on optimal anticoagulation therapy (with surgically or endovascularly accessible FFT) may be considered for thrombectomy (open or endovascular), preferably after MDT discussion. Acute stroke patients with FFT who received TT with i.v. rtPA should be monitored for signs of recurrent thromboembolism. The 2021 SVS, AHA, and ESO guidelines provide no advice about the management of symptomatic patients with FFT. The 2021 German-Austrian guidelines advise that (in selected patients) CEA or CAS should be performed within the first hours of the index event after consultation with stroke specialists.[3]

Recommendation 58 — New

For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus within the carotid artery, therapeutic anticoagulation is recommended.

Class	Level	References	ToE
I	C	Bhatti *et al.* (2007)[49], Fridman *et al.* (2019)[54]	

Recommendation 59 — New

For patients presenting with recent carotid territory symptoms and free floating thrombus who develop recurrent symptoms whilst receiving anticoagulation therapy, surgical or endovascular removal of the thrombus may be considered.

Class	Level	References
IIb	C	Consensus

Recommendation 60 — New

For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus, intravenous thrombolysis is not recommended.

Class	Level	References	ToE
III	C	Fridman *et al.* (2019)[54]	

4.14. Management of carotid webs

A carotid web (CaW) is a ridge like filling defect in the posterior aspect of the carotid bulb and studies suggest it may be an intimal variant of fibromuscular dysplasia. Its incidence is unknown, but in non-selected patients with ischaemic stroke, the prevalence was 1.2% (0.7% ipsilateral).[426] In a cohort of the Mr CLEAN RCT and registry (which randomised acute stroke patients to intra-arterial treatment plus usual care *vs.* usual care alone, see section 4.9), 30 / 3 439 (0.9%) patients with an anterior circulation stroke resulting from large vessel occlusion who had CTA of the carotid bifurcation and two years surveillance post-MT had CaW.[19] In another cohort of 466 patients undergoing MT for large vessel occlusion stroke, 10.7% with embolic stroke of undetermined source had CaW *versus* 0.7% in those with a known source of embolism.[427] Logistic regression analysis showed a statistically significant association between embolic stroke of undetermined source and ipsilateral CaW after adjusting for age, sex, and vascular risk factors (OR 12.5; 95% CI 2.1 — 71, $p = .005$).[427]

CaW may act as a pocket for thrombus accumulation and cerebral embolisation. Antiplatelet monotherapy may be insufficient to prevent recurrent events and there is no current evidence supporting anticoagulation.[69,112] A systematic review identified 37 observational studies ($n = 158$). Median age was 46 years (range 16 — 85), 68% were female, and 76% were symptomatic. In the symptomatic cohort, 56% of those initially treated medically had recurrent stroke at a median of 12 months after symptom onset (range 0 — 97) and 72% ultimately underwent an intervention (50% CAS, 50% CEA).[112] In the Mr CLEAN cohort, 1% of patients with anterior circulation stroke resulting from large vessel occlusion and no CaW had recurrent ipsilateral stroke by two years, *versus* 13% in CaW patients (adjusted HR 8.1; 95% CI 1.4 — 46.8).[19] Treatment includes CAS or web resection plus patching or segmental resection and anastomosis. No guideline has made any recommendation regarding the optimal management of symptomatic patients with carotid webs, although the AHA identified it as an area warranting future research.[1]

Recommendation 61 — New

For symptomatic patients with a carotid web in whom no other cause for stroke can be identified after detailed neurovascular work up, carotid endarterectomy or carotid artery stenting may be considered to prevent recurrent stroke.

Class	Level	References	ToE
IIb	C	Gugliemi *et al.* (2021)[19], Kim *et al.* (2019)[69], Zhang *et al.* (2013)[241], Choi *et al.* (2015)[426], Laberyie *et al.* (2021)[427]	

4.15. Management of chronic ocular ischaemia syndrome

Chronic ocular ischaemia syndrome presents with progressive visual impairment/loss, with dilated conjunctival or episcleral vessels and narrowing of retinal arteries with or without dilated retinal veins.[428] It is usually associated with 90—99% stenoses but has been reported with > 50% stenoses.[429] Patients may develop pain as a result of elevated intra-ocular pressure and neovascular glaucoma, rubeosis iridis (coarse dilated vessels on the surface and stroma of the iris),[430] or retinal haemorrhages from fragile retinal neovascularisation.[429] Ocular ischaemia syndrome may also present with ipsilateral monocular blurring, dimming, or whiteout of vision in response to haemodynamic triggers or sudden bright lights due to low flow retinopathy.

Management requires expert ophthalmic treatment to limit neovascularisation and control elevated intra-ocular pressures and neovascular glaucoma, along with risk factor control and BMT (section 4.2). Carotid interventions can preserve visual acuity by limiting further ischaemia induced neovascularisation, which leads to worsening neovascular glaucoma or retinal haemorrhages. CEA may reverse

rubeosis iridis and improve visual acuity in 60%, with no change in 40%.[431] Carotid revascularisation is less likely to improve visual acuity in patients with established neovascularisation related glaucoma due to severe ocular hypoperfusion,[429] but treatment options have not been subject to randomised comparison. In a systematic review of 14 observational studies ($n = 589$), revascularisation led to increases in peak systolic velocity in the ipsilateral ophthalmic artery, with improvement in ocular ischaemic symptoms in 93%.[83] No other international guidelines have provided any recommendations regarding the optimal management of ocular ischaemia syndrome.

Recommendation 62			New
For patients with confirmed ocular ischaemia syndrome and a 50–99% ipsilateral carotid stenosis, carotid endarterectomy or carotid stenting should be considered to prevent further ischaemia induced retinal neovascularisation.			
Class	**Level**	**References**	**ToE**
IIa	C	Nana *et al.* (2021)[83], Kawaguchi *et al.* (2012)[431]	

4.16. Symptomatic patients with > 50% stenosis and atrial fibrillation

A 2021 meta-analysis (20 observational studies) reported that 12% of AF patients had a > 50% carotid stenosis, while in 25 observational studies, 9% of patients with > 50% carotid stenosis had AF.[84] This suggests that about one in 10 patients with > 50% carotid stenosis will have AF and vice versa. Not all strokes in AF patients are cardioembolic. In six stroke registries (1 720 AF patients with acute ischaemic stroke), 14% were deemed atherothrombotic.[432] Regarding long term stroke risk in AF patients with a 50–99% stenosis, the FibStroke registry reported that at 3.5 years, the risk of stroke was 21.2% in patients with AF plus a > 50% carotid stenosis at baseline, *versus* 12.7% with AF alone ($p = .005$). After multivariable analysis, stenosis > 50% was an independent predictor of late stroke recurrence (HR 2.02; 95% CI 1.37 – 3.01, $p = .001$).[145]

This highlights a conundrum as to whether patients presenting with a recent carotid territory TIA or ischaemic stroke with an ipsilateral 50–99% carotid stenosis and newly diagnosed or known AF should undergo carotid revascularisation followed by long term anticoagulation, or anticoagulation alone, without carotid revascularisation. There are no RCTs to guide practice (ECST, NASCET, ICSS, CREST excluded patients with a potential cardioembolic source) and a pragmatic approach is required. This is greatly aided by MDT involvement. Investigations should aim to determine whether the TIA/ischaemic stroke was probably cardioembolic (i.e., the carotid stenosis is asymptomatic and an urgent carotid intervention is unnecessary) or probably atherothrombotic (expedited carotid intervention appropriate, followed by post-operative anticoagulation). If it is not possible to determine the probable aetiology, TOAST would define these TIA/strokes as being of undetermined aetiology as there are two potential causes (section 2.3).

There are no definitive diagnostic tests for discriminating between cardioembolic or carotid sources of embolisation and management decisions will have to be based on probability, guided by access to basic or more complex investigative modalities. If CT/MRI shows acute ischaemia or infarction in additional territories (contralateral carotid or VB) other than the ipsilateral symptomatic carotid, then cardiac embolism is the likeliest cause. The patient should be anticoagulated, and the carotid stenosis treated as asymptomatic. Although ipsilateral carotid territory ischaemia/infarction supports a diagnosis of carotid embolism, cardiac embolism cannot be excluded. In this situation, centres with access to more complex neurovascular work up may be able to gain additional diagnostic information.

More complex imaging strategies might include T1 fat saturated MRI to look for IPH in the carotid plaque, which is associated with acutely symptomatic carotid plaques. Transoesophageal echocardiography can diagnose left atrial appendage thrombus or other cardiac sources of embolism. Transoesophageal echocardiography (plus bilateral TCD) with i.v. microbubble contrast media in conjunction with a Valsalva manoeuvre can diagnose a patent foramen ovale (suggesting paradoxical embolisation). Finally, 30 – 60 minutes of bilateral simultaneous TCD monitoring of both MCAs can diagnose spontaneous embolisation. In a series of 123 recently symptomatic patients with 50–99% stenoses, 40% of patients undergoing 30 minutes of TCD monitoring within seven days of TIA/stroke onset had ongoing ipsilateral MCA embolisation.[433] Bilateral embolisation, however, suggests a cardioembolic source. To date, no guidelines have offered advice regarding the management of patients with recent carotid territory symptoms, an ipsilateral carotid stenosis, and AF.

Pragmatic decision making

1. Acute ischaemia/infarction in multiple vascular territories suggests cardioembolism. Patients should be anticoagulated, and the carotid stenosis considered asymptomatic.
2. Acute ischaemia/infarction in the ipsilateral carotid territory is suggestive of a carotid source of embolism and (in some centres) this would be considered sufficient to recommend CEA/CAS. However, this diagnosis can be made with greater certainty if supported by ipsilateral embolism on TCD, IPH in the ipsilateral carotid plaque, and no evidence of left atrial appendage thrombus.
3. If a patient is anticoagulated (on the basis that cardioembolism was the likeliest aetiology) but then suffers recurrent event(s) in the territory ipsilateral to the 50–99% carotid stenosis while on therapeutic anticoagulation, it is reasonable to consider CEA or CAS (see section 4.2.6.3 for management of peri-operative anticoagulation).

4. If investigations are neither diagnostic nor informative and more complex imaging is unavailable, the MDT will have to make an empirical management decision, following discussion of diagnostic uncertainties and potential implications with the patient.

Recommendation 63		New
For patients presenting with a transient ischaemic attack or minor ischaemic stroke in the presence of newly diagnosed or known atrial fibrillation and an ipsilateral 50–99% carotid stenosis, comprehensive neurovascular work up with multidisciplinary team review is recommended to determine whether urgent carotid revascularisation or anticoagulation alone is indicated.		
Class	**Level**	**References**
I	C	Consensus

Recommendation 64		New
For patients who have been started on anticoagulation (on the basis that cardiac embolism was considered the most likely cause of their transient ischaemic attack or stroke) but who then report recurrent event(s) in the territory ipsilateral to a 50–99% carotid stenosis whilst on therapeutic levels of anticoagulation, carotid endarterectomy or carotid artery stenting is recommended.		
Class	**Level**	**References**
I	C	Consensus

5. OPEN SURGICAL TECHNIQUES

5.1. Carotid endarterectomy

5.1.1. Pre-operative checklist. Responses to key questions should be documented in the casenotes prior to CEA. The aim is to minimise morbidity/mortality and lessen medico-legal censure. They include: Has the indication for CEA been documented? Are there atypical symptoms warranting further investigation? Is the degree of stenosis appropriate for CEA? Have procedural risks quoted to the patient been documented? Is the patient prescribed optimal BMT? Is high carotid disease possible? Are there pre-existing CNIs? Has the operation side been marked?

Four of these are particularly important: (i) Has the surgeon quoted their own procedural risks during the consent process, rather than RCT data? (ii) If the patient has previously undergone contralateral CEA, total/partial thyroidectomy, or radical neck surgery, indirect laryngoscopy must exclude contralateral RLN palsy as bilateral RLN palsies can be fatal (as can bilateral hypoglossal). If a contralateral vocal cord palsy is identified, the rationale for CEA must be reviewed. If the patient is asymptomatic, CEA should be cancelled, and CAS considered (if still deemed appropriate). If the patient is symptomatic, CAS should still be considered. If it is not possible to safely perform CAS and the indication for intervening is compelling, the patient must be warned about the consequences of bilateral RLN palsies (permanent tracheostomy) and an Ear Nose and Throat surgeon should be present at extubation. In addition, the surgeon should avoid a retrojugular approach to the bifurcation, as this is associated with higher risks of temporary RLN injury (section 5.1.6). (iii) It is important to ensure the patient is receiving optimal medical therapy (section 3.1 and 4.2) and (iv) the surgeon must anticipate the possibility of distal ICA disease. If this is considered likely, the surgeon must ensure that CEA can be done safely. It may be necessary to plan a more complicated exposure (section 5.1.14).

5.1.2. Staged or synchronous bilateral carotid interventions? Some patients present with bilateral severe stenoses. Most will be asymptomatic, or one side will be symptomatic and the other asymptomatic. It is extremely rare for both stenoses to be simultaneously symptomatic. Some have suggested that synchronous bilateral CEAs should be considered,[434] but the most dangerous complication is injury to both RLNs or hypoglossal nerves, which can be fatal. Accordingly, if bilateral revascularisation is deemed necessary, it is safer to consider bilateral CAS, unilateral CEA + contralateral CAS[435] or staged bilateral CEAs.

5.1.3. Carotid endarterectomy under general versus locoregional anaesthesia? There is controversy on whether to perform CEA under locoregional anaesthesia (LRA) or general anaesthesia (GA). The General Anaesthesia Local Anaesthesia trial ($n = 3\ 526$) was the largest RCT and reported no difference in peri-operative death, stroke, or MI between GA (4.8%) and LRA (4.5%).[436] However, pooled data from five CEA *versus* CAS RCTs showed reduced 30 day stroke/death for CEA under LRA (adjusted RR 0.70; 95% CI 0.50 − 0.99),[70] while NIBLs were more common with GA (17.1% *vs.* 6.7%; $p = .031$).[437] In the American College of Surgeons National Surgical QIP, LRA incurred lower CNI rates, shorter operation times and hospital stays, fewer re-admissions, less post-operative pneumonia, and reduced blood transfusion.[130,149] However, LRA attracted lower patient satisfaction (65% *vs.* 93%) and future preference (61% *vs.* 97%).[438] In a large meta-analysis (25 observational studies, six RCTs [$n = 152\ 376$]), LRA was associated with statistically significantly shorter operation times, lower peri-operative stroke (OR 0.76; 95% CI 0.62 − 0.92, $p = .006$), fewer cardiac complications (OR 0.59; 95% CI 0.47 − 0.73, $p < .001$), and lower mortality (OR 0.72; 95% CI 0.59 − 0.90, $p = .003$) in observational studies.[60] However, there were no statistically significant differences in any endpoint in RCTs.[60] Some believe that RCTs lack statistical power,[58] but an alternative interpretation may be that CEA under GA may be more challenging surgically (suggested by higher CNI rates, longer operation times, increased blood transfusion) and that observational study data reflect selection biases which are avoided in RCTs.

Most studies on CEA under LRA include patients on aspirin monotherapy. However, with the increasing use of

combination APRx (section 4.2.2.2), there are concerns about neck haematoma formation. In a systematic review of 69 observational studies ($n = 10\ 081$), combined deep + superficial cervical plexus blockade was associated with statistically significantly higher complication rates (OR 2.13; $p = .006$) *versus* superficial or intermediate blockade.[439] No guidance has been published regarding neck haematoma risks after deep cervical plexus blockade in LRA patients. In a working party consensus on LRA in patients with coagulation abnormalities, there was no mention of adverse events relating to combination APRx and no advice about performing CEA under deep cervical plexus blockade.[440] There are no published data on whether it is safe to perform deep cervical plexus blockade in CEA patients on combination APRx.[441] Given that an increasing proportion of symptomatic patients undergo CEA on combination APRx, surgeons and anaesthetists need to establish protocols regarding APRx strategies and choice of anaesthesia. It would be inappropriate to stop clopidogrel and delay CEA for 7 − 10 days to perform deferred CEA under LRA, as this increases the likelihood of recurrent embolic stroke. Intraoperative DUS may enable safer infiltration of LRA, with visualisation of the cervical transverse processes and VAs. ESVS recommendations regarding LRA *versus* GA are the same as in the SVS and German-Austrian guidelines.[3,4]

Recommendation 65			Unchanged
In patients undergoing carotid endarterectomy, decisions regarding choice of anaesthesia (locoregional, general) should be considered at the discretion of the surgeon/anaesthetist performing the procedure, taking account of local experience, patient preference, and preferred antiplatelet strategy.			
Class	**Level**	**References**	**ToE**
IIa	**B**	Hajibandeh *et al.* (2018)[58], Knappich *et al.* (2019)[70], Grieff *et al.* (2021)[130], Malik *et al.* (2019)[149], Trial Collaborative GALA (2008)[436]	

5.1.4. Hospital and surgeon volumes. Interpretation of data is confounded by interstudy heterogeneity regarding presentation (symptomatic *vs.* asymptomatic), urgency (emergency *vs.* elective), and non-standardised definitions of low *versus* high volume surgeons or hospitals (actual numbers *vs.* quintiles). A meta-analysis of 25 studies (900 000 USA based CEAs) reported notable benefit when CEA was performed in higher volume centres, with a threshold of 79 CEAs per centre per year.[442] In a similar analysis of 18 248 UK CEAs, there was a volume−outcome relationship favouring higher volume centres,[443] with an annual threshold of 35 CEAs per hospital. The differing thresholds probably relate to higher operative risks in symptomatic patients. Most UK CEAs involve SCS patients, while in the USA most are asymptomatic.

A systematic review of 233 411 CEAs in Europe reported an inverse relationship between hospital volume and perioperative stroke/death in elective patients (no threshold reported), but no association with emergency CEAs. Univariable analyses suggested an inverse relationship between surgeon volume and outcome, but this did not persist after adjusting for confounding variables.[88] AbuRahma analysed the influence of surgeon volume on 30 day stroke/death in 953 CEAs. High volume surgeons ($\geq$ 30 CEAs/year) had lower 30 day stroke/death (1.3%) than did surgeons performing $<$ 30 CEAs/year (4.1%). Thirty day death/stroke was statistically significantly higher when CEA was performed by non-vascular surgeons *versus* vascular trained surgeons in ACS patients (3.2% *vs.* 0.72%; $p = .033$).[444] In an Australia and New Zealand audit ($n = 16\ 765$), there was a small but statistically significant inverse association between operator volume and in hospital stroke/death, which was 2.2% for the lowest three volume quintiles ($\leq$ 17 CEAs per year), *versus* 1.76% in surgeons with the two highest volume quintiles ($\geq$ 18 CEAs per year). There was, however, no hospital volume−outcome relationship.[128]

In a meta-analysis of 25 studies on hospital volume, nine on surgeon volume, and seven on surgeon specialty, there was no association between hospital volume and outcome, but the definition of a high volume hospital ranged from $>$ 20 to $>$ 164 CEAs annually. Similarly, seven out of nine studies showed an inverse relationship for surgeon volume, but the definition of a high volume surgeon ranged from $>$ 10 to $>$ 50 CEAs per year,[445] making it difficult to establish the optimal volume threshold. Finally, seven out of eight studies reported that specialist vascular training was associated with lower death/stroke after CEA *versus* non-vascular training, but only for low volume surgeons. For high volume surgeons, specialty had no impact.[445] In a Canadian study ($n = 14\ 301$), 30 day stroke was higher when CEA was performed by non-vascular surgeons (3.6%), than by vascular surgeons (2.5%) (OR 1.38; 95% CI 1.11 − 1.71).[133]

The situation regarding hospital and/or surgeon volume thresholds is now being confounded by temporal changes in vascular workload. In 2012, the UK centralised major arterial procedures (including CEA) into larger volume centres, each serving a population of $\geq$ 800 000. At the time, it was advised that each vascular unit should perform $\geq$ 50 CEAs per year.[158] However, the UK has seen a 25% decline in CEA numbers in symptomatic patients between 2011 and 2017, and a 65% decline in ACS patients, which was not associated with parallel increases in CAS numbers.[135] The decline in CEA numbers in the UK, attributed to improvements in primary and secondary cardiovascular prevention, was the main reason for the Vascular Society of Great Britain and Ireland to recommend (in 2021) that the minimum annual hospital volume of CEAs should now be reduced from 50 to 35 (which will inevitably influence individual surgeon volumes as well).[160]

While there is evidence that better outcomes are achieved when vascular surgeons perform CEA compared with non-vascular surgeons, data regarding hospital and surgeon volume outcomes are conflicting. Only the German-Austrian guidelines have made a recommendation about annual caseload, advising CEA should only be performed in hospitals performing $>$ 20 CEAs per year.[3]

Recommendation 66			New
For patients undergoing carotid endarterectomy, it is recommended that the operation be performed by trained vascular surgeons, rather than by surgeons from other specialties.			
Class	**Level**	**References**	**ToE**
I	B	Hussain *et al.* (2018)[133], AbuRahma *et al.* (2013)[444], Killeen *et al.* (2007)[445]	

5.1.5. Transverse or longitudinal incision? The standard approach is a longitudinal anterior sternomastoid incision, but CEA can be performed via a transverse skin crease incision which may confer better cosmesis and a lower CNI rate.[446] Others, however, have reported no difference in CNI and it may be more difficult to insert a shunt with transverse incisions.[447] A modified approach involves DUS marking of the bifurcation and a smaller longitudinal incision, which is extended as required. This reduces incision length and offers good cosmesis.[448] Surgeons can, therefore, use whichever incision they prefer. If DUS suggests the bifurcation is not too high with a focal stenosis, a transverse crease incision will probably give the best cosmetic result. If there is any question about the bifurcation being high, or if the lesion is extensive, a longitudinal incision is preferable.

5.1.6. Antegrade or retrojugular exposure? A retrojugular approach avoids mobilising the hypoglossal nerve and may optimise access to the distal ICA, by sweeping (anteriorly) the sternocleidomastoid artery, hypoglossal nerve, and ansa cervicalis.[449] A meta-analysis (four observational studies, two RCTs [740 CEAs]) found no evidence that retrojugular (*vs.* antegrade) exposure reduced peri-operative death (0.6% *vs.* 0.5%) or stroke (0.9% *vs.* 0.7%). However, a retrojugular approach was associated with higher rates of RLN palsy (8.1% *vs.* 2.2%) and no reduction in hypoglossal injury (1.3% *vs.* 1.3%).[450]

Recommendation 67			Unchanged
For patients undergoing carotid endarterectomy, decisions regarding carotid exposure (antegrade, retrojugular) should be left to the operating surgeon.			
Class	**Level**	**References**	**ToE**
IIa	B	Antoniou *et al.* (2014)[450]	

5.1.7. Carotid sinus nerve blockade? The hypothesis that carotid sinus nerve blockade reduces hypotension, hypertension, or dysrhythmias during/after CEA was not supported by a meta-analysis of four RCTs.[451] A fifth single centre RCT led to similar conclusions.[452]

Recommendation 68			Unchanged
For patients undergoing carotid endarterectomy, routine carotid sinus nerve blockade is not recommended.			
Class	**Level**	**References**	**ToE**
III	A	Tang *et al.* (2007)[451], Adjuk *et al.* (2011)[452]	

5.1.8. Protamine reversal of heparin? Evidence supports more routine use of protamine during CEA. A 2016 meta-analysis in 3 817 patients undergoing CEA who received protamine and 6 070 patients undergoing CEA who did not receive protamine, reported that protamine statistically significantly reduced re-exploration for neck haematomas (OR 0.42; 95% CI 0.22 — 0.8, $p = .008$), with no evidence that protamine increased peri-operative stroke (OR 0.71; 95% CI 0.49 — 1.03, $p = .07$).[453] The proportion of US surgeons using protamine increased from 43% (2003) to 62% (2010)[454] and 73% by 2018.[154] VSGNE (10 059 CEAs) also reported that protamine statistically significantly reduced re-exploration for neck haematoma (0.6% *vs.* 1.4%; $p = .001$), without increasing peri-operative stroke/death (1.1% *vs.* 1.0%) or MI (1% *vs.* 1.2%).[454] In a 2020 SVS-VQI audit (72 787 elective CEAs for ACS), re-operation for bleeding was higher in patients not receiving protamine (1.4% *vs.* 0.7%; OR 2.0, 95% CI 1.8 — 2.6).[154] This is important as re-interventions for neck haematoma are associated with increases in peri-operative MI, stroke, and death.[137] ESVS recommendations regarding protamine reversal of heparin are the same as the 2021 SVS and German-Austrian guidelines.[3,4]

Recommendation 69			Unchanged
For patients undergoing carotid endarterectomy, protamine reversal of heparin should be considered.			
Class	**Level**	**References**	**ToE**
IIa	B	Stone *et al.* (2020)[154], Kakisis *et al.* (2016)[453], Patel *et al.* (2013)[454]	

5.1.9. Shunting: routine, never, selective? Carotid clamping can cause haemodynamic stroke, which is prevented by shunt insertion. Surgeons tend to be routine, selective or never shunters, based on training. There is a paucity of quality data for guiding practice. While there are numerous methods for monitoring brain perfusion during clamping (electroencephalography [EEG], stump pressure, backflow, TCD, transcranial cerebral oximetry, near infrared spectroscopy), the only reliable method is the patient's neurological status with CEA under LRA. A Cochrane review (six RCTs; 1 270 CEAs) concluded that (based on poor data) no meaningful recommendations could be made regarding shunt strategies.[455] Analysis of 28 457 CEAs from a SVS-VQI audit (4 128 routine, 1 740 never, and 12 489 selective) found no differences in peri-operative TIA/stroke.[162] A VQI update that included 5 683 CEA procedures performed within 14 days of symptom onset, showed no difference in peri-operative stroke rates following routine *versus* no shunting (OR 1.39; 95% CI 0.91 — 2.13).[146] Shunting was a risk factor for increased 30 day stroke/death in patients undergoing CEA in the CSTC database.[70] ESVS recommendations regarding shunting are the same as the SVS and German-Austrian guidelines.[3,4]

Recommendation 70			Unchanged
For patients undergoing carotid endarterectomy, decisions regarding shunting (routine, selective, never) should be considered at the discretion of the operating surgeon.			
Class	**Level**	**References**	**ToE**
IIa	C	Levin *et al.* (2020)[146], Wiske *et al.* (2018)[162], Chongruksut *et al.* (2014)[455]	

5.1.10. Patching: routine, never, selective? A meta-analysis of 23 RCTs compared primary closure ($n = 753$), eversion CEA ($n = 431$), vein patch ($n = 973$), polytetrafluoroethylene (PTFE) patch ($n = 948$), polyester patch ($n = 828$), bovine pericardial patch ($n = 249$), and polyurethane patch ($n = 258$). Eversion CEA (eCEA) and patched CEA (PTFE, bovine pericardium) had the lowest 30 day stroke/death rates, with primary closure having the highest 30 day death/stroke rate. Lowest re-stenosis rates were observed with eCEA, then patched CEA (PTFE, bovine pericardium), with the highest rates in patients with primary closure or polyester patching. Vein patch blow out and patch infection were reported in 0.2%.[73]

A meta-analysis of 10 RCTs ($n = 2\,157$) observed that routine patching (*vs.* routine primary closure) was associated with statistically significant reductions in 30 day ipsilateral stroke (1.5% *vs.* 4.5%; OR 0.2, 95% CI 0.1 — 0.6, $p = .001$) and 30 day ICA thrombosis (0.5% *vs.* 3.1%; OR 5.6, 95% CI 2.4 — 12.5, $p < .001$). Patients randomised to primary closure were more likely to return to theatre within 30 days (3.1% *vs.* 1.1%; OR 2.9, 95% CI 1.3 — 6.3, $p = .01$). There were no notable differences regarding peri-operative death, fatal stroke, death/stroke, and CNI.[456,457] An SVS-VQI registry reported lower peri-operative stroke/TIA when the arteriotomy was closed with bovine pericardium (OR 0.59; 95% CI 0.48 — 0.72) or polyester patches (OR 0.56; 95% CI 0.43 — 0.72) *versus* vein patch, PTFE patch, or primary closure. Bovine pericardial patches (OR 0.57; 95% CI 0.44 — 0.75), polyester patches (OR 0.70; 95% CI 0.50 — 0.98), and vein patches (OR 0.72; 95% CI 0.53 — 0.98) had lower one year re-stenosis rates *versus* primary closure.[122]

Routine patching (*vs.* routine primary closure) was associated with statistically significant reductions in late ipsilateral stroke (1.6% *vs.* 4.8%; OR 0.3, 95% CI 0.2 — 0.6, $p = .001$), late any stroke (2.4% *vs.* 4.6%; OR 0.49, 95% CI 0.3 — 0.9, $p = .002$), and late re-stenosis (4.3% *vs.* 13.8%; OR 0.2, 95% CI 0.2 — 0.3, $p < .01$). No RCTs have compared routine with selective patching.[456,457] No RCTs have evaluated selective patching strategies. ESVS recommendations regarding patching are similar to 2021 SVS guidelines,[4] while the German-Austrian guidelines advise that the choice of CEA technique (eCEA *vs.* patched CEA) should be left to the operating surgeon.[3]

Recommendation 71			Unchanged
For patients undergoing conventional carotid endarterectomy, routine patch closure is recommended, rather than routine primary arteriotomy closure.			
Class	**Level**	**References**	**ToE**
I	A	Lazarides *et al.* (2021)[73], Rerkasem *et al.* (2011)[456], Ren *et al.* (2013)[457]	

Recommendation 72			Unchanged
For patients undergoing carotid endarterectomy, the choice of patch closure material should be considered at the discretion of the operating surgeon.			
Class	**Level**	**References**	**ToE**
IIa	A	Lazarides *et al.* (2021)[73]	

5.1.11. Eversion carotid endarterectomy *versus* conventional carotid endarterectomy? During eCEA, the ICA is transected obliquely at its origin and a cylinder of atheroma expelled by eversion of the outer media and adventitia. The distal intimal step is examined for flaps, which are excised. The ICA can be shortened and then re-anastomosed to the bifurcation. Advantages include no prosthetic infection, it is quicker than patched CEA, bifurcation geometry is preserved, and the distal ICA is shortened where necessary. Disadvantages are that a shunt cannot be inserted until eCEA is completed and there may be problems accessing the distal ICA.

A meta-analysis (one RCT, six observational studies [$n = 1\,275$]) reported that eCEA was associated with more post-CEA hypertension than conventional CEA (cCEA) (OR 2.75; 95% CI 1.82 — 4.16). Conversely, cCEA was associated with higher rates of hypotension (OR 11.37; 95% CI 1.95 — 66.46).[458] In an SVS-VQI audit ($n = 72\,787$), eCEA was an independent risk factor for re-interventions for bleeding (OR 1.4; 95% CI 1.1 — 1.7), possibly because of more extensive dissection.[154] In a systematic review of five RCTs and 20 observational studies (16 249 eCEA and 33 251 cCEA), outcomes were different between RCTs and observational studies.[86] In five RCTs, eCEA (*vs.* cCEA) was not associated with reduced 30 day stroke, death/stroke, or death/stroke MI, but eCEA was associated with fewer re-stenoses (OR 0.40; $p = .001$). In 20 observational studies, eCEA (*vs.* cCEA) was associated with statistically significant reductions in 30 day death (OR 0.46; $p < .001$), stroke (OR 0.58; $p < .001$), death/stroke (OR 0.52; $p < .001$), and late re-stenosis (OR 0.49; $p = .032$). However, when eCEA outcomes were compared with patched CEA in observational studies, there were no statistically significant differences in 30 day death, stroke or death/stroke,[86] suggesting that cCEA provides equivalent outcomes to eCEA, provided the arteriotomy is patched. ESVS recommendations regarding eCEA *versus* cCEA, are similar to SVS guidelines.[4] The German-Austrian guidelines advise that the choice of eCEA or cCEA should be left to the operating surgeon.[3]

Recommendation 73			Unchanged
For patients undergoing carotid endarterectomy, eversion endarterectomy or patched endarterectomy is recommended over routine primary arteriotomy closure.			
Class	**Level**	**References**	**ToE**
I	A	Paraskevas *et al.* (2018)[86]	

Recommendation 74			Unchanged
For patients undergoing carotid endarterectomy, the choice between eversion or patched endarterectomy should be considered at the discretion of the operating surgeon.			
Class	**Level**	**References**	**ToE**
IIa	A	Paraskevas *et al.* (2018)[86]	

5.1.12. Management of coils, kinks, and loops. In DUS studies involving 19 804 patients aged > 25 years, 13.5% had coils, kinks, or loops.[459] Half had histology consistent with fibromuscular dysplasia,[460] in whom an increased incidence of spontaneous dissection was observed.[461] One RCT compared surgical correction with BMT in 182 patients with hemispheric or non-hemispheric symptoms and isolated ICA coils or kinks, with independent neurologist assessment.[460] Patients randomised to surgery had 0% thrombosis at 5.9 years, *versus* 5.5% with BMT ($p = .020$). Late stroke was 0% after surgery, *versus* 6.6% with BMT ($p = .010$). ESVS recommendations regarding treatment of coils/kinks are similar to SVS guidelines.[4]

Recommendation 75			Unchanged
For patients with asymptomatic isolated coils/kinks of the internal carotid artery, surgical correction is not recommended.			
Class	**Level**	**References**	
III	C	Consensus	

Recommendation 76			Unchanged
For symptomatic patients with isolated coils/kinks, surgical correction may be considered, but only following multidisciplinary team review and provided no other cause for transient ischaemic attack or stroke symptoms can be identified.			
Class	**Level**	**References**	**ToE**
IIb	B	Ballotta *et al.* (2005)[460]	

5.1.13. Monitoring and quality control after carotid endarterectomy. Quality control (QC) is not the same as monitoring. The role of monitoring is to ensure adequate brain perfusion, (especially during clamping or shunting), using TCD, CEA under LRA, stump pressure, ICA backflow, or near infrared spectroscopy. Loss of cerebral electrical activity is assessed by somatosensory evoked potentials (SSEPs) or EEG. The aim of QC is to identify and correct technical error, such as embolisation during carotid mobilisation (TCD), ensuring the shunt is functioning (TCD, CEA under LRA), identifying luminal thrombus *before* flow restoration (angioscopy), identifying luminal thrombus *after* flow restoration (DUS, angiography), diagnosing intimal flaps (angioscopy, DUS, angiography), diagnosing residual stenoses (DUS, angiography), and diagnosing the rare patient thrombosing the operated ICA during neck closure (increasing embolisation followed by declining MCA velocities on TCD).[309]

A meta-analysis of 34 observational studies compared procedural risks in patients undergoing (*vs.* not undergoing) completion imaging after CEA (angiography = 53 218; DUS = 20 030; flowmetry = 16 812; angioscopy = 2 291). No study evaluated combination completion imaging and no RCTs have been performed. Completion angiography and DUS reduced peri-operative stroke (RR 0.83; 95% CI 0.76 — 0.91) and death (RR 0.86; 95% CI 0.76 — 0.98). Flowmetry conferred no benefit. Completion angioscopy was associated with reductions in peri-operative stroke (RR 0.48; 95% CI 0.033 — 0.68, $p = .001$).[71] ESVS recommendations regarding monitoring and QC are similar to the German-Austrian guidelines.[3] The SVS guidelines concluded there was insufficient evidence to recommend completion imaging.[4]

Recommendation 77			New
For patients undergoing carotid endarterectomy, intra-operative completion imaging with angiography, duplex ultrasound or angioscopy should be considered in order to reduce the risk of peri-operative stroke.			
Class	**Level**	**References**	**ToE**
IIa	B	Knappich *et al.* (2021)[71]	

5.1.14. Management of high internal carotid artery lesions. High bifurcation or disease extending behind the jaw poses technical challenges and increases operative risks. If DUS cannot image above the lesion, CTA/MRA must be performed to evaluate operability. Distal disease should prompt the surgeon to reconsider whether CEA remains appropriate in ACS patients. If the patient is symptomatic and the surgeon is concerned about their ability to complete the procedure, referral to a more experienced surgeon is advised. CAS is an alternative, but longer lesions increase stroke rates after CAS.[44,171] Simple measures to facilitate distal access include nasopharyngeal intubation (which opens up the angle between the mastoid process and the jaw), division of various ECA branches, and division of the posterior belly of the digastric muscle. More complex strategies, including temporomandibular subluxation, must be planned in advance as these cannot be done once CEA is under way. An alternative operative strategy (which can be used intra-operatively) involves extending the incision anterior to the ear with mobilisation of the superficial lobe of parotid.[462] This increases access to the upper ICA, but usually requires input from Ear Nose and Throat or Maxillofacial colleagues. ESVS recommendations regarding distal disease extension are similar to SVS guidelines.[4]

Recommendation 78			Unchanged
For patients undergoing carotid endarterectomy, it is recommended that the surgeon should anticipate the presence of distal disease extension pre-operatively and plan for this in advance.			
Class	**Level**	**References**	
I	C	Consensus	

5.1.15. Wound drainage. Drain placement after CEA should (in theory) prevent haematoma formation which can compromise the airway and increase peri-operative death/stroke,[137] as well as predisposing to abscess formation and patch infection. There is controversy about whether drains make a difference, with one RCT showing no difference in drain volumes or haematoma size on DUS.[463] In 47 752 CEA patients in a VQI database, 41% had drain placement. However, drains did not reduce re-interventions for neck haematoma (1% *vs.* 0.83%; OR 1.28, 95% CI 1.03 — 1.58) but were associated with

increased length of stay (2.4 *vs.* 2.1 days; OR 2.2, 95% CI 1.5 — 3.7).[153] In a meta-analysis of five observational studies (drain = 19 832; no drain = 28 465), wound drainage was associated with statistically significantly higher rates of re-exploration, *versus* no drains (OR 1.24; 95% CI 1.03 — 1.49, $p = .020$),[89] while in a VQI audit ($n = 28\,683$), wound drainage did not protect against re-operation for bleeding (OR 1.06; 95% CI 0.76 — 1.48, $p = .72$).[137] ESVS recommendations regarding wound drainage are similar to SVS guidelines.[4]

Recommendation 79			New
For patients undergoing carotid endarterectomy, selective wound drainage should be considered.			
Class	**Level**	**References**	**ToE**
IIa	B	Rivolta *et al.* (2021)[89], Smolock *et al.* (2020)[153]	

5.1.16. Ward, high dependency or intensive care post-operatively? Patients benefit from three to six hours of close neurological and intra-arterial BP monitoring in theatre recovery. Few need overnight monitoring in a high dependency unit (HDU) or intensive care unit (ICU). Most are then transferred to the vascular ward for hourly non-invasive BP and neurological monitoring for the first 24 hours (four to six hourly thereafter until discharge). Up to 40% may require treatment for post-CEA hypertension,[464] with half needing treatment in the first three post-operative hours (section 7.1.3.3). If there are no additional hypertensive surges, patients can return to the ward two to three hours later. Patients requiring ongoing i.v. hypertensive therapy should remain in theatre recovery or go to HDU/ITU for intra-arterial BP monitoring. Two hours after i.v. treatment has been completed (with no further BP surges), it is reasonable to transfer patients to the vascular ward for ongoing monitoring. Anyone suffering a major intra-operative cardiac event should be transferred to ICU or coronary care for further evaluation.

5.2. Carotid bypass

5.2.1. Indications. Carotid bypass may be indicated in the treatment of patch infection, carotid stent explantation, restenosis, or technical problems during CEA (arterial wall thinning, damage to arterial wall). Other indications include extensive atherosclerotic disease, ICA fibrosis secondary to radiotherapy, or revascularisation after *en bloc* removal of a neck tumour.[465–474]

5.2.2. Technique. There are several techniques including interposition with proximal and distal end to end anastomoses, or end to side anastomosis to the distal common carotid artery (CCA) and either end to side or end to end anastomosis to the distal ICA. The ECA can be preserved or ligated. Conduits include reversed saphenous vein (from the thigh),[466,467,470,474] PTFE,[465,466,468,469,472,474] or polyester.[471]

5.2.3. Results. Outcomes from observational studies are detailed in Table 32. Late patency of prosthetic and vein grafts appeared comparable with CEA. Late prosthetic graft infection was rare (3/987; 0.3%).

5.3. Extracranial to intracranial bypass

The rationale for extracranial to intracranial (EC-IC) bypass in patients with extracranial ICA occlusion (usually from the superficial temporal artery to the ipsilateral MCA), is that it reduces long term ipsilateral ischaemic stroke. A Cochrane review (two RCTs, 19 observational studies [$n = 2\,591$]) concluded that EC-IC bypass conferred no benefit over BMT regarding 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, $p = .25$).[475] A third RCT included patients with recently symptomatic ICA occlusion and haemodynamic impairment in the ipsilateral hemisphere.[476] The two year risk of ipsilateral stroke (including 30 day death/stroke) was 21% (95% CI 12.8 — 29.2) after EC-IC bypass, *versus* 22.7% (95% CI 13.9 — 31.6) with BMT ($p = .78$). There is currently no role for EC-IC bypass in patients with atherosclerotic ICA occlusion.

Recommendation 80			Unchanged
For recently symptomatic patients with an extracranial atherosclerotic internal carotid artery occlusion, extracranial to intracranial bypass surgery is not recommended.			
Class	**Level**	**References**	**ToE**
III	A	Fluri *et al.* (2010)[475], Powers *et al.* (2011)[476]	

Table 32. Thirty day and late outcomes following carotid bypass surgery

Author	Patients	Conduit type (*n*)	30 d death/stroke	Primary patency	Late infection
Ricco[465]	198	PTFE	1 / 198 (0.5)	98% at 10 y	0
Dorafshar[466]	31	PTFE	1 / 31 (3.2)	90% at 4 y	1/31
Roddy[468]	22	PTFE	0 / 22 (0)	95% at 2 y	0
Veldenz[469]	51	PTFE	1 / 51 (1.9)	96% at 2 y	0
Illuminati[472]	66	PTFE	0 / 66 (0)	93% at 5 y	0
Ricco[473]	42	PTFE (31), GSV (11)	0 / 42 (0)	N/A	0
Stilo[474]	13	PTFE (7), GSV (6)	0 / 13 (0)	100% at 41 mo	N/A
Koncar[471]	292	Polyester	19 / 292 (6.5)	96% at 32 mo	2/292
Dorafshar[466]	10	GSV	1 / 10 (10)	80% at 4 y	N/A
Lauder[467]	50	GSV	3 / 50 (6.0)	83% at 3 y	N/A
Branchereau[470]	212	GSV	14 / 212 (6.6)	92% at 10 y	N/A

Data are presented as *n* or *n* (%) unless stated otherwise. PTFE = polytetrafluoroethylene; GSV = greater saphenous vein; N/A = not available.

6. CAROTID ARTERY STENTING

6.1. Adjuvant medical therapy

Most operators administer 5 000 IU i.v. heparin to prevent thrombosis, plus 0.6 — 1.2 mg atropine (0.6 mg glycopyrrolate) before balloon inflation to prevent hypotension, bradycardia, or asystole.[477,478]

Recommendation 81			Changed
For patients undergoing carotid artery stenting, intravenous atropine or glycopyrrolate is recommended prior to balloon inflation to prevent hypotension, bradycardia or asystole.			
Class	**Level**	**References**	**ToE**
I	C	Gupta *et al.* (2005)[477], Trocciola *et al.* (2006)[478]	

6.2. Access routes

6.2.1. Transfemoral. Access in RCTs comparing CEA *versus* CAS was mostly via the common femoral artery (CFA), with other routes reserved for CFA disease, tortuosity, or disease of both iliac arteries and distal aorta. Unfavourable arch anatomy (type III, bovine arch) and severe atheromatous disease of the aortic arch or supra-aortic arteries increase the risk of cerebral embolisation during catheter navigation via the CFA, which has encouraged the development of alternative access strategies.

6.2.2. Transcarotid. Direct access to the proximal CCA (via a cervical incision) avoids manipulation of wires and catheters in the arch. TCAR provides cerebral protection via proximal CCA clamping plus ICA flow reversal via an extracorporeal circuit from the CCA to femoral vein[479] or ipsilateral jugular vein (allowing the stenosis to be stented during protected flow reversal) with statistically significantly fewer NIBLs (13% *vs.* 33%) after TFCAS ($p = .03$).[480] No RCTs have evaluated TCAR, but registries have reported outcomes. ROADSTER-2 enrolled 692 patients deemed 'high risk for CEA' with 99.7% technical success, despite 81% of operators being TCAR naive.[481] Procedural success (technical success without death/stroke/MI < 30 days) was 96.5%, with 30 day stroke rates of 1.9%, mortality 0.4%, MI 0.9%, and CNI 1.4%. Thirty day stroke/death was 2.3%. However, only a minority (26%) were symptomatic.[481] An SVS-VQI registry compared TCAR ($n = 638$) with TFCAS ($n = 10\ 136$) and reported that TFCAS was associated with statistically significantly higher in hospital TIA/stroke/death *versus* TCAR (OR 2.1; 95% CI 1.08 — 4.08, $p = .03$).[148] However, only 33% of the TCAR cohort were symptomatic, *versus* 42% in the TFCAS cohort ($p < .001$). A second SVS-VQI registry compared TCAR with CEA and reported fewer CNIs after TCAR (0.6% *vs.* 1.8%; $p < .001$), but no difference in hospital stroke/death (OR 1.3; 95% CI 0.8 — 2.2, $p = .28$).[152] Only 32% of the TCAR cohort were symptomatic. An SVS-VQI study developed a TCAR risk score calculator to aid patient selection, but recency of symptoms was excluded.[147] A systematic review of TCAR (18 observational studies; $n = 8\ 380$) reported low 30 day stroke rates (1.2—5.2%), MI (0—2.1%), and death (0—2.7%),[51] while another meta-analysis of 13 observational studies ($n = 837$) reported that carotid dissection following TCAR was 2% (95% CI 1 — 3).[82] Outcome data when TCAR was performed < 14 days of symptom onset are detailed in section 4.5.5.

6.2.3. Radial or brachial. RADCAR (RADial access for CARotid artery stenting) randomised 260 patients to transradial access (TRA) or TFCAS. Procedural success was 100%, with 10% crossover during TRA and 1.5% with TFCAS ($p < .05$).[35] Access complications were low (0.9% *vs.* 0.8%), as were major cardiac and/or cerebral events (0.9% *vs.* 0.8%), but radiation doses to the patient were higher with TRA.[35] In a single centre series (101 TRA; 674 TFCAS), in hospital cardiac and/or cerebral events were similar (2% *vs.* 3.6%), with a crossover of 4.9% from TRA to TFCAS.[482] Navigating from the right radial artery (RA) into the CCA (especially the left) is challenging. In a multicentre series ($n = 214$) undergoing TRA CAS, distal filter deployment was not possible in 7%, while proximal protection was not possible in 1.6%.[483] A meta-analysis of seven observational studies involving 723 ACS and SCS patients undergoing TRA CAS, reported minor stroke/TIA in 1.9% (95% CI 0.6 — 3.8), major stroke rate 1.0% (95% CI 0.4 — 1.8) and RA occlusion rates of 5.9% (95% CI 4.1 — 8.0).[64]

Recommendation 82			New
For patients selected to undergo carotid artery stenting, transradial or transcarotid artery revascularisation should be considered as an alternative to transfemoral carotid artery stenting, especially where transfemoral access may confer a higher risk of complications.			
Class	**Level**	**References**	**ToE**
IIa	B	Ruzsa *et al.* (2014)[35], Jaroenngarmsamer *et al.* (2020)[64], Malas *et al.* (2019)[148], Kashyap *et al.* (2020)[481], Mendiz *et al.* (2016)[482], Montorsi *et al.* (2016)[483]	

6.3. Wires, catheters, and stent design

Access to the CFA, brachial, or RA is secured and a .035" hydrophilic guide wire used to access the CCA. Long sheaths (6 — 8 Fr) or guiding catheters secure a stable position in the CCA, typically after exchange of a .035" support wire in the ECA. For stent placement and balloon angioplasty (requiring rapid exchange systems) .014" floppy tip guide wires are advised.

6.3.1. Carotid stent design. Carotid stent design is summarised in Table 33 as open cell (more flexible, suited for tortuous anatomy), closed cell (more rigid, better plaque coverage), or hybrid (closed cell in middle, open cell at the edges).

There are conflicting data regarding open *versus* closed cell stents. Two small RCTs reported no outcome differences,[484,485] although NIBLs were more common with open cell stents ($p = .020$).[485] A CSTC meta-analysis ($n = 1\ 557$) reported that open cell stents incurred statistically significantly higher 30 day stroke/death (10.3% *vs.* 6%) than closed cell (RR 1.7; 95% CI

Table 33. Characteristics of open cell, closed cell, and hybrid design stents

Characteristic	Open-cell	Closed-cell	Hybrid design
Free cell area	Large	Small	Mid segment: small; edges: large
Strut interconnections	Few	Many	Mid segment: many; edges: few
Flexibility	Good	Limited	Moderate
Plaque coverage	Limited	Good	Good

1.23 — 2.52, $p = .002$) after adjusting for age and symptom status.[108] However, after the peri-operative period, late stroke risks are similar (HR 0.78; 95% CI 0.35 — 1.75).[33] In the German CAS registry ($n = 13\,086$) there was a non-statistically significant trend towards lower in hospital stroke/death with closed cell stents (RR 0.86; 95% CI 0.65 — 1.14, $p = .30$),[141] while in an SVS-VQI registry (1 384 closed cell *vs.* 1 287 open cell), multivariable analyses revealed that closed cell stents were associated with higher stroke/death when deployed across the bifurcation (OR 5.5; 95% CI 1.3 — 22.2, $p = .020$).[123] In a meta-regression analysis ($n = 46\,728$), open cell stents were associated with statistically significantly higher 30 day death/stroke and NIBLs (RR 1.25; $p = .030$), with no differences regarding re-stenosis, stent fracture, or intraprocedural haemodynamic depression.[53]

Dual layer mesh covered stents (DLS) combine the close vessel wall apposition of open cell stents (soft nitinol outer layer) and prevention of plaque prolapse associated with closed cell stents (micromesh inner layer with very small cell size). A small RCT ($n = 104$ with lipid rich plaques) reported that proximal protection reduced MES by 76—83% *versus* distal filter protection ($p < .001$), while DLS reduced MES by 13—29% *versus* closed cell stents ($p = .02$).[483] A meta-analysis of four observational studies revealed one year death/stroke rates of 3.8% with DLS and 2.1% re-stenosis.[98] A Japanese study enrolled 140 DLS patients (39% SCS), reporting that the risk of peri-operative death/stroke/MI and/or ipsilateral stroke at one year was 1.4%. Outcomes were similar irrespective of age, CEA risk, and presentation.[486] Caution should be exercised if considering DLS in acute stroke treatment, as a registry has reported higher rates of acute stent thrombosis with DLS (45% *vs.* 3.7%) than with single layer stents ($p = .001$).[487]

Recommendation 83 — New

For patients undergoing carotid artery stenting, decisions regarding stent design (open cell, closed cell) should be considered at the discretion of the operator.

Class	Level	References	ToE
IIa	B	de Vries *et al.* (2019)[53], Faateh *et al.* (2021)[123], Knappich *et al.* (2017)[141]	

Recommendation 84 — New

For patients undergoing elective carotid artery stenting, dual layer mesh covered stents may be considered.

Class	Level	References	ToE
IIb	C	Imamura *et al.* (2021)[486]	

6.4. Pre-dilation and post-dilation

Pre-dilation of the target lesion facilitates advancement of distal protection systems and stent catheters, as well as allowing stent expansion, which is also the aim of post-dilation. Pre-dilation is generally avoided unless the stent or protection device cannot cross a tight lesion. Severe calcification (circumferential or exophytic) is a contraindication to CAS because of high procedure failure rates.[172] Pre- and post-dilation may also cause embolisation and vessel injury. In a CSTC meta-analysis ($n = 1\,557$), 30 day death/stroke was unaffected by pre-dilation (RR 0.96; 95% CI 0.67 — 1.44, $p = .92$) or post-dilation (RR 0.87; 95% CI 0.47 — 1.62, $p = .67$).[108] However, another meta-analysis (six observational studies [$n = 4\,652$]) reported greater haemodynamic instability when post-dilation was performed (OR 1.69; 95% CI 1.14 — 2.56).[113] Single *versus* double dilation was associated with statistically significantly fewer neurological events (RR 0.67; 95% CI 0.47 — 0.97, $p = .030$), as was less aggressive pre-dilation (balloon diameter < 5 mm) compared with > 5 mm balloons (RR 0.27; 95% CI 0.09 — 0.86, $p = .026$). In a series of 255 ACS and SCS patients, primary stenting (without pre- or post-dilation), was associated with a 1.2% 30 day risk of death/stroke.[488] In an SVS-VQI audit, primary stenting was associated with similar 30 day stroke/death *versus* CAS with pre- and/or post-dilation (OR 1.15; 95% CI 0.72 — 1.83, $p = .55$).[131]

Recommendation 85 — New

For patients undergoing carotid artery stenting, when pre-dilatation is planned, balloon diameters <5 mm should be considered in order to reduce the risk of peri-procedural stroke or transient ischaemic attack.

Class	Level	References	ToE
IIa	C	Ziapour *et al.* (2020)[113]	

Recommendation 86 — New

For patients undergoing carotid artery stenting, post-dilatation is not recommended when the residual stenosis is <30%, in order to reduce haemodynamic instability.

Class	Level	References	ToE
III	B	Ziapour *et al.* (2020)[113]	

6.5. Cerebral protection devices

The role of cerebral protection devices (CPDs) is controversial, despite embolic material being regularly retrieved from filters.[489] In a meta-analysis of 13 RCTs and 193 registries ($n = 54\,713$), 22 studies ($n = 11\,655$) reported lower

peri-operative stroke/death favouring CPDs (OR 0.57; 95% CI 0.43 − 0.76, $p < .01$).[490] However, a CSTC meta-analysis of three RCTs ($n = 1\,557$) reported that CPDs did not reduce 30 day stroke/death (RR 1.1; 95% CI 0.71 − 1.70, $p = .67$).[108] The German National registry ($n = 13\,086$) observed that CPDs were associated with lower rates of major stroke/death (RR 0.60; 95% CI 0.43 − 0.84) and any stroke (RR 0.57; 95% CI 0.43 − 0.77).[141] An SVS-VQI audit ($n = 10\,074$) also reported higher 30 day stroke/death when CPDs were not used (OR 3.97; 95% CI 2.47 − 6.37).[131]

Proximal CPDs protect the brain by reversing blood flow in the bifurcation during stenting (section 6.2.2). Proximal CPDs should, however, be avoided in patients with severe ECA or CCA disease.[491] The best CAS results in RCTs involving asymptomatic patients were reported by CREST-1 and ACT-1, where CPDs were mandatory and practitioners were trained in their use.[224,316] Contradictory reports have led to conflicting opinions among CAS practitioners, with some claiming CPDs are unnecessary, while others would never perform unprotected CAS. Given the lack of RCTs, ESVS recommendations are based on a consensus among CAS practitioners that CPDs should be considered when performing CAS. ESVS recommendations regarding access for CAS, protection devices, and pre- and post-dilation are similar to the 2021 SVS guidelines.[4]

Recommendation 87 — Unchanged

For patients undergoing carotid artery stenting, cerebral protection systems should be considered.

Class	Level	References	ToE
IIa	C	Rosenfield *et al.* (2016)[224], Brott *et al.* (2010)[316], Touze *et al.* (2009)[490]	

Recommendation 88 — New

For patients undergoing carotid artery stenting, decisions regarding choice of cerebral protection (filter, proximal flow reversal) should be considered at the discretion of the operator.

Class	Level	References	ToE
IIa	B	Wodarg *et al.* (2018)[108], Hicks *et al.* (2018)[131], Knappich *et al.* (2017)[141], Rosenfield *et al.* (2016)[224], Brott *et al.* (2010)[316], Touze *et al.* (2009)[490]	

Recommendation 89 — Unchanged

For patients undergoing carotid artery stenting, it is not recommended to deploy proximal cerebral protection devices in patients with advanced common carotid disease or external carotid artery disease (if an occlusion balloon is to be positioned in the external carotid artery) or in patients with contralateral occlusion and insufficient collateralisation.

Class	Level	References	ToE
III	C	Cremonesi *et al.* (2015)[491]	

6.6. Hospital and individual operator volumes

Low volume hospitals (< 20 CAS/year) had a statistically significantly higher 30 day stroke rate than higher volume hospitals (HR 1.5; 95% CI 1.06 − 2.12, $p = .023$).[132] In a Healthcare Cost and Utilisation Project, higher CAS volumes were associated with lower mortality/morbidity, shorter length of stay, and reduced hospital costs.[492] In a 'high risk for CEA' registry, a lifetime experience of 72 procedures was required to achieve 30 day death/stroke rates < 3% in non-octogenarian ACS patients.[493] Thirty day mortality in Centre for Medicare and Medicaid beneficiaries was higher if practitioners performed fewer than six CAS a year *versus* > 24 (OR 1.9; 95% CI 1.4 − 2.7, $p < .001$).[494] In a single centre series ($n = 2\,124$), a lifetime experience of > 100 interventions was associated with fewer peri-operative strokes (OR 0.81; 95% CI 0.67 − 0.95), while < 50 procedures was a predictor for increased peri-operative stroke ($p < .001$).[495]

A CSTC meta-analysis of three European RCTs ($n = 1\,557$ SCS patients) reported that 30 day death/stroke was not influenced by lifetime CAS experience,[496] but 30 day death/stroke was higher with lower volume operators (≤ 3.2 CAS/year) *versus* higher volume operators (> 5.6 CAS/year) (OR 2.3; 95% CI 1.36 − 3.87).[496] CSTC concluded that a minimum of six CAS procedures per year was necessary to remain competent.[496] However, others advise that in an era of low CAS volumes, 25 lifetime procedures is reasonable to achieve competency, plus 10 − 15 procedures annually.[497] A 2021 audit from Australia and New Zealand ($n = 1\,350$) demonstrated higher peri-operative stroke/death rates with lower volume CAS operators (2.63% for operators doing < 11 annual cases) *versus* 0.37% for operators performing ≥ 12 cases annually (OR 6.11; 95% CI 1.27 − 29.33, $p = .024$).[128] In the CHOICE registry ($n = 5\,841$), operator volume (but not hospital volume) was an independent predictor of 30 day death/stroke/MI, with a 5% increase in adverse outcomes per additional month between consecutive CAS procedures (OR 1.05; 95% CI 1.02 − 1.09, $p = .005$).[498] SVS guidelines made no recommendation regarding annual CAS volumes, but the German-Austrian guidelines advised that CAS should only be performed in hospitals performing > 10 CAS procedures per year.[3]

Recommendation 90 — New

For patients undergoing transfemoral carotid stenting, at least twelve carotid stent procedures per year (per operator) may be considered an appropriate operator volume threshold in order to maintain optimal outcomes.

Class	Level	References	ToE
IIb	C	Giurgius *et al.* (2021)[128], Badheka *et al.* (2014)[492], Shishehbor *et al.* (2014)[498]	

7. COMPLICATIONS AFTER CAROTID INTERVENTIONS

7.1. Peri-operative

7.1.1. Stroke after carotid endarterectomy

7.1.1.1. Intra-operative. Intra-operative stroke is a new neurological deficit (worsening of pre-existing deficit), apparent following recovery from anaesthesia (or during CEA under LRA), lasting > 24 hours. Most follow intra-operative embolisation (carotid mobilisation, shunt insertion, flow restoration, accumulation of thrombus on endarterectomy zone). A minority (20%) are haemodynamic after carotid clamping or shunt malfunction.[499] In a 21 year audit (n = 2 300), most intra-operative strokes followed embolisation of luminal thrombus at flow restoration, with the source being bleeding from transected vasa vasorum onto the endarterectomised surface.[309] One advantage of CEA under LRA is that the timing of new deficits can be accurately determined. For patients undergoing CEA under GA, abrupt EEG changes predict the likeliest time of onset.[500] Patients with a triad of hemiplegia, homonymous hemianopia, and higher cortical dysfunction on recovery from anaesthesia are likely to have suffered ICA or MCA occlusion. If one to two triad components are present, occlusion of one or more MCA branches is likely.[501]

Previously, patients recovering from anaesthesia with a new neurological deficit underwent immediate re-exploration to exclude thrombus within the endarterectomy zone. This remains the recommendation in the 2021 SVS guidelines.[4] However, a recent Delphi consensus study concluded that immediate re-exploration remained appropriate in patients experiencing a new deficit when flow was restored with CEA under LRA, but in all other peri-operative phases, rapid imaging of carotid vessels and brain was advised before re-exploration.[502] In ACST-1, there was no difference in rates of disabling/fatal stroke between patients who underwent immediate re-exploration *versus* those who did not.[503] The priority, therefore, is to quickly identify patients with ICA thrombosis, as they will benefit from immediate re-exploration. TCD aids decision making, as MCA velocities with ICA thrombosis are identical to those during carotid clamping. Thrombosis is also preceded by increasing rates of embolisation.[309] DUS can confirm flow in the endarterectomy zone, but subcutaneous air makes it difficult to interpret early post-operative findings. At re-exploration, thrombus should be removed. If thrombus extends distally, it should be carefully removed with a Fogarty catheter. Following thrombectomy, technical errors are corrected, and a completion angiogram performed. Embolic occlusion of the ipsilateral anterior or middle cerebral artery can be treated by re-exploration (to remove thrombus in the endarterectomy zone) followed by intra-arterial thrombolysis.[504] Emergency MT is another option in patients with embolic MCA mainstem occlusion. No RCTs have been done, but targeted intra-operative neuromonitoring (TCD, EEG) and QC assessment (completion angioscopy, DUS, angiography) have been associated with significant reductions in intra-operative stroke.[71,309,500,505]

7.1.1.2. Post-operative. This is defined as a new neurological deficit (or worsening of a pre-existing deficit) after an uneventful recovery from anaesthesia, with symptoms lasting > 24 hours. In the first six hours, the most common cause is ICA thrombosis or embolism from mural thrombus in the endarterectomy zone. A Delphi consensus recommended rapid imaging before re-exploration.[502] After six hours, CT and extracranial and intracranial CT/CTA will exclude ICA thrombus, cerebral oedema, or parenchymal haemorrhage. In ICSS, the commonest cause of post-operative stroke was hyperperfusion syndrome (HS).[385] HS is discussed in more detail in section 7.1.3.5.

7.1.1.3. Predictors of stroke after carotid endarterectomy. In ECST, predictors included (i) female sex (10.4% *vs.* 5.8%, p = .001); (ii) PAD (12.0% *vs.* 6.1%, p = .001); (iii) pre-operative SBP (< 120 mmHg = 3.4%; 121 − 159 = 6.5%; 160 − 180 = 7.7%; > 180 mmHg = 13.0%, p = .040); and (iv) presentation (retinal [3.2%], hemispheric stroke [6.3%], TIA [9.1%], p = .006).[352] Predictive features in NASCET were (i) hemispheric *versus* retinal events (6.3% *vs.* 2.7%; OR 2.3; 95% CI 1.1 − 5.0); (ii) left *versus* 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 *versus* smooth plaques (5.5% *vs.* 3.7%; OR 1.5, 95% CI 1.1 − 2.3).[506] In ICSS, stroke was more frequent in females (RR 1.98; 95% CI 1.02 − 3.87, p = .05) and with increased DBP (RR 1.30 per +10 mmHg; 95% CI 1.02 − 1.66, p = .04), but unrelated to CEA method or GA *versus* LRA.[507] In a multivariable model, increased DBP was the only independent predictor of stroke, MI, or death.[507] In ACST-1, DBP was also an independent predictor for stroke.[13]

Recommendation 91			New
For patients experiencing a peri-operative stroke, it is recommended to differentiate between an intra-operative and a post-operative stroke.			
Class	**Level**	**References**	**ToE**
I	C	Meershoek *et al.* (2021)[502]	

Recommendation 92			New
For patients who develop an ipsilateral neurological deficit after flow is restored following carotid clamp release when carotid endarterectomy is performed under locoregional anaesthesia, immediate re-exploration of the carotid artery is recommended.			
Class	**Level**	**References**	**ToE**
I	C	Meershoek *et al.* (2021)[502]	

7.1.2. Stroke after carotid artery stenting.

In a meta-analysis of SCS patients in RCTs, the risk of stroke on the day of CAS was 4.7% with an additional 2.5% during days 1 − 30. Most were ischaemic (94%), with 91% ipsilateral to the stented ICA.[48] Important causes include embolisation, in stent thrombosis, ICA/CCA dissection, HS, and ICH.

Prevention of embolic stroke is a role for CPDs (section 6.5), but embolism can still occur as a result of incomplete deployment, malpositioning, or incomplete aspiration of debris. If a neurological deficit occurs during CAS, no additional imaging is required prior to MT or intra-arterial TT. In patients developing a stroke after CAS, the usual rules of acute stroke management should be followed, which includes ICH exclusion (and other stroke mimics) and assessment of cerebral perfusion.

Treatment options in patients developing a new neurological deficit during CAS include MT with or without intra-arterial TT. Mechanical removal of embolic material from the distal ICA out to the distal M2 MCA segment is possible using dedicated neuro-interventional retrieval devices.[508] Accordingly, most interventionists now advocate MT in CAS patients suffering acute stroke as a result of ICA or M1/M2 MCA branch occlusions. Intra-arterial TT is less effective in acute stroke during CAS as the embolus usually comprises plaque, rather than fibrin clot. In patients with acute stent thrombosis, TT should be considered with rTPA delivered as a 5 mg bolus, followed by slow infusion (maximum dose 20 mg), ensuring the catheter remains positioned within the thrombus. If the thrombus dissolves, the microcatheter tip is advanced into the remaining thrombus. Selective intra-arterial administration of 5 mg abciximab followed by an i.v. bolus of 5 mg abciximab has been effective in treating distal embolisation during CAS.[508] While no RCTs have addressed the treatment of acute stroke caused by ICA thrombosis, or M1/M2 embolic branch MCA occlusions, management should be no different to stroke occurring without a prior carotid intervention. It would be preferable that, in the future, a neuro-interventional service is available in any institution performing CAS.

Recommendation 93		New
For patients who develop an ipsilateral or contralateral stroke at any time period following carotid endarterectomy or carotid artery stenting, urgent diagnostic neurovascular imaging of both carotid arteries and the brain is recommended.		
Class	**Level**	**References**
I	C	Consensus

7.1.2.1. Predictors of stroke after carotid stenting. A Delphi consensus identified anatomical features associated with increased difficulty for CAS novices including (i) type III arch (where the vertical distance between the brachiocephalic artery origin and top of the arch exceeds two left CCA diameters); (ii) bovine arch (where the brachiocephalic artery shares a common origin with the left CCA); (iii) severe arch atheroma; (iv) diseased or occluded ECA; (v) angulated distal ICA (severity not specified); (vi) long stenoses; and (vii) pinhole stenoses.[509] The Delphi Anatomical Risk score was validated in 883 CAS patients and a score in the highest quartile was an independent predictor for stroke/TIA (OR 3.79; 95% CI 1.7 − 8.3, $p = .001$).[168] However, in ICSS there was no correlation between the Delphi Anatomical Risk score and peri-operative stroke.[13] In CREST, plaque features associated with increased stroke risk after CAS included plaque length $>$ 13 mm or sequential lesions extending remotely from the ICA stenosis.[171] However, in an ICSS-MRI substudy, none of the CREST plaque features were associated with higher rates of NIBLs on MRI.[510] In ICSS, features associated with statistically significantly higher rates of NIBLs included arch type II/III (OR 2.8; 95% CI 1.1 − 7.1, $p = .027$) and a greater ICA angle ($\geq 60^\circ$ *vs.* $< 60^\circ$; OR 4.1, 95% CI 1.7 − 10.1, $p = .002$).[32]

In a CSTC meta-analysis (section 2.3.5), CAS incurred higher rates of death/stroke (*vs.* CEA) in the first seven days after symptom onset (8.3% *vs.* 1.3%; RR 6.7, 95% CI 2.1 − 21.9).[170] In a propensity matched analysis involving octogenarians undergoing CEA or CAS, urgent interventions (OR 2.12; 95% CI 1.68 − 2.69, $p < .001$), COPD (OR 1.52; 95% CI 1.11 − 2.09, $p = .009$), and ASA grade $>$ 3 (OR 1.46; 95% CI 1.15 − 1.86, $p = .002$) were independent predictors of post-operative stroke.[120] ICSS reported that CAS patients with an age related white matter change (ARWMC) score $\geq$ 7 on CT/MRI had higher rates of peri-operative stroke, *versus* patients whose ARWMC score was $<$ 7 (HR 2.76; 95% CI 1.17 − 6.51, $p = .021$). There was no association between ARWMC score and stroke after CEA (HR 1.18; 95% CI 0.4 − 3.55, $p = .76$).[173] CAS was associated with statistically significantly higher rates of peri-operative stroke (*vs.* CEA) if the ARWMC score was $>$ 7 (HR 2.98; 95% CI 1.29 − 6.93, $p = .011$), with no difference between CEA and CAS when the ARWMC score was $<$ 7.[173] Of interest, a high ARWMC score was also associated with silent cerebral embolisation during transcatheter aortic valve implantation.[511]

7.1.3. Haemodynamic instability

7.1.3.1. Post-endarterectomy hypotension. Post-CEA hypotension is attributed to exposure of carotid sinus baroreceptors to the pulse pressure, without the dampening effect of the excised plaque.[512] Its relevance is variable, with some reporting increases in peri-operative stroke/MI,[513] while others consider it a benign phenomenon.[512] There is no consensus regarding what BP threshold should be used for treatment. Management of post-CEA hypotension is the same as for CAS.

7.1.3.2. Post-stenting hypotension. In a meta-analysis of 27 observational studies ($n = 4\,204$), 12% of CAS patients were treated for hypotension, 12% for bradycardia, while 13% had treatment for both. Persistent haemodynamic instability (more than one hour vasopressor support) affected 19% of CAS patients.[514] There was a noteworthy association between persistent haemodynamic depression after CAS and a history of ipsilateral CEA,[514] calcification, involvement of the carotid bulb, severe stenosis, eccentric plaque,[515,516] and nitinol stents,[515] although the latter was not corroborated in a meta-analysis of two RCTs and 66 cohort studies ($n = 46\,728$).[53] Avoiding post-dilation was protective against persistent haemodynamic depression in a meta-analysis of six cohort studies involving 4 652 patients (RR

0.59; 95% CI 0.39 − 0.87, $p = .030$).[113] Meta-analysis of 27 observational studies ($n = 4\ 204$) suggested no differences in peri-operative stroke in CAS patients with or without haemodynamic instability (OR 1.0; 95% CI 0.57 − 1.75).[514]

Preventing haemodynamic instability during CAS involves hydration, withholding antihypertensive medications on the morning of CAS, continuous ECG/BP monitoring, and venous access. Glycopyrrolate (synthetic atropine derivative) was compared with atropine in a retrospective study ($n = 115$) and was more effective in preventing post-operative bradycardia (30% *vs.* 72%, $p = .002$), and hypotension (2.5% *vs.* 36%, $p = .001$), with lower rates of compensatory hypertension (2.5% *vs.* 16%, $p = .047$).[517] Treatment of hypotension includes i.v. crystalloid and volume expanders, but this may be inadequate because of decreased peripheral vascular resistance with loss of sympathetic tone, rather than hypovolaemia. Titrated i.v. vasopressors (norepinephrine, dobutamine, phenylephrine) may be necessary to maintain SBP $>$ 90 mmHg. Major adverse events (MI, dysrhythmia, cardioversion) were more common in patients receiving dopamine *versus* norepinephrine/phenylephrine ($p = .040$). Midodrine (selective α-1 agonist) causes arteriolar and venous vasoconstriction without stimulating cardiac β adrenergic receptors and is as effective as dopamine for treating hypotension after CAS.[518]

7.1.3.3. Post-endarterectomy hypertension. Post-CEA hypertension can affect up to two thirds of patients, depending on its definition.[464] Causes include carotid bulb denervation and increased norepinephrine and/or renin production.[519–521] Post-CEA hypertension is associated with pre-operative hypertension,[464,522] GA,[523] and eCEA.[458] The association between GA and post-CEA hypertension is attributed to increased neuroendocrine stress hormone levels, while the association with eCEA is attributed to carotid bulb denervation.[524] In a meta-analysis of six observational studies, patients undergoing eCEA were more likely to require vasodilator therapy in the early post-operative period than those undergoing cCEA (OR 2.75; 95% CI 1.82 − 4.16).[458] However, evidence suggests that (in the long term) there is no statistically significant difference in BP measurement between eCEA and cCEA.[42] In a prospective study ($n = 100$), poorly controlled pre-operative BP and impaired baroreceptor function (but not impaired autoregulation) were associated with post-CEA hypertension.[464] Intra-operative predictors include poorly controlled or labile hypertension at induction of anaesthesia. No other variable (including magnitude of MCA velocity increase with flow restoration) was predictive of post-CEA hypertension.[525] Poorly treated post-CEA hypertension is associated with increased rates of post-operative TIA/stroke[309,522,526] and is a risk factor for neck haematoma, HS, and ICH.[309,527] There are various published strategies for when and how to treat post-CEA hypertension[309,528] but because units tend to adopt different thresholds for intervening, it is difficult to define a consensus treatment protocol. However, it is important that units performing CEA/CAS have written guidance for the treatment of post-CEA hypertension,[309,528] so that management decisions are not delayed.

7.1.3.4. Post-stenting hypertension. Post-CAS hypertension required treatment in 9.9% of CAS patients in an SVS-VQI database and was associated with higher rates of stroke/death (OR 3.39; 95% CI 2.3 − 5.0, $p < .001$). The management of post-CAS hypertension is the same as for CEA.

7.1.3.5. Hyperperfusion syndrome. There are no consensus criteria for diagnosing HS, which affects 1% of CEA and 3% of CAS patients.[529,530] HS may be characterised by headache, confusion, atypical migraineous phenomena, seizures, hypertension, decreased consciousness, nausea and vomiting, and (ultimately) a neurological deficit, which can be due to vasogenic oedema, ischaemia, or haemorrhage.[529] The average time of symptom onset is 12 hours post-operatively, although it can occur up to four weeks later.[63,531] MRI typically shows vasogenic oedema (not always located in the ipsilateral carotid territory) with evidence of perfusion within the oedema (i.e., this is not an evolving ischaemic infarct[532]). Other MRI features include hyperintense signal change on T2 weighted and fluid attenuated inversion recovery (FLAIR) MRI, without restricted diffusion on DWI. There may also be a high T1 signal with hyperacute haemorrhage.

Pathophysiological mechanisms include impaired baroreceptor function and disturbances to the trigeminovascular reflex. Female sex, older age, chronic kidney disease, and a treated left carotid artery were associated with HS after CAS.[129] Impaired CVR increased the risk of HS after CAS, while hypertension and a significant contralateral stenosis (both risk factors for HS after CEA) and male sex did not.[63] Risk factors for HS after CEA include female sex, recent major stroke, CAD, and a contralateral stenosis $\geq$ 70%.[161] Several imaging modalities have been proposed as predictors for HS including TCD, SPECT, near infrared spectroscopy, perfusion CT, and quantitative MRA. However, TCD is probably the most reliable, with studies suggesting that 99% of patients with increases in mean MCA velocity $<$ 100% at 24 hours (compared with baseline) did not develop HS.[533]

HS associated ICH appears more common after CAS than CEA,[63,134] possibly because CAS is associated with intra-procedural hypotension followed by compensatory hypertension, which may persist beyond discharge and also because CAS patients are routinely prescribed DAPT.[63,134] In a meta-analysis of 41 observational studies ($n = 28\ 956$) hypertension and ipsilateral high grade stenosis were risk factors for ICH after both CEA and CAS.[45] Untreated HS progresses through regional vasogenic oedema to petechial haemorrhages then ICH.[531] Any patient with suspected HS should have elevated BP reduced urgently (section 7.1.3.3), while seizures should be controlled with appropriate anti-epileptic drugs. ESVS recommendations regarding the management of post-intervention hypotension, hypertension, and HS are similar to the 2021 SVS and German-Austrian guidelines.[3,4]

Recommendation 94			Unchanged
For patients with post-carotid hypotension, administration of intravenous crystalloids and volume expanders should be considered as first line treatment. If this fails to improve blood pressure, titrated intravenous vasopressors should be considered to maintain systolic blood pressure >90 mmHg.			
Class	**Level**	**References**	**ToE**
IIa	C	Chung *et al.* (2010)[517], Sharma *et al.* (2008)[518]	

Recommendation 95		Unchanged
For patients undergoing carotid interventions, regular blood pressure monitoring is recommended for the first 3–6 hours after carotid endarterectomy, as well as in carotid stent patients who develop haemodynamic instability during the procedure.		
Class	**Level**	**References**
I	C	Consensus

Recommendation 96		Unchanged
For carotid stenting patients who develop haemodynamic instability during the procedure, regular blood pressure monitoring is recommended for the first 24 hours after carotid revascularisation.		
Class	**Level**	**References**
I	C	Consensus

Recommendation 97			Unchanged
In centres performing carotid interventions, it is recommended that they have written criteria for treating post-procedural hypertension.			
Class	**Level**	**References**	**ToE**
I	C	Naylor *et al.* (2013)[309]	

7.1.4. Wound haematoma after carotid endarterectomy. Most neck haematomas occur in the first six hours post-operatively, usually following untreated hypertension.[527] In a meta-analysis of six RCTs ($n = 2\,988$), 2.2% (95% CI 1.2 — 3.9) developed a haematoma requiring re-exploration.[48] In GALA, the incidence of haematoma needing re-operation was 2.6% under GA *versus* 2.3% under LRA ($p =$ ns).[436] In an SVS-VQI registry ($n = 72\,787$), eCEA was an independent risk factor for re-exploration for neck haematoma (OR 1.4; 95% CI 1.1 — 1.7, $p = .002$).[154] In another SVS-VQI audit ($n = 28\,683$), re-exploration for neck haematoma was associated with statistically significantly higher in hospital risks *versus* patients not re-explored (stroke: 3.7% *vs.* 0.8%, $p < .001$; MI: 6.2% *vs.* 0.8%, $p < .001$; death: 2.5% *vs.* 0.2%, $p < .001$; stroke/death: 5.0% *vs.* 0.9%, $p < .001$).[137] The effect of combination APRx on neck haematoma after CEA is discussed in section 4.2.2.4, while the role of protamine in reducing re-exploration for neck haematoma is discussed in section 5.1.8. Recommendations regarding wound drains are in section 5.1.15. ESVS recommendations regarding the management of neck haematoma are similar to the 2021 SVS and German-Austrian guidelines.[4]

Recommendation 98		Unchanged
In a patient who develops a post-operative neck haematoma in association with stridor or tracheal deviation, immediate re-exploration is recommended.		
Class	**Level**	**References**
I	C	Consensus

7.1.5. Cranial nerve injury. Cranial nerve injury (CNI) refers to partial or total loss of function of one or more of the 12 cranial nerves. In a meta-analysis of 7 535 patients in 13 RCTs, CNI after CAS was 0.5% (95% CI 0.3 — 0.9) *vs.* 5.4% (95% CI 4.7 — 6.2) after CEA (OR 0.07; 95% CI 0.04 — 0.1).[48] In ICSS, CNI occurred in 5.5% of patients, but only 1.3% had symptoms at 30 days and only one patient (0.12%) had a disabling CNI six months after CEA.[534] In CREST, CNI was observed in 4.6% after CEA. Overall, one third resolved in < 30 days, with 81% resolving in less than one year. CNI impacted on swallowing at two to four weeks, but not thereafter.[535] In a meta-analysis of four RCTs and 22 observational studies ($n = 16\,749$), CNIs affected the RLN (4.2%), hypoglossal (3.8%), mandibular branch of facial nerve (1.6%), glossopharyngeal (0.2%), and the spinal accessory (0.2%), with CNI prevalence declining over the last 30 years.[536] CNI predictors include urgent procedures, re-exploration for bleeding or neurological deficit,[536] GA (OR 1.68; 95% CI 1.19 — 2.39),[130] previous neck radiation,[56] and redo CEA (OR 13.61; 95% CI 5.43 — 34.16).[102]

7.1.6. New post-operative ischaemic brain lesions. In ICSS, a subgroup ($n = 161$) underwent DWI-MRI pre-operatively, with a second MRI scan one to three days post-operatively and a third at 27 — 33 days to evaluate the incidence of NIBLs.[537] Sixty two of 124 CAS patients (50%) and 18/107 CEA patients (17%) had at least one NIBL at the first post-operative scan (OR 5.21; 95% CI 2.78 — 9.79, $p < .001$). At one month, there were persisting FLAIR-MRI changes in 28/86 CAS patients (33%) *versus* 6/75 (8%) after CEA (OR 5.93; 95% CI 2.25 — 15.62, $p < .001$).[537] In a meta-analysis (two RCTs, 18 observational studies), NIBLs were more common after CAS *versus* CEA (40% *vs.* 12%; OR 5.17, 95% CI 3.31 — 8.06, $p < .001$).[538] In a meta-analysis of two RCTs and 44 observational studies ($n = 5\,018$), predictors for NIBLs after CEA included prior TIA/stroke, impaired CVR, and raised inflammatory markers. Predictors for NIBLs after CAS included increasing age, plaque vulnerability, and complex carotid and aortic arch anatomy.[92] In a third meta-analysis (five RCTs, three observational studies [$n = 357$]), proximal protection *versus* filter CPDs was associated with fewer NIBLs.[98]

The clinical relevance of NIBLs is unclear. In carotid RCTs, there was no evidence of any association with cognitive impairment,[48] possibly because cohorts were too small. The NeuroVISION study, which reported the incidence and significance of NIBLs after non-cardiac surgery in 1 114 patients (but not including CEA patients), observed that 7% developed NIBLs, of whom 42% developed cognitive impairment at one year *versus* 29% in patients with no NIBLs (HR 1.98; 95% CI 1.22 − 3.2).[166] In ICSS, five year recurrent stroke/TIA was 22.8% in patients with NIBLs *versus* 8.8% in patients without NIBLs (HR 2.85; 95% CI 1.05 − 7.72, $p = .040$).[167] NeuroVISION also reported increased rates of stroke/TIA at one year in patients with NIBLs (HR 4.13; 95% CI 1.14 − 14.99).[166] ICSS concluded that NIBLs may be a marker of recurrent cerebrovascular events and that patients may benefit from more aggressive and prolonged combination APRx,[167] although this has not been tested in RCTs. In future, NIBLs might become a surrogate endpoint in carotid intervention trials as they have a plausible biological relationship with stroke.[92] A meta-analysis of nine RCTs and 76 observational studies ($n = 6\ 970$) concluded that for an underlying 3% ARR in procedural stroke among revascularisation techniques, a 90% sample size reduction could be achieved if NIBLs were used, instead of 30 day death/stroke.[104] No guidelines have made any recommendations about the prevention or management of NIBLs.

7.2. Late complications

7.2.1. Prosthetic patch and stent infection. Patch infection complicates 1% of CEAs.[74,106,539–541] About half present within three months of CEA (abscess/neck mass), with 55% presenting after more than six months (usually with a draining sinus).[542] Patch rupture or anastomotic dehiscence with pseudoaneurysm formation is relatively rare (11%), and mostly occurs in the first three months.[74,106,540–542] *Staphylococci* and *Streptococci* are the infecting organism in 90% of cases, with *S. aureus* predominating in early infections and *S. epidermidis* in later infections.[74,106,539–542] Antibiotic therapy should be determined by an MDT approach, based on likely micro-organisms in the absence of cultures. DUS (first line) may reveal patch corrugation (can precede overt infection by 11 months[543]), deep collections, or pseudo-aneurysm formation. DUS should be followed by CTA/MRI in patients being considered for re-exploration.

Conservative therapy is not advised in fit patients, because of the high risk of secondary haemorrhage or tracheal compression following anastomotic dehiscence or wall necrosis.[544] It is helpful to review the original operation note to establish whether the patient developed ipsilateral neurological symptoms, coma, or seizures during carotid clamping (if CEA was performed under LRA) or had EEG/SSEP abnormalities or MCA velocities < 15 cm/sec on TCD during clamping under GA. If the answer is "YES" to any of these, the patient is highly likely to suffer a stroke should ligation or endovascular coil embolisation of the carotid artery become necessary.[542] Patch excision with autologous reconstruction (vein patch, bypass) remains the gold standard.[74,106,539,542,544] Reconstruction with prosthetic material should be avoided because of high reinfection rates.[542] Limited case reports ($n = 18$), but with good early and midterm results (10 − 60 months), suggest that selected patients may be treated with covered stents, especially in an emergency. Stent insertion can be combined with EndoVAC or wound drainage.[74,541] The EndoVAC technique is a novel, three step strategy, involving relining the infected reconstruction with a stent graft, followed by debridement, vacuum assisted therapy, and long term antibiotic therapy to allow granulation and secondary healing. Where radical surgery or conservative management is not considered safe, EndoVAC may be an option.[545] Carotid ligation should only be considered as a last resort, unless the artery is already thrombosed, or the patient tolerated carotid clamping at the original operation (see above). Peri-operative risks are increased (*vs.* primary CEA) and this needs to be discussed with the patient (mortality = 3.6%, stroke = 6.4%, CNI = 13%). The long term re-infection rate is 3.5% following autologous reconstruction.[74,106,539–542]

Only nine carotid stent graft infections have been reported, culturing *S. aureus*, *Streptococcus*, and *Candida.*[74,546] Clinical presentation included abscess/neck mass, bleeding, and septic embolisation. Treatment involves excision of infected material and autologous reconstruction. In four cases, stent grafts were removed without reconstruction (known carotid thrombosis). In another, stent excision was followed by EC-IC bypass.[546] There were three peri-operative deaths, two strokes, one major bleeding event, and one late re-infection.[74] ESVS recommendations regarding patch infection are similar to SVS and German-Austrian guidelines.[3,4]

Recommendation 99			Unchanged
For patients with prosthetic patch infection or carotid stent infection excision and autologous venous reconstruction is recommended.			
Class	**Level**	**References**	**ToE**
I	C	Lejay *et al.* (2018)[74], Naylor (2016)[542]	

Recommendation 100			Unchanged
For patients with carotid patch or stent infection, excision and prosthetic reconstruction is not recommended.			
Class	**Level**	**References**	**ToE**
III	C	Lejay *et al.* (2018)[74], Naylor (2016)[542]	

Recommendation 101			New
In selected high risk for surgery patients or emergency patients with suspected prosthetic patch infection, insertion of a covered stent may be considered, as part of the three stage EndoVAC technique.			
Class	**Level**	**References**	**ToE**
IIb	C	Lejay *et al.* (2018)[74], Bannazadeh *et al.* (2020)[541], Thorbjornsen *et al.* (2016)[545]	

7.2.2. Re-stenosis after carotid interventions

7.2.2.1. Pathophysiology. "Recurrent" lesions within six weeks represent residual atherosclerotic disease. In a meta-analysis of 13 observational studies ($n = 4\,163$ CEA and CAS patients), factors associated with re-stenosis after CEA included DM, dyslipidaemia, chronic kidney disease, SCS, stenosis > 70%, and primary arteriotomy closure. Female sex and smoking were associated with re-stenosis after CEA, but not after CAS.[103] In a multivariable analysis of data from ICSS, older age, female sex, current or past smoking, non-insulin dependent DM, history of angina, a greater severity of stenosis in the contralateral carotid artery at randomisation, raised SBP and DBP at randomisation, and higher total serum cholesterol at randomisation increased the risk of re-stenosis independently of each other and for both CEA and CAS patients.[39]

7.2.2.2. Duplex ultrasound criteria for diagnosing re-stenosis severity. DUS criteria for diagnosing re-stenosis may be different to diagnosing primary atherosclerotic stenoses. After CEA, it has been proposed that peak systolic velocity (PSV) thresholds for diagnosing > 50% re-stenosis should be 213 cm/sec and 274 cm/sec for > 70% re-stenosis.[547] DUS velocities after CAS are more difficult to interpret as the stent causes increased in stent velocities, even when fully deployed.[548] Higher PSV thresholds have been proposed including > 220cm/sec (ICA/CCA ratio ≥ 2.5) for diagnosing > 50% re-stenosis and ≥ 300 cm/sec (end diastolic velocity ≥ 90 cm/sec; ICA/CCA ratio ≥ 3.8) for diagnosing > 70% re-stenosis.[549,550] However, ICSS (which compared DUS derived PSV with CTA in re-stenosis patients after CAS) found no evidence that PSV thresholds needed to be increased when diagnosing > 50%.[551]

7.2.2.3. Duplex ultrasound surveillance after carotid interventions. No evidence supports routine surveillance in all CEA/CAS patients. It is, therefore, reasonable to assume that subgroups with increased risks of re-stenosis, (DM, chronic kidney disease, females, smokers) might benefit from surveillance out to two years. Two high risk subgroups do warrant DUS surveillance, because an asymptomatic re-stenosis > 70% would be an indication for redo CEA or CAS. The first includes patients developing neurological symptoms during carotid clamping under LRA, or during balloon inflation or proximal flow reversal during CAS. The second are patients with major EEG/SSEP changes during carotid clamping, or MCAV < 15 cm/sec on TCD monitoring during carotid clamping under GA. A threshold of 15 cm/sec has been shown to correlate with loss of cerebral electrical activity on EEG.[552] In both subgroups, progression to occlusion could cause a major haemodynamic stroke.

7.2.2.4. Duplex ultrasound surveillance of the contralateral carotid artery. Surveillance allows monitoring of disease progression in the contralateral ICA, with progression depending on disease severity at the time of CEA. With DUS surveillance of the contralateral asymptomatic ICA in 599 patients after CEA, there was progression to severe stenosis in 48% with a moderate ICA stenosis at baseline. Only 1% with a mild stenosis progressed to severe stenosis. The rate of neurological events ipsilateral to the contralateral ICA was 3.2% (19/599), with most affecting patients with progression from moderate to severe stenoses.[553] The cost effectiveness of contralateral surveillance has, however, been questioned. In a series of 151 patients undergoing serial imaging of the non-operated ICA, cumulative freedom from stroke in the non-operated hemisphere was 99%, 96%, and 86% at one, five, and 10 years, respectively (mean stroke incidence 1% per year). No late stroke was associated with a > 70% contralateral ACS,[554] indicating that none could have been prevented by surveillance.[554] It would, however, be reasonable to offer DUS surveillance to patients with > 50% contralateral ACS, as those progressing to a 60–99% stenosis with at least one clinical or imaging feature that make them higher risk of stroke on BMT, would then be considered for a carotid intervention (section 3.6).

Table 34. Meta-analyses of rates of re-stenosis > 70% after carotid endarterectomy (CEA) and carotid artery stenting (CAS)

Author	Procedure	RCTs – *n*	Non-RCTs – *n*	Patients	Mean FU time	Re-stenosis >70% or occlusion (95% CI)	*p* value
Kumar[555]	Any CEA	11		4 249	47 mo	5.8% (4.1–8.2%)	
	Patched CEA	5		1 078	32 mo	4.1% (2.0–8.4%)	
	CAS or CA	6		2 916	60 mo	10.3% (6.4–16.4%)	
	CAS	5		2 716	62 mo	10.0% (6.0–16.3%)	
Xin[109]	CEA	15	12		6 mo	2.04%	
	CAS	15	12		6 mo	4.12%	
	CEA *vs.* CAS			20 479		OR 0.49 (0.29–0.86)	.013
Xin[109]	CEA	15	12	1 578	120 mo	8.4%	
	CAS	15	12	1 610	120 mo	10.2%	
	CEA *vs.* CAS					OR 0.92 (0.42–2.04)	
Li[75]	CEA	8		3 136	48 mo	8.0%	
	CAS	8		3 869	48 mo	11.3%	
	CAS *vs.* CEA					OR 1.48 (0.93–2.35)	.10
Jung[65]	CEA	8		2 798	>10 y	7.1%	
	CAS	8		2 757	>10 y	9.9%	
	CEA *vs.* CAS					OR 0.68 (0.48–0.97)	

RCTs = randomised controlled trials; FU = follow up; OR = odds ratio; CI = confidence interval.

7.2.2.5. Incidence of re-stenosis after carotid interventions. In a Cochrane review (nine RCTs; $n = 5\ 477$), CAS had statistically significantly higher re-stenosis rates > 50% than CEA (HR 2.0; 95% CI 1.12 − 3.6, $p = .02$).[79] Table 34 details rates of re-stenosis > 70% in various meta-analyses. In ICSS, the cumulative incidence of ≥ 50% re-stenosis at one year was 18.9% (patch closure), 26.1% (primary closure), and 17.7% after eCEA.[43] At five years, the cumulative incidence of re-stenosis ≥ 50% was 25.9%, 37.2%, and 30%, respectively. Primary arteriotomy closure incurred a statistically significantly higher risk of re-stenosis ≥ 50% than patch angioplasty (HR 1.45; 95% CI 1.06 − 1.98, $p = .019$), while there was no statistically significant difference in re-stenosis rates between patched and eCEA.[43]

7.2.2.6. Asymptomatic re-stenosis and recurrent ipsilateral symptoms. Table 35 details stroke rates ipsilateral to an asymptomatic > 70% re-stenosis from a meta-analysis of DUS surveillance involving seven RCTs (2 839 CEA patients) and four RCTs (1 964 CAS patients). The Principal Investigator of each RCT provided additional data about re-stenosis severity on the surveillance scan *preceding* stroke onset.[555] The five year ipsilateral stroke was 0.8% in CAS patients with re-stenosis > 70% *versus* 2% without re-stenosis > 70% (OR 0.87; 95% CI 0.24 − 3.21, $p = .83$).[555] By contrast, > 70% asymptomatic re-stenosis after CEA was associated with a higher risk of ipsilateral stroke (5.2%) at three years *versus* 1.2% without re-stenosis > 70% (OR 4.77; 95% CI 2.29 − 9.92).[555]

7.2.2.7. Management of re-stenosis.

7.2.2.7.1. Symptomatic re-stenosis. No RCTs have been performed. It is, however, customary to adopt similar management to SCS patients with atherosclerotic stenoses (section 4.3). If a patient reports carotid territory symptoms with an ipsilateral 50—99% re-stenosis, they should be considered for redo CEA or CAS within 14 days of symptom onset. Recently symptomatic patients with < 50% ipsilateral re-stenosis should be treated medically unless they develop recurrent symptoms on BMT.

7.2.2.7.2. Asymptomatic re-stenosis. The management of asymptomatic re-stenosis is controversial, with no RCTs to guide practice. Despite being considered benign,[256] a meta-analysis of 13 observational studies ($n = 1\ 132$) found that two thirds undergoing re-intervention were asymptomatic.[556] A meta-analysis (Table 35) suggested that patients with asymptomatic re-stenosis > 70% after CAS would gain little benefit from re-intervening, as stroke risks were very low (0.8% over four years) and 97% of late ipsilateral strokes involved patients with < 70% re-stenosis.[555] Asymptomatic re-stenosis > 70% after CEA was associated with a 5.2% risk of ipsilateral stroke over three years. Operating on 100 patients might prevent five ipsilateral strokes,[555] but at a cost of two to three peri-operative strokes,[556] and 85% of late ipsilateral strokes would still occur in patients with re-stenosis < 70%.

7.2.2.7.3. Redo endarterectomy or stenting? Once a decision has been made to re-intervene, options include surgery (redo CEA, bypass) or CAS, neither tested in RCTs. In a meta-analysis (13 observational studies; 4 163 patients), 30 day stroke was 2.6% after redo CEA *versus* 2% after CAS (p = ns). Permanent CNI was 3.3% after redo CEA *versus* 0% after CAS.[102] In an SVS-VQI database on treating in stent re-stenosis after CAS (117 CEA; 511 redo CAS); 30 day stroke after CEA was 1.5% *versus* 1.4% after redo CAS ($p = .91$), while death/stroke was 4.5% after CEA *versus* 1.9% after redo CAS ($p = .090$).[116]

Recommendation 102 — **Changed**

For patients experiencing a late ipsilateral stroke or transient ischaemic attack in the presence of an ipsilateral 50—99% re-stenosis, re-do carotid endarterectomy or carotid artery stenting is recommended.

Class	Level	References	ToE
I	B	Rothwell *et al.* (2003)[357]	

Recommendation 103 — **Changed**

For patients experiencing a late ipsilateral stroke or transient ischaemic attack in the presence of an ipsilateral <50% re-stenosis, medical therapy is recommended.

Class	Level	References	ToE
I	B	Rothwell *et al.* (2003)[357]	

Recommendation 104 — **Unchanged**

For carotid endarterectomy patients with an asymptomatic 70—99% re-stenosis, re-intervention may be considered following multidisciplinary team review.

Class	Level	References	ToE
IIb	A	Kumar *et al.* (2017)[555]	

Table 35. Meta-analysis of late ipsilateral stroke in carotid endarterectomy (CEA) and carotid artery stenting (CAS) patients with and without an asymptomatic re-stenosis >70% of carotid artery in randomised controlled trials (RCTs)*

Procedure	RCTs / patients	Mean follow up time − mo	Stroke ipsilateral to >70% re-stenosis or occlusion†	Stroke ipsilateral to re-stenosis <70%	OR (95% CI)
Any CEA	7‡ / 2 810	37	7 / 135 (5.2)	40 / 2 704 (1.2)	4.77 (2.29–9.92)
CAS	4§ / 1 964	50	1 / 125 (0.8)	37 / 1 839 (2.0)	0.87 (0.24–3.21)

OR = odds ratio; CI = confidence interval.

* Data derived from Kumar.[555]

† Re-stenoses had been asymptomatic prior to stroke onset.

‡ EVA-3S; SPACE-1; CREST-1; AbuRahma 2002; AbuRahma 2008; Naylor 2004; Stone 2014.

§ EVA-3S; SPACE-1; CREST-1; Steinbauer.

Recommendation 105			Unchanged
For carotid stent patients who develop an asymptomatic re-stenosis >70%, medical management is recommended.			
Class	**Level**	**References**	**ToE**
I	A	Kumar *et al.* (2017)[555]	

Recommendation 106		Unchanged
For patients who developed focal neurological symptoms or seizures during carotid clamping when carotid endarterectomy is performed under local anaesthesia, or during balloon inflation (or proximal flow reversal) during carotid stenting, serial post-operative surveillance and re-intervention for asymptomatic restenoses >70% is recommended.		
Class	**Level**	**References**
I	C	Consensus

Recommendation 107		Unchanged
For carotid endarterectomy patients who develop significant electrophysiological changes during carotid clamping, or whose mean middle cerebral artery velocities fell below 15 cm/sec on transcranial Doppler monitoring during carotid clamping under general anaesthesia, serial post-operative surveillance and re-intervention for asymptomatic re-stenoses >70% is recommended.		
Class	**Level**	**References**
I	C	Consensus

Recommendation 108		Unchanged
For patients with re-stenosis in whom a decision has been made to undertake revascularisation, it is recommended that the choice of re-do endarterectomy or stenting be based on multidisciplinary team review, local surgeon and interventionist preference and patient choice.		
Class	**Level**	**References**
I	C	Consensus

The SVS and German-Austrian guidelines, regarding post-operative DUS surveillance, differ from the ESVS. German-Austrian guidelines recommend DUS before discharge, again at six months and then annually (unless a re-stenosis develops, when it remains every six months).[3] The SVS recommends DUS at three months and then annually for two years, then biennially unless a re-stenosis develops.[4] The management of re-stenosis also differs slightly. The SVS and German-Austrian guidelines advise re-intervening in patients with a symptomatic 50—99% re-stenosis[3,4] (same as ESVS). For asymptomatic 70—99% re-stenoses, German-Austrian guidelines advise that re-intervention may be considered in patients having ESVS criteria that make them high risk for stroke if a re-stenosis progressed to occlusion.[3] The SVS advises that early asymptomatic re-stenoses after CEA should be treated conservatively, unless they become symptomatic, progressive, or pre-occlusive (80—99%). After CAS, the SVS recommends that early asymptomatic 70—99% re-stenoses be treated medically, unless they are progressive or symptomatic. The SVS also advised that CEA and CAS patients with late restenosis should be treated as if they had primary atherosclerosis.[4]

8. MANAGEMENT OF CONCURRENT CORONARY AND CAROTID DISEASE

8.1. Stroke after cardiac surgery

The incidence of stroke after CABG is 1—2%[557] and differentiation between intra- and post-operative stroke is helpful, as the aetiologies differ. Most intra-operative strokes (70—80%) follow thromboembolism, usually after aortic manipulation/cannulation. A minority (20—30%) follow hypoperfusion secondary to hypotension. Post-operative stroke within seven days is usually due to dysrhythmias, while those between seven and 30 days are usually due to generalised atherosclerosis. Peri-operative stroke also impacts on survival. In a meta-analysis of 174 000 cardiac operations, patients with intra-operative stroke had a 30 day mortality of 29%, *versus* 18% with post-operative stroke, *versus* 2.4% in patients with no stroke ($p < .001$). At eight years, mortality was 12% in patients with intra-operative stroke who survived 30 days *versus* 9% after post-operative stroke *versus* 3% with no stroke.[55]

8.2. Is carotid disease an important cause of stroke during cardiac surgery?

The prevalence of $>$ 50% carotid stenosis in CABG patients is 9%. The prevalence of stenosis $>$ 80% is 7%.[557] A meta-analysis of 106 observational studies reported that CABG patients with $>$ 50% stenosis had a 7% risk of peri-operative stroke, increasing to 9% with $>$ 80% stenosis.[558] While these risks appear high (and supportive of a role for synchronous/staged carotid interventions), the data need to be interpreted carefully, as stroke risks vary with unilateral *versus* bilateral disease, symptomatic *versus* asymptomatic stenoses, and stenoses *versus* occlusion.

CABG patients with prior TIA/stroke or carotid occlusion have the highest rates of post-operative stroke. D'Agostino reported post-CABG stroke in 18% of patients with an unoperated symptomatic unilateral 70—99% stenosis, increasing to 26% with bilateral 70—99% stenoses (or contralateral occlusion).[559] CABG patients with carotid occlusion had an 11% risk of post-CABG stroke.[557] In a systematic review (106 observational cohorts) which excluded patients with occlusion (not candidates for CEA) and SCS patients, the risk of peri-operative stroke was $\leq$ 2% in patients undergoing isolated CABG with a unilateral (non-operated) 50—99% ACS, 70—99% ACS, or 80—99% ACS.[558] In the same systematic review, 6.5% with bilateral 50—99% ACS had a post-CABG stroke, while 9.1% died or had a stroke.[558] In a pooled series of 23 557 patients undergoing isolated CABG, 95% of 476 post-CABG strokes could not be attributed to carotid disease.[560—562] A carotid bruit is a predictor of severe aortic arch disease,[563] while $>$ 70% stenosis is also an independent predictor of severe aortic

arch disease.[564] In a 2019 systematic review of 36 observational studies ($n = 174\ 969$), meta-regression analyses revealed that prior stroke was the most important predictor of peri-operative stroke ($p < .001$), while carotid stenoses were not statistically significantly predictive ($p = .13$).[55] The evidence suggests no causal relationship between unilateral ACS and post-CABG stroke in most cases, that is, other aetiologies play a more important role, particularly aortic arch athero-embolism, for which ACS is a marker.[563,564] As CABG patients increase in age, so too does the incidence of severe ACS, severe aortic arch disease, and post-CABG stroke (Table 36).

8.3. Screening cardiac surgery patients for asymptomatic carotid stenosis

Given the lack of a causal association between ACS and post-CABG stroke, routine screening for ACS before CABG cannot be supported. However, selective screening in CABG patients aged > 70, or with a history of TIA or stroke, or who have a carotid bruit or left mainstem disease,[566] allows the patient to be better informed about increased peri-operative mortality in CABG patients with concurrent carotid disease.

8.4. Are carotid interventions indicated in cardiac surgery patients?

In 22 355 patients in the Society of Thoracic Surgeons Adult Cardiac Surgery Database (where two thirds undergoing staged or synchronous carotid procedures were neurologically asymptomatic and 73% had unilateral ACS), there was no difference in in hospital stroke in patients undergoing CABG + CEA (OR 0.93; 95% CI 0.72 − 1.21, $p = .60$) or 30 day mortality (OR 1.28; 95% CI 0.97 − 1.69, $p = .080$), *versus* patients undergoing isolated CABG.[567] A similar observation was made for in hospital stroke (OR 0.8; 95% CI 0.37 − 1.69, $p = .55$) and 30 day mortality (OR 0.78; 95% CI 0.35 − 1.72, $p = .54$) in patients undergoing off bypass CABG with/without CEA.[567] In a review of 5 924 cardiac surgery patients, 2 482 underwent a pre-operative carotid DUS and 7.4% had a > 70% carotid stenosis (majority unilateral and asymptomatic).[568] Patients undergoing CEA prior to cardiac surgery had higher peri-operative stroke (10.3% *vs.* 1.4%) than after isolated CABG in patients with confirmed or presumed normal ICAs ($p = .008$), plus statistically significantly higher rates of peri-operative MI (13.8% *vs.* 0.4%; $p < .001$). Patients undergoing isolated CABG with confirmed or presumed normal ICAs had similar rates of peri-operative stroke (1.4%) *vs.* 3.2% in CABG patients with known severe ICA disease who did not undergo CEA ($p > .050$).[568]

Two RCTs have evaluated synchronous or staged CEA in CABG patients with unilateral ACS. Illuminati randomised 185 patients with unilateral 70—99% ACS to CEA prior to or synchronous with CABG *versus* isolated CABG followed by deferred CEA. Thirty day mortality was 1% in each group, while 30 day death/stroke was 4% (deferred CEA) *versus* 1% (staged/synchronous CEA) ($p =$ ns). Ninety day death/stroke was 9% for deferred CEA *versus* 1% for staged/synchronous CEA ($p = .020$). The authors concluded that prophylactic CEA was potentially beneficial in CABG patients with unilateral 70—99% ACS to reduce 90 day ipsilateral stroke, rather than peri-operative stroke.[569] CABACS (involving 17 centres in Germany and the Czech Republic) randomised 129 CABG patients with unilateral 80—99% ACS to synchronous CEA + CABG *versus* CABG alone. Patients undergoing synchronous CEA + CABG had a 30 day stroke/death rate of 18.5% *versus* 9.7% after isolated CABG (ARI 8.8%; 95% CI 3.2 − 20.8, $p = .12$).[36] For secondary endpoints at 30 days and one year, there was no significant difference, although patients undergoing isolated CABG tended to have better outcomes.[36] Unfortunately, CABACS was terminated after funding was withdrawn.

8.5. What surgical and endovascular options are available?

Options include (1) staged CEA then CABG; (2) staged CABG then CEA; (3) synchronous CEA plus CABG; (4) staged CAS then CABG; and (5) same day CAS + CABG. Table 37 summarises data from meta-analyses of non-randomised studies. The majority (> 80%) were neurologically asymptomatic with unilateral ACS. Table 38 presents similar data from administrative dataset registries. Thirty day death/stroke ranged from 6% to 10% in predominantly ACS patients, with the highest rates of death/stroke being observed in patients with a history of stroke/TIA undergoing staged or synchronous CEA + CABG (14%) or CAS then CABG (44%).[570] Performing CABG off pump was associated with lower rates of post-CABG stroke, possibly due to avoiding cannulation of a diseased aortic arch.[567,571]

A 2017 meta-analysis of 31 observational studies included 2 727 patients undergoing staged or same day CAS-CABG, reported a 30 day death/stroke rate of 7.9%.[577]

Table 36. Prevalence of post-coronary artery bypass grafting (CABG) stroke and its association with age and prevalence of carotid and aortic arch disease

Age − y	Post-CABG stroke[557] − %	Carotid stenosis >70% on screening in males/females* [206] − %	Severe aortic arch disease[565] − %
50–59	1–2	0.2 / 0.1	9
60–69	2–3	0.8 / 0.2	18
70–79	4–7	2.1 / 1.0	22
≥80	8–9	3.1 / 0.9	33

* Prevalence of carotid stenosis based on population screening (section 2.2.2.4) rather than screening in CABG patients.

Table 37. Meta-analyses of 30 day outcomes from non-randomised studies regarding revascularisation strategies in patients with combined carotid and cardiac disease

Study	Patients − *n*	Death − %	Stroke − %	MI − %	Death / stroke − %	Death / stroke / MI − %
Staged CEA then CABG, all						
Brener 1996[572]	407	9.4	5.3	11.5		
Borger 1999[573]	920	2.9	3.2		5.7	
Naylor 2003[574]	917	3.9	2.5	6.5	6.1	10.2
Sharma 2014[575]	7 552	3.4	1.9		6.2	
Staged CABG then CEA, all						
Brener 1996[572]	213	3.6	10.0	2.7		
Naylor 2003[574]	302	2.0	5.8	0.9	7.3	
Synchronous CEA and CABG, all						
Brener 1996[572]	2 308	5.6	6.2	4.7		
Borger 1999[573]	844	4.7	6.0		9.5	
Naylor 2003[574]	7 753	4.6	4.6	3.6	8.7	11.5
Sharma 2014[575]	17 469	4.0	4.3	3.6	7.9	
Giannopoulos 2019[57]	16 712	4.0	3.0	5.0		
Synchronous CEA and CABG, symptomatic						
Naylor 2003[576]	514	5.8	6.8	1.9	7.6	8.1
Synchronous CEA and CABG, asymptomatic						
Naylor 2003[576]	925	3.6	3.7	2.2	4.5	4.5
Synchronous CEA and CABG, off bypass						
Fareed 2009[571]	324	1.5			2.2	3.6
Synchronous CEA and CABG, pre bypass						
Naylor 2003[576]	5 386	4.5	4.5	3.6	8.2	11.5
Synchronous CEA and CABG, on bypass						
Naylor 2003[576]	844	4.7	2.1	2.9	8.1	9.5
Same day CAS and CABG, all						
Paraskevas 2017[577]	531	4.5	3.4	1.8	5.9	6.5
Staged CAS-CABG, all						
Guzman 2008[578]	277	6.8	7.6		12.3	
Naylor 2009[579]	760	4.2	5.5	1.8	9.1	9.4
Paraskevas 2017[577]	2 196	4.8	5.4	4.2	8.5	11.0
Giannopoulos 2019[57]	985	2.0	3.0	5.0		

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

The majority (80%) were neurologically asymptomatic with unilateral ACS, in whom 30 day death/stroke was 6.7%. Given the low risk of stroke attributable to unilateral ACS (section 8.2), it is unlikely that CAS + CABG will benefit CABG patients with unilateral ACS any more than CEA + CABG. Staged or same day CAS + CABG in patients with a history of TIA/stroke was associated with 15% rates of 30 day death/stroke.[577] In another meta-analysis of five observational studies, (n = 16 712), outcomes following synchronous CEA + CABG were compared with staged CAS followed by CABG in patients with ACS and SCS (Table 37). Rates of peri-operative stroke (3.0% *vs.* 3.0%) and MI (5.0% *vs.* 5.0%) were not substantially different, but patients undergoing synchronous CEA + CABG incurred higher mortality (OR 1.8; 95% CI 1.05 − 3.06).[58] The need for aspirin + clopidogrel combination APRx with CAS can complicate staged CAS-CABG, as it increases MI risk during the delay between each procedure and increases bleeding risks during CABG. Evidence suggests that CAS can be performed on the same day as CABG using aspirin or heparin, with thienopyridine APRx starting 6 − 12 hours after CABG.[577]

The Agency for Healthcare Research and Quality Healthcare Cost and Utilisation Project evaluated outcomes in 22 501 CABG patients (95% ACS, 5% SCS): (i) 15 402 (68%) had synchronous CEA + CABG; (ii) 6 297 (28%) staged CEA then CABG, while (iii) 802 (4%) had staged CAS then CABG.[125] Peri-operative stroke rates were comparable (synchronous CEA + CABG 2.8%; staged CEA + CABG 1.9%; staged CAS + CABG 3.0%; p_{trend} = .37), but adjusted stroke rates were lower in both surgical groups *versus*

Table 38. Thirty day procedural risks after carotid endarterectomy (CEA) or carotid artery stenting (CAS) and coronary artery bypass grafting (CABG) stratified for treatment strategy in administrative dataset registries

Procedure	Registry	Patients − *n*	Death − %	Stroke − %	Death / stroke − %
Staged CEA and CABG					
All cases					
Gopaldas 2011[580]	NIS 1998−2007	6 153	4.2	3.5	7.1
Feldman 2017[125]	NIS 2004−2012	6 297	3.8	1.9	5.4
Off bypass					
Gopaldas 2011[580]	NIS 1998−2007	2 004	4.0		7.0
On bypass					
Gopaldas 2011[580]	NIS 1998−2007	4 149	4.3		7.7
Staged or synchronous CEA and CABG					
All cases					
Dubinsky 2007[581]	NIS 1993−2002	7 073	5.6	4.9	9.7
Timaran 2008[570]	NIS 2000−2004	25 249	5.4	3.9	8.6
*Symptomatic**					
Timaran 2008[570]	NIS 2000−2004	948		14.2	
Synchronous CEA and CABG					
All cases					
Gopaldas 2011[580]	NIS 1998−2007	16 639	4.5	3.9	7.7
Feldman 2017[125]	NIS 2004−2012	15 402	4.4	2.8	6.8
Klarin 2020[567]	STS ACSD	3 972	6.0	6.2	
Off bypass					
Gopaldas 2011[580]	NIS 1998−2007	5 280	4.2		
Klarin 2020[567]	STS ACSD	566	2.1	2.3	6.5
On bypass					
Gopaldas 2011[580]	NIS 1998−2007	11 359	4.5		7.4
Klarin 2020[567]	STS ACSD	3 406	3.9	3.9	
Staged CAS then CABG					
All cases					
Feldman 2017[125]	NIS 2004−2012	802	1.9	3.0	4.2
*Symptomatic**					
Timaran 2008[570]	NIS 2000−2004	25		44	

NIS = National Inpatient Sample; STS ACSD = Society of Thoracic Surgeons Adult Cardiac Surgery Database.
* Prior stroke or transient ischaemic attack.

CAS + CABG (CEA + CABG: OR 0.65; 95% CI 0.42 − 1.01, $p = .06$), (staged CEA + CABG: OR 0.50; 95% CI 0.31 − 0.8, $p = .004$).[125] In summary, the literature supports staged or synchronous carotid interventions in CABG patients with a prior history of stroke/TIA[559] and in patients with bilateral 70−99% ACS, or 70−99% ACS with contralateral occlusion Figure 8.

8.6. Managing patients with unstable coronary artery disease

The Carotid Artery Revascularisation and Endarterectomy (CARE) registry involved 255 urgent CABG patients undergoing CAS and 196 undergoing CEA. Thirty day death/stroke/MI was 15% after CAS *versus* 22% after CEA. CARE did not differentiate between staged or synchronous CEA +

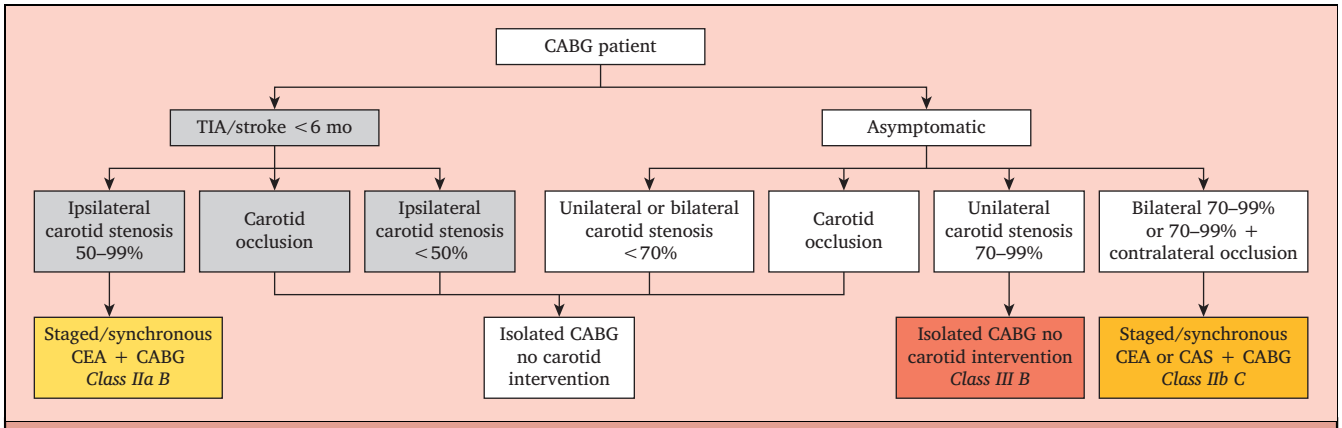


Figure 8. Managing coronary artery bypass grafting (CABG) patients with symptomatic and asymptomatic carotid disease. TIA = transient ischaemic attack; CEA = carotid endarterectomy; CAS = carotid artery stenting.

CABG, regional practice variations existed, and 60% of interventions involved ACS patients.[582]

Recommendation 109			Unchanged
For patients undergoing open heart surgery, routine screening for carotid disease is not recommended.			
Class	Level	References	
III	C	Consensus	

Recommendation 110			Unchanged
For patients undergoing coronary artery bypass surgery, duplex ultrasound screening for carotid disease should be considered in patients aged >70 years, and those with a history of transient ischaemic attack or stroke or who have a carotid bruit or left mainstem disease, so that the patient can be better informed of the increased risks associated with coronary artery bypass if they have concurrent carotid disease.			
Class	Level	References	ToE
IIa	C	Naylor *et al.* (2002)[557], Aboyans *et al.* (2009)[566]	

Recommendation 111			Unchanged
For coronary artery bypass surgery patients with a history of stroke or transient ischaemic attack in the preceding six months and a 50–99% carotid stenosis, a staged or synchronous carotid intervention should be considered.			
Class	Level	References	ToE
IIa	B	Naylor *et al.* (2002)[557], D'Agostino *et al.* (1996)[559]	

Recommendation 112			Unchanged
For coronary artery bypass surgery patients with a history of stroke or transient ischaemic attack in the preceding six months and a 50–99% carotid stenosis, a staged or synchronous carotid endarterectomy should be considered instead of carotid stenting plus coronary bypass surgery.			
Class	Level	References	ToE
IIa	B	Timaran *et al.* (2008)[570], Naylor *et al.* (2003)[574], Paraskevas *et al.* (2017)[577], Naylor *et al.* (2009)[579]	

Recommendation 113			Unchanged
For coronary artery bypass patients with an asymptomatic unilateral 70–99% carotid stenosis, a staged or synchronous carotid intervention is not recommended for the prevention of post-operative stroke.			
Class	Level	References	ToE
III	B	Naylor *et al.* (2011)[558], Klarin *et al.* (2020)[567], Ashrafi *et al.* (2016)[568]	

Recommendation 114			Unchanged
For coronary artery bypass patients with bilateral asymptomatic 70–99% carotid stenoses, or a 70–99% stenosis with contralateral occlusion, a staged or synchronous carotid intervention may be considered.			
Class	Level	References	ToE
IIb	C	Naylor *et al.* (2011)[558]	

Recommendation 115			Unchanged
For asymptomatic carotid stenosis patients in whom a carotid intervention is deemed necessary if they are undergoing coronary artery bypass surgery, the choice between carotid endarterectomy or carotid stenting should be considered based on the urgency of performing surgery, choice of antiplatelet therapy during coronary bypass, individual patient characteristics, symptom status and local expertise.			
Class	Level	References	ToE
IIa	C	Hajibandeh *et al.* (2018)[58], Feldman *et al.* (2017)[125]	

The German-Austrian guidelines made no recommendation regarding CABG patients with a unilateral 70–99% ACS, while the rest were identical to ESVS.[3] The SVS recommendations were also identical to ESVS, the only exception being that SVS indicated that managing CABG patients with unilateral 70–99% ACS was controversial but did not make any further recommendation.[4]

9. CAROTID DISEASE AND MAJOR NON-CARDIAC SURGERY

Vascular surgeons are often asked whether prophylactic CEA or CAS should be considered in ACS patients scheduled for major non-cardiac surgery, to prevent peri-operative stroke.

9.1. Incidence of stroke after major non-cardiac surgery

The incidence of peri-operative stroke depends on the nature and complexity of the procedure, risk factors and timing after recent TIA/stroke (Table 39). The incidence of stroke was < 1% in all but two cohorts, suggesting that stroke is rarely a problem after major non-cardiac surgery.

9.2. Predicting stroke after major non-cardiac surgery

Table 40 summarises predictors for peri-operative stroke after non-cardiac surgical procedures. The most consistent were increasing age and a history of stroke.

9.3. Timing of major surgery after recent stroke

In a study of 481 183 adults undergoing elective, non-cardiac surgery, 7 137 (1.5%) had a history of stroke, in whom the rate of peri-operative stroke was 11.9% if operations were performed within three months of the stroke, declining to 4.5% where three to six months had elapsed and 1.8% where six to 12 months had elapsed *versus* 0.1% in patients with no history of stroke.[585]

Table 39. Incidence of peri-operative stroke stratified for type of procedure

Author	Population	Subpopulation	Patients − *n*	Stroke risk − %
Axelrod[583]	Major vascular surgery	Aortic operations	5 296	0.5
		Lower limb bypasses	7 299	0.4
		Major amputations	7 442	0.6
Sharifpour[584]	Major vascular surgery	Major amputations	8 077	0.7
		Lower limb bypasses	21 962	0.5
		Open aortic	7 888	0.8
		EVAR	9 823	0.5
Jorgensen[585]	Non-cardiac, including vascular		481 113	0.1
Sonny[586]	Non-cardiac, including vascular		2 110	2.6
Kikura[587]	General, orthopaedic, thoracic, non-carotid vascular		36 634	0.3
Parvizi[588]	Knee arthroplasty		1 636	0.4
Bateman[589]	Hemicolectomy		131 067	0.7
	Hip replacement		201 235	0.2
	Lung resection		39 339	0.6
Huang[590]	Caesarean section		303 862	0.05
Mashour[591]	Non-cardiac (low risk) general, orthopaedic, urology, ENT, plastics, thoracic, gynaecology		523 059	0.1
Biteker[592]	Non-cardiac, non-vascular		1 340	2.3

EVAR = endovascular aortic aneurysm repair; ENT = ear, nose and throat.

9.4. Is there a role for prophylactic carotid endarterectomy or stenting?

Patients undergoing major non-cardiac surgery with three to four cardiovascular risk factors (age, CAD, renal failure, hypertension, DM, smoking, BMI > 35 kg/m^2, COPD, prior stroke/TIA) had a 0.7% risk of peri-operative stroke. With at least five risk factors, peri-operative stroke increased to 1.9%,[591,592] emphasising the

Table 40. Predictors for peri-operative stroke following major non-cardiac procedures

Author	Population	Stroke predictors	OR (95% CI)
Axelrod[583]	Major vascular surgery	Aortic operation *vs.* lower extremity	1.7 (1.0–2.8)
Sharifpour[584]	Major vascular surgery	Each 1 y increase in age	1.02 (1.01–1.04)
		Cardiac history *vs.* none	1.4 (1.1–1.9)
		Female sex *vs.* male	1.5 (1.1–1.9)
		History of stroke *vs.* no stroke	1.7 (1.3–2.3)
		Acute/chronic renal failure *vs.* no history	2.0 (1.4–3.0)
Kikura[587]	General, orthopaedic, thoracic, non-carotid vascular	Age >70 y *vs.* <70 y	23.6 (9.6–58.1)
		Diabetes *vs.* no diabetes	2.2 (1.4–3.3)
		Coronary disease *vs.* none	2.3 (1.3–4.1
		CCF *vs.* no CCF	1.7 (1.1–2.7)
		AF *vs.* no AF	5.5 (2.8–10.9)
		Prior stroke *vs.* no stroke	7.1 (4.6–11)
Bateman[589]	Hemicolectomy, hip replacement, lung resection	Renal impairment *vs.* none	3.0 (2.5–3.5)
		AF *vs.* no AF	2.0 (1.7–2.3)
		Prior stroke *vs.* no stroke	1.6 (1.3–2.1)
		Valvular heart disease *vs.* none	1.5 (1.3–1.9)
		CCF *vs.* no CCF	1.4 (1.2–1.7)
		Diabetes *vs.* no diabetes	1.2 (1.0–1.4)
Mashour[591]	Non-cardiac, non-neurosurgery, general, orthopaedics, urology, ENT, plastics, thoracic, gynaecology, minor vascular	Acute renal failure vs. none	3.6 (2.3–5.8)
		History of stroke *vs.* none	2.9 (2.3–3.8)
		History of TIA *vs.* none	1.9 (1.3–2.6)
		On dialysis *vs.* not on dialysis	2.3 (1.6–3.4)
		Hypertension *vs.* no	2.0 (1.6–2.6)
		COPD *vs.* no COPD	1.8 (1.4–2.4)
		Smoking *vs.* non smoking	1.5 (1.1–1.9)
Biteker[592]	Non-cardiac, non-vascular	History of stroke *vs.* no stroke	3.6 (1.2–4.8)
Jorgensen[585]	Non-cardiac	Stroke <3 mo *vs.* no stroke	67.6 (52.3–87.4)
		Stroke 3–6 mo *vs.* no stroke	24.0 (15.0–38.4)
		Stroke 6–12 mo *vs.* no stroke	10.4 (6.2–17.4)

BMI = body mass index; OR =odds ratio; CI = confidence interval; CCF = congestive cardiac failure; AF = atrial fibrillation; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease; ENT = ear, nose and throat operations.

importance of optimising cardiovascular risk prior to major non-cardiac surgery.[590,593] Most strokes were ischaemic and secondary to cardiac embolism. The peri-operative period also involves complex haemodynamic stresses involving hypercoagulable and systemic inflammatory responses, which increase the risks of peri-operative stroke, especially if anticoagulation or anti-platelet therapies are withdrawn.

ACS patients undergoing major non-cardiac surgery were evaluated in one RCT and one observational study. Seventy nine patients with 70—99% ACS were randomised to CEA within one week of the scheduled procedure ($n = 40$) *versus* deferred CEA ($n = 39$). There were no peri-operative deaths/strokes in either group.[594] An observational study evaluated whether ACS predisposed patients undergoing non-cardiac surgery to increased peri-operative stroke. Over a five year period, 2 110 patients had DUS less than six months from, or one month after, surgery (37% had ACS > 50%, 13% had > 70% ACS). Overall, 54 (3%) suffered a stroke. Neither of the ACS stenosis thresholds (> 50%; > 70%) were associated with increased rates of peri-operative stroke.[586] It is, of course, possible that ACS patients with impaired CVR may be at higher risk of stroke after major non-cardiac surgery, but no association has been proven.[595]

The Society of Thoracic Surgeons and American College of Cardiology evaluated whether carotid disease increased stroke rates in 29 143 patients undergoing transcatheter aortic valve replacement, where 22% had a carotid stenosis > 50%. In hospital stroke was 2% in patients with no stenosis, 2.5% with moderate stenoses, 3% with severe stenosis, and 2.6% with carotid occlusion. The Registry concluded there was no association between carotid disease and stroke after transcatheter aortic valve replacement.[139]

Recommendation 116 — **Unchanged**

For patients undergoing elective, non-cardiac surgery with a history of stroke or transient ischaemic attack within the preceding six months, carotid artery imaging is recommended.

Class	Level	References	ToE
I	B	Jorgensen *et al.* (2014)[585]	

Recommendation 117 — **Unchanged**

For patients with a history of stroke or transient ischaemic attack in the preceding six months attributable to an ipsilateral 50—99% carotid stenosis and who are scheduled to undergo elective, non-cardiac surgery, it is recommended that carotid revascularisation be performed before the non-cardiac surgical procedure.

Class	Level	References	ToE
I	B	Rothwell *et al.* (2003)[357], Jorgensen *et al.* (2014)[585]	

Recommendation 118 — **Unchanged**

For patients with a history of prior stroke and no significant carotid artery disease, it is recommended that, where possible, elective non-cardiac surgery should be delayed by 6 months. The decision to proceed with semi-urgent elective surgery will have to be individualised, based upon the underlying pathology.

Class	Level	References	ToE
I	B	Jorgensen *et al.* (2014)[585]	

Recommendation 119 — **Unchanged**

For asymptomatic patients undergoing non-cardiac surgery procedures, routine carotid imaging is not recommended.

Class	Level	References	ToE
III	B	Azelrod *et al.* (2004)[583], Sharifpour *et al.* (2013)[584]	

Recommendation 120 — **Unchanged**

For patients undergoing major non-cardiac surgical procedures, it is recommended that they should undergo a comprehensive cardiovascular risk assessment to aid the consent process regarding the risk of peri-operative stroke.

Class	Level	References	ToE
I	B	Mashour *et al.* (2011)[591], Mashour *et al.* (2014)[593]	

Recommendation 121 — **Unchanged**

For patients with asymptomatic 50—99% carotid stenoses undergoing a major non-cardiac procedure, it is recommended not to stop statin therapy prior to surgery. Antithrombotic therapy withdrawal should be based on an assessment of thromboembolic and haemorrhagic risks.

Class	Level	References	ToE
III	B	Huang *et al.* (2010)[590], Mashour *et al.* (2014)[593]	

Recommendation 122 — **Unchanged**

For patients with an asymptomatic 50—99% carotid stenosis undergoing a major non-cardiac surgical procedure, prophylactic carotid endarterectomy or carotid stenting is not recommended.

Class	Level	References	ToE
III	B	Sonny *et al.* (2014)[586], Ballotta *et al.* (2005)[594]	

The German-Austrian guidelines made no comment about managing patients with carotid stenoses scheduled to undergo major, non-cardiac procedures.[3] The SVS guidelines simply stated that patients with carotid disease undergoing non-cardiac surgery should have the same indications for intervention as the general population, without clarifying what this meant.[4]

10. OCCLUSIVE DISEASE OF COMMON CAROTID AND INNOMINATE ARTERIES

10.1. Introduction

The incidence of stenosis or occlusion at the aortic arch branch vessel origins is 0.5—6.4%, with a higher frequency in the innominate (IA) and left subclavian arteries *versus* left CCA.[596] CCA occlusion occurs in 2—4% undergoing angiography for cerebrovascular disease.[597] Patients with a symptomatic branch origin stenosis have a 2% annual risk of developing a stenosis in other arch vessels, while tandem disease of the carotid bifurcation occurs in 17%.[596]

10.2. Clinical presentation

Left CCA lesions cause left hemisphere and left retinal symptoms. Left subclavian lesions cause VB, or left arm symptoms, while IA lesions can affect the right carotid, VB, and right arm. Most are atherosclerotic, but arteritis and dissection are more common in younger patients.

10.3. Indications for revascularisation

The natural history of isolated CCA and IA disease is unknown. In patients with neurological symptoms or upper limb ischaemia, indications for revascularisation are straightforward. There is no evidence supporting open or endovascular interventions in asymptomatic patients.

10.4. Endovascular versus open reconstruction

Historically, treatment of supra-aortic disease was mainly possible via open surgery, involving bypasses from the arch or subclavian artery, CCA transposition or CCA endarterectomy. CCA transposition to the subclavian artery provides direct autogenous revascularisation but may not always be feasible. CCA endarterectomy can be performed via open or retrograde semi-closed endarterectomy. A meta-analysis of 77 observational studies ($n = 1\ 969$) evaluated 30 day and midterm outcomes in patients with stenoses affecting the proximal CCA or IA who underwent isolated open surgery ($n = 686$) or an isolated endovascular approach ($n = 583$).[90] In the open surgery group (78% involving IA), the 30 day death/stroke was 7%, with a late ipsilateral stroke rate of 1% at a median 12 years follow up. Late re-stenosis within bypasses arising from the aortic arch was 2.6%. In the isolated endovascular group (52% IA), the majority (84%) were done percutaneously, with 30 day death/stroke rates of 1.5%. Late ipsilateral stroke was 1% at a median four years follow up with a 9% re-stenosis rate.[90] In a VSGNE audit of outcomes after a totally endovascular approach to treating tandem stenoses/occlusions of the innominate or proximal CCA and stenoses of the ipsilateral ICA in asymptomatic patients (not included in Robertson's meta-analysis), 30 day death/stroke was significantly higher compared with stenting isolated asymptomatic ICA stenoses (OR 1.85; 95% CI 1.03 − 3.33, $p = .039$).[119]

10.5. Open revascularisation: cervical versus transthoracic

Options include bypass via a transthoracic route (median sternotomy or trapdoor incision), or an extrathoracic (cervical) approach. Cervical reconstructions are less invasive with fewer risks. Patients with isolated subclavian or CCA lesions (with a patent ipsilateral carotid or subclavian artery) should undergo transposition or bypass via a cervical approach. Saphenous vein was previously the preferred conduit, but it is often small calibre and prone to kinking *versus* prosthetic grafts, which offer durable patency and low morbidity.[598] At the other extreme is the patient with involvement of 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, and better long term patency.[90,599]

10.6. Tandem proximal inflow and internal carotid artery disease

Tandem disease refers to lesions affecting the IA or proximal CCA in the presence of notable disease of the ipsilateral ICA. Most now undergo a hybrid approach, where open retrograde angioplasty/stenting of the IA or proximal CCA is followed by CEA of the ipsilateral ICA. In a systematic review ($n = 700$), 30 day death/stroke was 3.3%, with a late ipsilateral stroke rate of 3.3% at a median six year follow up. Late re-stenosis was 10.5% for proximal CCA or IA and 4.1% in the ICA.[90] In symptomatic patients, data cautiously support an endovascular first strategy for isolated proximal CCA or IA lesions with a hybrid approach for tandem CCA or IA and ICA stenoses. ESVS recommendations regarding the management of patients with tandem IA or proximal CCA and bifurcation disease, are the same as 2021 SVS recommendations.[4]

Recommendation 123		Unchanged
For asymptomatic patients with proximal common carotid artery or innominate artery stenoses/occlusions, open or endovascular interventions are not recommended.		
Class	**Level**	**References**
III	C	Consensus

Recommendation 124		Unchanged
For symptomatic patients with proximal common carotid artery or innominate stenoses, open retrograde angioplasty and stenting should be considered.		
Class	**Level**	**References** ToE
IIa	C	Robertson *et al.* (2020)[90], Van de Weijer *et al.* (2015)[596]

11. MANAGEMENT OF ASYMPTOMATIC VERTEBRAL ARTERY DISEASE

11.1. Optimal medical therapy

No RCTs have evaluated the effects of APRx, statin, or antihypertensive therapy in patients with asymptomatic VA

stenoses. Accordingly, it is reasonable to adopt the same BMT recommendations as for ACS patients (section 3.1).

11.2. Screening for asymptomatic vertebral artery disease

No RCTs have evaluated VA screening. Accordingly, it is reasonable to adopt the same strategy as for ACS (section 3.2).

11.3. Interventions for asymptomatic vertebral artery disease

Within a cohort of 3 717 patients with atherosclerotic disease in the SMART Registry, 7.6% had an asymptomatic VA stenosis > 50%, in whom the annual stroke risk was only 0.2%.[600]

Recommendation 125			Unchanged
For patients with asymptomatic vertebral artery atherosclerotic lesions, open or endovascular interventions are not recommended.			
Class	**Level**	**References**	**ToE**
III	C	Compter *et al.* (2011)[600]	

12. MANAGEMENT OF SYMPTOMATIC VERTEBRAL ARTERY DISEASE

12.1. Aetiology of vertebrobasilar stroke

About 20% of ischaemic strokes are VB, mostly due to cardioembolism, LAA, and small vessel disease.[601] Atherosclerosis of VAs or basilar arteries (BA) accounts for 20—25% of VB strokes. Stenoses mainly occur at the VA origin but can affect distal or intracranial VAs and BAs. Intracranial stenoses are more common with sub-Saharan or East-Asian ethnic origins. A haemodynamic aetiology was thought to be the most common cause of VB symptoms. However, in a prospective registry, only 13/407 patients (3%) had symptoms due to haemodynamic ischaemia and this was most commonly seen in patients with bilateral intracranial VA disease.[602] Cardiac embolism (usually AF) accounted for 25% of strokes/TIAs, with 25% being due to disease of small penetrating arteries arising from the intracranial VA, BA, and PCA arteries, causing lacunar stroke.[602] Thromboembolism was the main cause of symptoms with VA stenoses.

12.2. Symptoms attributable to vertebral artery disease

Being recently symptomatic refers to VB symptoms in the preceding six months (Table 13, section 4.1). In a series of VB strokes, common symptoms included dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%), and nausea/vomiting in (27%).[603]

12.3. Imaging strategies in vertebral artery disease

DSA has been replaced by CEMRA/CTA due to angiogram related stroke. CEMRA/CTA can image the entire VB system, enabling simultaneous detection of extra- and intracranial stenoses. In a systematic review and meta-analysis (11 observational studies) which measured VA stenoses as 50—99%, sensitivity was 100% for CTA (95% CI 15.8 — 100), 94% for CEMRA (95% CI 79.8 —99.3) and 70% for DUS (95% CI 54.2 — 83.3). Specificities for CTA were 95% (95% CI 83.8 —99.4), 95% for CEMRA (95% CI 91.1 — 97.3), and 98% for DUS (95% CI 95.2 —99.1).[604] The proximal VA can be visualised on DUS, but not the distal VA, so the likelihood of distal VA disease must be inferred from waveform abnormalities.[605] DUS can estimate VA size and flow direction and may differentiate between hypoplasia, stenosis, occlusion and aplasia.[605,606] It can also diagnose subclavian steal syndrome with pre-steal (transient midsystolic flow deceleration), partial steal (flow reversal during systole), and complete steal (retrograde flow throughout cardiac cycle). For detecting VB infarcts, MRI is more sensitive than CT,[607] reflecting higher spatial resolution, especially with small infarcts in the brainstem. DWI-MRI is the most sensitive method for detecting acute ischaemia and may be positive for approximately two weeks after symptom onset.

Recommendation 126			Unchanged
For patients with suspected vertebrobasilar ischaemia, computed tomographic angiography or contrast enhanced magnetic resonance angiography is recommended as the first line vascular imaging modality.			
Class	**Level**	**References**	**ToE**
I	B	Khan *et al.* (2007)[604], Davis *et al.* (1986)[606]	

12.4. Optimal medical therapy

No RCTs have evaluated APRx, statin, or antihypertensive therapy in symptomatic VA stenosis patients. It is reasonable to adopt the same recommendations as for SCS patients (section 4.2).

12.5. Role of vertebral revascularisation in positional vertigo

A diagnosis of positional VB ischaemia is often assumed in patients with dizziness or vertigo during neck movement. However, the syndrome is overdiagnosed, usually without further investigation. A systematic review reported no changes in VA or PCA flow in seven series, while 13 described varying changes (reversal, occlusion, reduced flow).[608] In a study involving 46 patients with a TCD window who presented with dizziness or vertigo on head movement, none had changes in extracranial VA flow during head movement, none had reversal of VA flow and there were no changes in PCA flow (directionality or flow velocities) during head turning.[609] Most symptoms relating to head/neck movement have other causes, including benign paroxysmal positional vertigo, vestibular neuritis, and (occasionally) exacerbation of vertigo associated with migraine.[610] In a

single centre experience, 74% were referred to a Balance Clinic, where 94% improved following a vestibular rehabilitation programme.[609]

Recommendation 127			Unchanged
For patients with vertigo or dizziness on head turning, it is recommended that a diagnosis of vertebrobasilar ischaemia (attributed to nipping of the vertebral arteries on head movement) should not be made, unless corroborated by vascular imaging showing clear disruption of blood flow during head turning.			
Class	**Level**	**References**	**ToE**
III	C	Mitchell *et al.* (2007)[608], Sultan *et al.* (2009)[609], Chandratheva *et al.* (2021)[610]	

12.6. Interventions in recently symptomatic patients

12.6.1. Non-randomised studies. The 90 day risk of recurrent VB stroke was 7% in the absence of VA disease, 16% with extracranial VA stenoses, and 33% with intracranial VA or BA stenoses.[611] In a review of 600 patients with symptomatic VA stenoses treated by angioplasty/stenting, intracranial stenting incurred higher procedural stroke risks (10.6%) *versus* extracranial VA stenoses (1.3%).[612]

12.6.2. Randomised studies

12.6.2.1. Meta-analysis of randomised trials. Table 41 details an individual patient meta-analysis of data from 354 symptomatic patients with 50—99% VA stenoses who were randomised within VIST, VAST, and SAMMPRIS.[29,613,614]

There were no data from VISSIT (did not collaborate) or CAVATAS (VA angioplasty only).[77] Of 168 BMT patients, 46 had intracranial VA stenoses and 122 had extracranial VA stenoses. In the stented cohort, 64 had intracranial VA stenoses and 121 had extracranial VA stenoses. Mean age was 66 years and 80% were male. There were higher peri-operative rates of stroke/death after stenting (*vs.* BMT), with statistically significant differences between extracranial and intracranial stenting (1% *vs.* 16%; $p < .001$). At five years, there were no differences in stroke rates between stenting and BMT.[77] In the carotid literature, interventions conferred maximum benefit if performed early (section 4.5). A subgroup analysis was undertaken in 161 patients randomised within 14 days of the most recent event. Stenting (*vs.* BMT) was associated with non-statistically significant reductions in cumulative stroke (HR 0.65; 95% CI 0.31 — 1.39), including in patients with extracranial VA stenoses (HR 0.56; 95% CI 0.17 — 1.87) and intracranial VA stenoses (HR 0.72; 95% CI 0.27 — 1.90, $p_{interaction}$ value = .77).[77] There are, however, limitations regarding this meta-analysis. SAMMPRIS patients were randomised more quickly after symptom onset (10 days) than in VIST or VAST (36 days) and there were imbalances in prescribing combination APRx. Stent cohorts were more likely to receive DAPT than BMT patients. The current evidence indicates that stenting intracranial VA stenoses carries a higher risk of death/stroke than stenting extracranial VA stenoses and that there is currently no evidence that stenting confers benefit over BMT.

Recommendation 128			New
For patients presenting with a vertebrobasilar territory transient ischaemic attack or stroke and a 50—99% vertebral artery stenosis, routine stenting is not recommended.			
Class	**Level**	**References**	**ToE**
III	A	Markus *et al.* (2019)[77]	

Recommendation 129			Unchanged
For patients with recurrent vertebrobasilar territory symptoms (despite best medical therapy) and a 50—99% extracranial vertebral artery stenosis, revascularisation may be considered.			
Class	**Level**	**References**	**ToE**
IIb	B	Markus *et al.* (2017)[29], Markus *et al.* (2019)[77], Compter *et al.* (2015)[613], Chimowitz *et al.* (2011)[614]	

The SVS guidelines advise that in low risk symptomatic patients with proximal VA stenoses, open surgical revascularisation is recommended.[4] However, no mention was made about managing a VA stenosis beyond its origin or on the role of VA stenting. The 2021 AHA guidelines advise there is no proven role for VA stenting in symptomatic patients.[1]

12.6.3. Endovascular techniques

12.6.3.1. Adjuvant medical therapy. Protocols regarding APRx, statins and i.v. heparin are as for CAS (sections 3.1 and 4.2).

Table 41. Main findings of meta-analysis of three randomised controlled trials (RCTs) comparing extracranial (EC) and intracranial (IC) vertebral artery (VA) stenting with best medical therapy (BMT) alone*

	30 d death or stroke		HR (95% CI) stent *vs.* BMT	Cumulative 5 y stroke		HR (95% CI) stent *vs.* BMT
	Stenting	BMT		Stenting	BMT	
All patients	11 / 185 (5.9)	4 / 168 (2.4)	2.20 (0.70—6.96)	23 / 186 (12)	24 / 168 (14)	0.81 (0.45—1.44)
EC VA stenosis	1 / 121 (1)		0.33 (0.03—3.18)			0.63 (0.27—1.46)
IC VA stenosis	10 / 64 (16)		7.46 (0.95—58.69)			1.06 (0.46—2.42)

Data are presented as *n* (%) unless stated otherwise.
HR = hazard ratio; CI = confidence interval.
* Data derived from Markus *et al.*[77].

12.6.3.2. Access. Most are performed under LA via the CFA (93%), although transbrachial (3%) and TRA (5%) have been used.[615]

12.6.3.3. Wires, catheters, and stent design. A 5F or 6F guiding catheter or long access sheath (if working via CFA) is navigated to a stable position in the subclavian artery. The VA ostium is cannulated, and the lesion crossed with .014" or .018" guide wires and treated using small balloons and stents. Monorail and over the wire systems are available. The former uses standard length wires, making catheter exchanges simpler. Dedicated VA stents are not available and coronary balloon expandable stents (BES) are used because of a low crossing profile, limited foreshortening, and easier navigation through tortuous vessels. One issue with VA stenting is optimal coverage of an ostial plaque. The use of a "dual balloon" (allows flaring of the subclavian edge of the stent) is one option. Self expanding stents (SES) are more difficult to deploy as precisely as BES (especially in ostial lesions) and they tend to be used in large diameter VAs. Meta-analyses of non-randomised studies report no differences between drug eluting stents (DES) and bare metal stents (BMS) regarding technical success and procedural complications. However, BMS patients had more recurrent symptoms (11.3% *vs.* 2.8%, OR 3.3; 95% CI 1.3 — 8.3, $p = .010$) and re-interventions (19.2% *vs.* 4.8%, OR 4.1; 95% CI 2.0 — 8.2, $p = .001$) than with DES.[616]

12.6.3.4. Cerebral protection devices. The use of CPDs in VA interventions has not been adequately investigated.[615]

12.6.3.5. Pre-dilation. Risks associated with pre-dilation in extracranial VA stenting have not been evaluated. Pre-dilation is indicated if the stent cannot pass through the VA stenosis.

12.6.4. Open surgical management. Options with VA origin lesions include transposition to ipsilateral CCA, VA re-implantation, vein bypass from subclavian artery, and trans-subclavian VA endarterectomy. Distal VA reconstruction can treat lesions within V2 or V3 segments, but worldwide experience is limited. Techniques for reconstructing the V3 segment (C2 to where the VA perforates the dura) include transposition and bypass. Transposition using the ECA, or occipital artery are options if there is no suitable graft available.[617]

12.6.5. Complications after vertebral artery interventions

12.6.5.1. Open surgery. Table 42 details outcomes after open VA reconstructions, mostly single centre series. While 30 day death/stroke rates after proximal and/or distal VA reconstructions were relatively low (2—7%), there was evidence that risks were higher if VA reconstructions were combined with carotid procedures (30 day death/stroke 8—33%). Paralysis of the spinal accessory nerve complicated 1—13% of procedures (average 7%), while Horner's syndrome (temporary or permanent) complicated 2—21% of procedures.

Recommendation 130			Unchanged
For patients with combined carotid and vertebral artery disease, synchronous carotid and vertebral artery revascularisations are not recommended.			
Class	**Level**	**References**	**ToE**
III	C	Kieffer *et al.* (2002)[617], Berguer *et al.* (2000)[619], Ramirez *et al.* (2012)[621], Coleman *et al.* (2013)[622]	

12.6.5.2. Endovascular interventions.

12.6.5.2.1. Peri-operative events. In a systematic review of 20 non-randomised studies (1 767 VA stented patients), only five peri-operative strokes (0.3%) were reported, access complications occurred in 0.7%, while 0.5% were

Table 42. Thirty day morbidity and mortality after vertebral artery (VA) reconstructions

Author	Operation	Patients — n	Symptomatic patients — %	Death — %	Any stroke — %	Carotid stroke	VB stroke — %	Death / stroke — %
Habozit[618]	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[619]	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[617]	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[620]	Proximal VA	29		0.0	0.0	0.0	0.0	0.0
Ramirez[621]	All VA ops	74	82	4.1	4.1			6.8
	VA ops only	39			2.6	0.0	2.6	5.1
	VA + carotid	35			5.7			8.5
Coleman[622]	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
Mert[623]	Proximal VA	43	100	2.3	4.7	4.7	0	7
	VA + carotid	11			18	18		18

VB = vertebrobasilar.

complicated by dissection.[624] In the absence of specific studies on treating procedural stroke after VA stenting, no recommendations can be made other than advising they should be treated in the same way as after CAS (section 7.1.2).

12.6.5.2.2. In stent re-stenosis after vertebral artery stenting. Table 43 summarises four systematic reviews on in stent re-stenosis (ISR) after VA stenting.

Risk factors for ISR include intracranial stenosis, ostial stenosis, stenosis > 10 mm, smaller stent size, BMS *versus* DES, higher residual stenosis, VA tortuosity, contralateral VA occlusion, DM, and smoking. A multicentre study (420 patients undergoing VA stenting with BMS ($n = 204$) or DES ($n = 216$), reported a mean ISR rate of 26% at 12 months. ISR was statistically significantly lower with DES *versus* BMS (OR 0.38; 95% CI 0.19 − 0.75, $p = .010$),[627] a finding corroborated in another study, where DES were associated with statistically significantly lower ISR rates (18% at one year) *versus* 31% with BMS (OR 2.6; $p = .020$).[628] In a single centre series, stent fracture rates were 5%, 15%, and 30% at one, three, and five years, respectively, but the majority were asymptomatic.[627]

There are no RCT data to guide management of ISR following VA stenting. In a multicentre, retrospective registry involving 72 patients with ISR ≥ 70% (83% asymptomatic), 48 (67%) underwent treatment by redo stenting ($n = 26$) or balloon angioplasty ($n = 22$), without complications.[174] However, the one year rate of stroke/TIA was not notably different in patients undergoing repeat interventions *versus* BMT, with recurrent re-stenoses developing in 33%. The rate of recurrent ISR was higher (50%) in patients undergoing balloon angioplasty alone *versus* 22% with redo stenting ($p = .009$).[174] Patients with recurrent VB symptoms after stenting should probably be considered for redo stenting (having ensured all were on optimal BMT). However, there are no data to guide practice in patients with an asymptomatic > 70% re-stenosis after VA stenting.

Recommendation 131			Unchanged
For patients undergoing vertebral artery stenting, drug eluting stents should be considered in preference to bare metal stents.			
Class	**Level**	**References**	**ToE**
IIa	C	Antoniou *et al.* (2012)[615], Tank *et al.* (2016)[616], Langwieser *et al.* (2014)[626], Li *et al.* (2019)[627], Li *et al.* (2020)[628]	

12.6.6. Surveillance after vertebral artery revascularisation. Open reconstructions for proximal VA lesions are associated with high rates of symptomatic improvement and low rates of re-stenosis. In 29 patients undergoing proximal VA reconstruction, only two developed recurrent VB symptoms, while only one developed a recurrent stenosis.[620] In another series of 36 patients, no re-stenoses or recurrent strokes occurred during a mean follow up of 54 months after VA to subclavian artery transposition.[629] VA stenting is associated with higher rates of ISR. While DUS can identify proximal VA stenoses, it is suboptimal for diagnosing re-stenoses within stented vessels. Accordingly, while a diagnosis of recurrent stenosis after CEA/CAS is more straightforward, surveillance after VA stenting is challenging. DSA was the gold standard, but its use in surveillance cannot be justified (angiographic stroke), especially as recurrent VB events are low. Accordingly, for those advocating surveillance after interventions in the V1 segment of the VA, DUS may be performed at six and 12 months and yearly thereafter. Suspected lesions should be corroborated by CTA/MRA (unless contraindicated) before considering DSA.[256,612] Anyone experiencing a recurrent VB stroke/TIA after VA revascularisations should be investigated as in section 12.3.

Recommendation 132			Unchanged
For patients undergoing vertebral artery interventions, serial surveillance with catheter angiography is not recommended.			
Class	**Level**	**References**	**ToE**
III	B	Antoniou *et al.* (2012)[615], Stayman *et al.* (2011)[625]	

Recommendation 133			Unchanged
For patients who have undergone an open or endovascular vertebral artery intervention, serial non-invasive imaging surveillance may be considered.			
Class	**Level**	**References**	**ToE**
IIb	C	Brott *et al.* (2011)[256], Eberhardt *et al.* (2006)[612]	

13. UNANSWERED QUESTIONS FROM THE 2023 ESVS GUIDELINES

During preparation of the 2023 guidelines, unanswered questions were identified by the GWC as being research priorities for the future. These involve situations where

Table 43. Meta-analyses on in stent re-stenosis (ISR) after vertebral artery (VA) stenting

Author	Years	Patients − *n*	BMS − *n*	DES − *n*	Mean follow up time − mo	Mean ISR − %	ISR BMS − %	ISR DES − %
Eberhardt[612]	1966−2005	313			12	25.7		
Stayman[625]		980	340	196	24		30	11.2
Antoniou[615]	1981−2011	1 010	801	209		23		12
Langwieser[626]	Up to 2013	457	287	170			23.7	8.2
Tank[616]	2006−2012	304	148	156	DES: 14 BMS: 20	24.4	33.6	15.5

BMS = bare metal stent; DES = drug eluting stent.

there were either no data, or conflicting evidence that did not allow recommendations to be made.

Should the 3% (asymptomatic) and 6% (symptomatic) 30 day risk thresholds for performing CEA or CAS be reduced?

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

The need for a validated algorithm for identifying 'high risk for stroke on BMT' asymptomatic patients in whom to target CEA and CAS.

Is stroke risk on modern BMT in ACS patients lower than when ACAS and ACST-1 were recruiting?

Are 80—99% ACS associated with higher rates of late ipsilateral stroke compared with 60—79% stenoses?

Does measurement of plasma biomarkers (to evaluate excessive endothelial and coagulation system activation) have the potential to aid risk stratification in patients with asymptomatic or symptomatic carotid stenosis?

Does severe ACS cause cognitive impairment and can carotid interventions either reverse or prevent cognitive decline?

What is the effectiveness of low dose rivaroxaban plus aspirin (vs. aspirin alone) in ACS patients?

In patients undergoing mechanical thrombectomy after acute ischaemic stroke, who should undergo synchronous CAS to treat tandem extracranial ICA stenoses and when should CAS (or CEA) be deferred?

For symptomatic patients with a 50—99% stenosis who have undergone thrombolysis, with no evidence of acute cerebral infarction on CT/MRI, should they still wait six days before undergoing a carotid intervention?

Should patients with NIBLs after carotid interventions receive more intense BMT (e.g., combination APRx)?

Are new ischaemic brain lesions after CEA or CAS associated with long term cognitive impairment?

Is carotid artery near occlusion as benign as previously thought in patients presenting with stroke/TIA?

Does intravenous heparin confer additional benefit over dual antiplatelet therapy in patients presenting with crescendo TIAs associated with an ipsilateral 50—99% carotid stenosis?

What is the effectiveness of long term low dose rivaroxaban plus aspirin (vs. aspirin alone) in patients presenting with a recently symptomatic carotid stenosis?

Can transcarotid artery revascularisation be performed safely in the first 7 — 14 days after symptom onset with procedural risks similar to CEA?

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

Should locoregional anaesthesia be preferred over general anaesthesia in CEA patients?

Does carotid revascularisation improve visual acuity in patients with established, neovascularisation related glaucoma?

Is there a role for routine pre- and post-operative troponin measurement in CEA or CAS patients?

What is the annual hospital or individual surgeon CEA volume needed to maintain competence and safety?

Is there a role for stenting within two weeks of TIA/stroke onset in patients with extracranial VA stenoses?

Is there a role for routine testing of antiplatelet high on-treatment platelet reactivity (HTPR) (previously termed antiplatelet resistance) to guide adjustment of the regimen or dose of antiplatelet therapy?

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

14. INFORMATION FOR THE PATIENT

The ESVS gratefully acknowledge the assistance of Mr Chris Macey (Irish Heart Foundation and the Stroke Alliance for Europe) for preparing this section and Dr Antonino Logiacco (Alma Mater Studiorum, University of Bologna) for designing the illustrations.

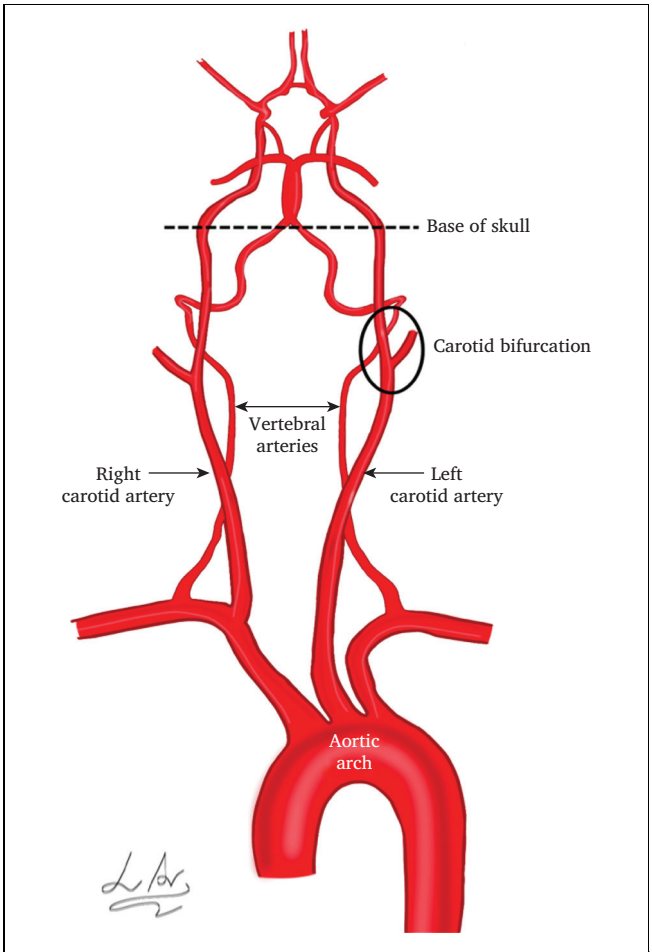


Figure 9. Main blood supply to the brain comes from the carotid and vertebral arteries.

The ESVS has commissioned guidelines for healthcare professionals involved in treating patients with carotid or vertebral artery disease. They were prepared by experts in the field representing vascular surgery, vascular neurology, stroke medicine, interventional radiology, and interventional cardiology.

The carotid arteries are the main arteries supplying blood to the eyes and front of the brain, while the vertebral arteries are the main blood supply to the back of the brain (Figure 9). One of the aims of the guideline is to optimise shared decision making, where you (the patient) have choice and control over how you want to be treated and that you are supported in how your care is delivered. This requires doctors to provide you with as much information as possible, which should include discussion of all available treatment options, together with their risks, benefits, and potential consequences in a manner that you can easily understand.

A carotid or vertebral artery narrowing (otherwise known as a stenosis) may develop because of a condition called atherosclerosis (hardening of the arteries), where deposits of fat and calcium develop in the artery walls. In the carotid artery, most narrowings develop at the point where the carotid artery divides in two. This area is known as the carotid bifurcation (Figure 9). Carotid and vertebral artery stenoses can cause a stroke or a transient ischaemic attack (TIA), which is otherwise known as a warning or mini stroke. The ESVS Guidelines Writing Committee was asked to review the available evidence about the management of carotid and vertebral artery narrowings (which mainly deals with prevention of TIA and stroke), and to make recommendations about how patients like you should be managed.

During the guideline process, all pieces of evidence are considered. A decision is then made about whether the evidence is strong enough to make a firm recommendation which all doctors should follow, or whether the evidence is not strong enough to make a recommendation. In some areas of practice, there is surprisingly little evidence to make a recommendation. The committee then decides whether a particular treatment is one that "Experts" would agree was best. For each recommendation, the committee awards a "level of evidence" from "A" (best quality evidence) to "C" (no real evidence or expert opinion). The committee also awards a "class of recommendation" from class I (strong recommendation and general agreement among experts that the treatment is beneficial, useful, or effective) to III (agreement that the treatment is not effective or may be harmful).

The following is a summary of the advice and recommendations in a format suitable for non-experts. It has been prepared by the ESVS Guidelines Committee in collaboration with patient organisations working to combat stroke.

14.1. How are carotid and vertebral artery narrowings classified, and can their appearance predict an individual patient's stroke risk?

Narrowings in the artery may stay small and localised (termed a plaque). Their extent and severity can be imaged and measured by ultrasound or other imaging techniques (e.g., computed tomographic (CT) scans or magnetic resonance imaging (MRI) scans). Over time, a plaque may become larger and cause the artery to become more furred up (or stenosed), which may lead to reduced blood flow beyond the narrowing (Figure 10A). If a plaque causes narrowing of an artery to half its original diameter, this is called a 50% stenosis. If three quarters of the artery is narrowed, this is called a 75% stenosis. If the whole artery is blocked off, this is called an occlusion (Figure 10B).

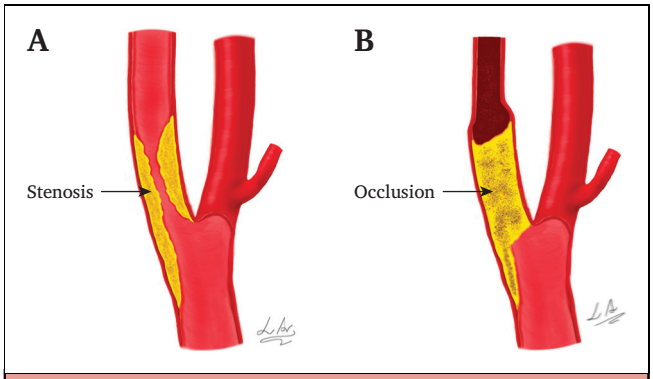


Figure 10. Stenosis in the carotid artery (A), and occlusion of the carotid artery (B).

14.2. Is screening for carotid artery stenosis worthwhile?

At present, screening is not recommended for everyone to see if they have carotid disease, even though this might seem like a sensible thing to do. This is because the chances of identifying someone with an important narrowing of the carotid artery (70% stenosed or more) at the age of 65 years is very small (about one in every 100 people screened).

In addition, even if asymptomatic narrowings are detected (these are stenoses that have never caused a TIA or stroke), in most cases, we would not normally recommend operating on or stenting the stenosis in question. The ESVS (and other national guidelines) sometimes recommend ultrasound screening in a subgroup of usually older patients who have several risk factors for vascular disease (e.g., heart disease, smokers, people with high blood pressure, vascular disease affecting the legs or those with high cholesterol).

It is important to remember that most people with an asymptomatic narrowing in their carotid artery will not experience a stroke (and therefore do not need an operation or intervention), but all will benefit from lifestyle modification and control of vascular risk factors.

14.3. What problems can carotid and vertebral artery disease cause and what warning signs should members of the public look out for?

Carotid and vertebral artery stenoses often cause no problems at all (termed asymptomatic stenoses which are picked up incidentally during other investigations), or they can be directly responsible for causing a TIA or stroke (where stenoses are termed symptomatic).

For every 100 TIAs or strokes, about 15 are due to narrowings of the carotid or vertebral arteries. The most common way in which narrowings cause a TIA or stroke is by small blood clots forming on the surface of the narrowed arteries. These

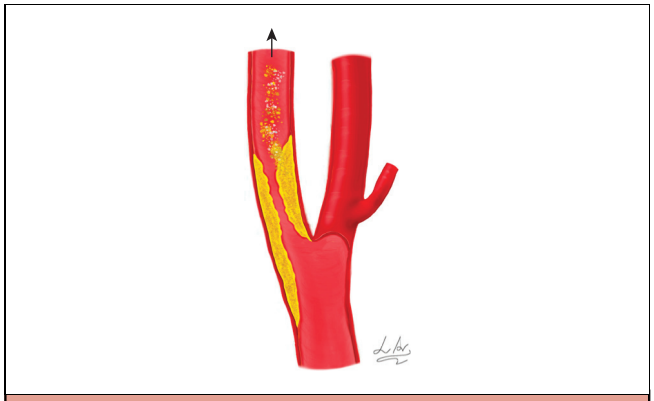


Figure 11. Emboli (made up of plaque debris and small blood clots) break off the narrowing and go up into the brain.

blood clots can then break off and go into the eye or brain where they can block off the eye or brain blood vessels. These small circulating blood clots are called emboli (Figure 11).

About 20% of strokes due to reduced blood supply to the eye or brain (called ischaemic stroke) are preceded by a TIA. A TIA is caused by a shorter, temporary reduction in blood supply to the brain. A TIA causes exactly the same symptoms as a stroke, but the symptoms usually resolve within minutes, definitely within 24 hours, which is the time based definition for TIA. This provides patients and doctors with an extremely important window of opportunity for urgent stroke prevention. This is why drugs (e.g., aspirin, clopidogrel, dipyridamole) are prescribed to reduce the risk of blood clot formation and so prevent further TIAs or stroke in people with carotid or vertebral narrowings, regardless of whether they need an operation or stent.

An easy way to remember the symptoms of a TIA or stroke is to remember that they can cause the "**S**" symptoms, involving **S**udden problems with:

Sight	Blurring or loss of vision or double vision
Speech	Impaired expression, understanding or slurring
Swallowing	Problems swallowing liquids or solids (more common with stroke than TIA)
Strength	Weakness of the face, arm and/or leg
Sensation	Usually numbness / reduced feeling and less commonly pins and needles in the face, arm, and/or leg
Stability	Sudden unsteadiness or a sense that you are moving or the environment around you is moving or spinning, called vertigo

If you experience any of these symptoms, you should seek immediate medical assessment by your family doctor that day or attend your local hospital emergency department (if your family doctor is not available). If you have symptoms of a stroke which are not immediately resolving, you or your relative must call an ambulance to arrange urgent transfer to your local emergency department for immediate investigations and stroke care.

14.4. Can doctors predict which people with carotid disease are most at risk of suffering a stroke?

There has been a lot of debate about whether patients with asymptomatic narrowings should undergo an operation to remove the narrowing, to prevent a stroke from happening. In fact, about 80% of people who have a severe asymptomatic narrowing will not have a stroke over a 10 year period, provided they follow lifestyle advice and take their prescribed medicines.

This means that only a relatively small number of people are at high risk of experiencing a stroke if the stenosis remains in place. Therefore, if they do not have higher risk features which predict an increased risk of TIA/stroke, most patients with asymptomatic carotid narrowings are advised to follow healthy lifestyle advice and to take appropriate medications alone.

In the past, it was difficult to predict who was more likely to have a stroke. The 2023 ESVS guidelines for managing patients with asymptomatic carotid stenosis recommend that several investigations should be performed before any decision is made about the need for an operation or stent. These tests look at the severity of the narrowing in the carotid artery and whether it has become more severe since the last scan (using ultrasound). Brain scans (CT/MRI) are used to see if there is evidence of old areas of reduced blood supply (called infarction), which can occur in some patients even if there have been no obvious symptoms.

Ultrasound scans can look directly at the narrowing to see whether there are any features that make a TIA or stroke more likely (e.g., very large or very soft plaques). It is also possible to detect if little blood clots (emboli) are silently breaking off the surface of the carotid narrowing and going up to the brain without your knowledge. If any of these tests show higher risk features, your doctor may recommend that you have an operation to remove the narrowing.

However, if you present with a TIA or minor stroke and are found to have at least a 50% narrowing of your carotid artery, then your risk of stroke in the next few weeks is increased. In this situation, most people (but not those with an occlusion) will be considered for an operation to remove the narrowing (carotid endarterectomy), or to insert a stent via an arterial puncture in the groin, arm, or neck, to open up the diseased artery (carotid artery stenting). This is especially true in patients with at least a 70% narrowing of the carotid artery.

14.5. Does carotid artery disease cause dementia?

Stroke can also cause problems with memory, language, and paying attention (known as cognitive impairment). Sometimes, stroke can cause dementia, particularly if patients have had multiple strokes. Therefore, it may be possible that a carotid stenosis can increase the risk of dementia. However, many people with carotid stenosis also have vascular disease affecting the small arteries deep inside the brain (especially if they have poorly treated high blood pressure, or have a history of smoking or diabetes), which can also increase the risk of cognitive impairment and dementia.

In patients who have never had any symptoms from their carotid stenosis, research has suggested a possible association with cognitive impairment. However, there is no definite evidence that this type of narrowing is directly responsible for causing dementia. It is possible that in a few patients, the combination of a very severe stenosis, together with markedly reduced brain blood flow, can make cognitive impairment more likely.

14.6. Are chronic kidney disease and carotid artery disease connected?

Not directly. However, if a patient has risk factors for vascular disease (conditions that make a patient more likely to develop narrowings in their arteries), then one or both conditions may co-exist. These risk factors might include untreated or poorly treated high blood pressure and diabetes (which over time, is associated with worsening kidney function, furring up of small arteries inside the brain, and carotid artery narrowings), or smoking (which increases the likelihood of narrowings developing in both carotid and kidney arteries).

14.7. What is meant by best medical therapy?

Everyone with a narrowing in their carotid or vertebral arteries (whether they have symptoms or not) will benefit from lifestyle advice (stopping smoking, losing weight, reducing alcohol intake, better diet, taking more exercise). These lifestyle changes will reduce the risk of having a TIA or stroke in the future.

It is also likely your doctor will advise you to take certain medications. The 2023 ESVS guidelines have greatly expanded its advice for doctors to enable them to prescribe the best possible combinations of medicines to reduce your long term risk of TIA, stroke, or other vascular events (such as heart attacks). These are detailed separately in the guidelines for asymptomatic patients and for symptomatic patients. They include "antiplatelet" tablets (e.g., aspirin, clopidogrel, dipyridamole), which thin the blood and reduce the chances of blood clots passing into the eye or brain and causing a TIA or stroke.

A small number of patients need stronger blood thinning drugs (anticoagulants), especially those with an irregular heartbeat called atrial fibrillation. But this aspect of TIA and stroke prevention and treatment is outside the remit of the current guidelines. If your blood pressure is elevated, you will be advised to take medicines, because treatment of high blood pressure greatly reduces your risk of TIA/stroke or other vascular events.

Patients need to know their own blood pressure readings, lipid profiles, and blood sugar readings (if diabetic) to empower them to work closely with their doctors to reach their treatment targets We advise aiming for the following targets in relation to blood pressure and cholesterol:

Blood pressure targets
Non-diabetic patients under 65 years: ≤130/80 mmHg
Non-diabetic patients of 65 years and over: systolic 130 −139 mmHg and diastolic <80 mmHg
Diabetic patients under 65 years: systolic 120−129 mmHg, diastolic 70−79 mmHg
Diabetic patients of 65 years and over: systolic 120−139 mmHg, diastolic 70−79 mmHg

Cholesterol level targets
Total cholesterol: <3.5 mmol/L (<135 mg/dL)
LDL 'bad' cholesterol: <1.8 mmol/L (<70 mg/dL)
LDL 'bad' cholesterol in higher risk patients: <1.4 mmol/L (<54 mg/dL)

Slightly different blood pressure targets are advised for patients with diabetes, as outlined in the table above. In addition, it is likely that your doctor will advise you to take a "statin" tablet (or something similar) to reduce levels of cholesterol and other harmful fats in your blood to further reduce your risk of TIA/stroke or other vascular events. If you have diabetes, your doctor will advise you regarding control of your blood sugar levels.

14.8. Which interventions are currently available?

Some patients with moderate to severe carotid narrowings will be advised to undergo an intervention, with the decision and urgency based on whether you have had recent symptoms or not. There are currently two options. **Carotid endarterectomy** is an operation which removes the stenosis from the carotid artery via an incision in your neck. **Carotid artery stenting** is a less invasive intervention. It involves passing a fine wire and tube (catheter) through the skin in the groin, arm, or neck, then into the narrowed artery in the neck to place a stent (a metallic meshlike cylinder) inside the carotid artery to open up the narrowing.

The highest risk period for having a stroke after presenting with a TIA or minor stroke is the first 7 — 14 days, which is why ESVS guidelines advise that carotid endarterectomy or stenting be performed as soon as possible after symptom onset. At present, the available evidence suggests that carotid endarterectomy is preferred to carotid artery stenting during this early time period. However, once you have recovered from your operation or stent insertion, there is good evidence that the long term results of both techniques are identical in terms of preventing further strokes from happening. The risks of developing a recurrent narrowing (re-stenosis) may be slightly higher after stenting than after surgery.

When it comes to planning which intervention is best for you, your doctor will consider a lot of factors (your age, blood vessel appearance, timing of symptoms, and your own preference) before advising which might be the best option for you.

14.9. What does carotid endarterectomy involve?

Carotid endarterectomy is an operation to remove the stenosis inside the carotid artery. It is performed under either local or general anaesthesia and involves an incision on the side of your neck. The carotid artery is identified (Figure 12A), and a medicine called heparin is given to prevent blood clots forming during the procedure. The carotid artery is then clamped and opened (Figure 12B).

Sometimes, a piece of plastic tubing (a shunt) is temporarily inserted to maintain blood flow to the brain during the operation, but this is not always necessary. The stenosis is then carefully removed, and a patch is usually inserted to close the incision in the artery (Figure 12C) to make it a little wider and so reduce the chance of further narrowings developing in the future. The operation takes about one to two hours. When it is finished, you will be kept in the

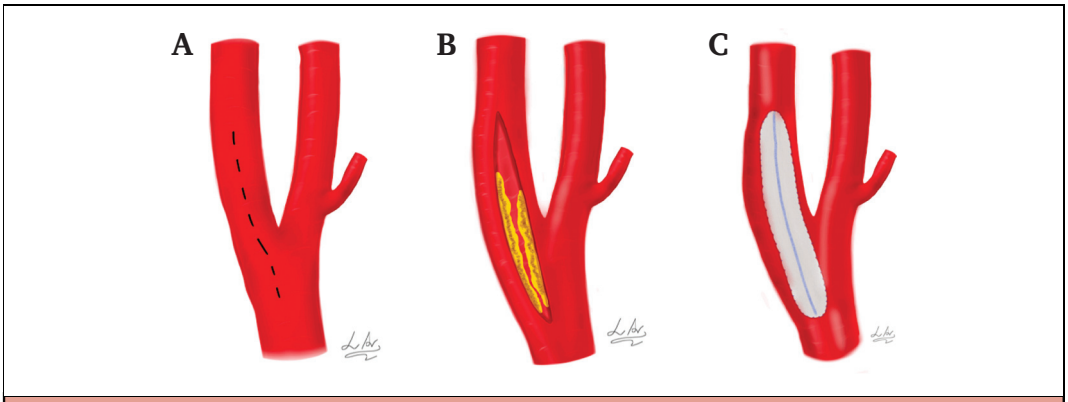


Figure 12. Site of incision in the carotid artery (dotted line) (A). Carotid artery is opened to reveal the narrowing (B). The narrowing is removed and the artery closed with a patch (C).

recovery area of theatre for about three hours, during which time you will be carefully monitored.

Most patients go back to the vascular ward or stroke unit, and most are discharged on the second post-operative day. The most common reason for delayed discharge is the need to control high blood pressure, which can sometimes increase after carotid surgery and stenting. Thereafter, you will need to continue taking the antiplatelet medications, lipid lowering medications, and any other medications which are prescribed by your doctor in the long term.

14.10. What does carotid artery stenting involve?

Carotid artery stenting is usually performed under local anaesthesia, but some are done under general anaesthesia. The procedure starts by having a small wire and tube (catheter) inserted into an artery in your groin, or arm or low down in your neck. Through this catheter, the stent delivery system is passed up into the carotid artery and then across the stenosis (Figure 13A). As with carotid endarterectomy, you will be given heparin to reduce the chance of blood clots forming on the surface of the stent.

Patients undergoing carotid stenting also receive medicines to prevent the heart rate from slowing down, because stretching up a narrowed carotid can sometimes cause this to occur. Most operators insert a brain protection device, which is designed to prevent blood clots (emboli) passing to the brain during the stent procedure.

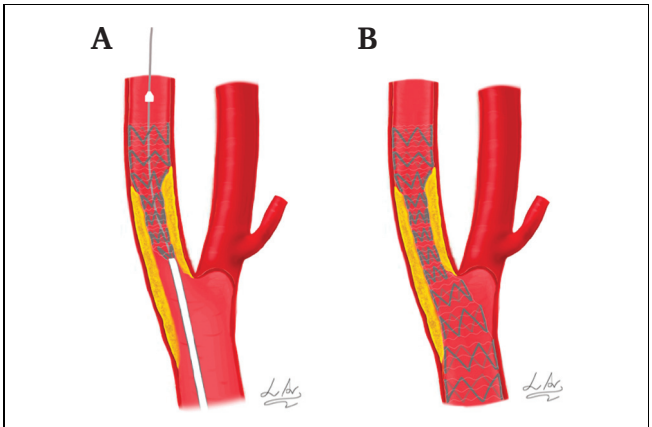


Figure 13. A catheter containing the stent is positioned within the stenosis and is then slowly opened out (A). Once the stent has opened, the wires and catheters are removed (B).

The stent is then carefully positioned within the narrowed artery and released, which causes it to open within the artery (Figure 13B). The operator will take lots of X ray pictures to make sure that the stent is positioned correctly. As with carotid endarterectomy, your blood pressure will be monitored for about three hours after the procedure before you return to the ward. Most patients undergoing stenting go home on day one or day two after the intervention.

Your doctor will arrange for you to have two antiplatelet drugs (usually aspirin and clopidogrel), which will have been started before stenting and which are then continued for at least a month after stent insertion. Thereafter, you usually only need to continue taking one of the antiplatelet medications, along with the rest of the medications which are prescribed by your doctor.

14.11. Following surgery or stenting, is scanning to detect a recurrent narrowing necessary?

Weeks to months after endarterectomy or stenting, it is usual to do a scan of the operation site, using an ultrasound scan. After carotid endarterectomy or carotid artery stenting, about 5—10% will develop an asymptomatic recurrent narrowing within the treated artery. This is called a re-stenosis. However, this very rarely causes patients to experience another TIA or stroke.

Health systems across Europe adopt varying approaches to surveillance (imaging arteries after treatment). Some keep everyone under surveillance (using ultrasound), some only keep a small subgroup under surveillance, whereas others do no surveillance at all. The 2023 ESVS guidelines advise post-operative surveillance in a subgroup of patients who either have a $>$ 50% narrowing of the non-operated carotid artery (on the other side of your neck), or who might be at higher risk of having a TIA/stroke should their operated artery block off sometime after your operation. Your doctor will explain the reasons why surveillance may or may not be necessary when your operation or stent

procedure is discussed with you, and again after it has been performed.

14.12. How can patients prevent recurrent symptoms or recurrent narrowings?

Evidence suggests that people who are at higher risk of developing a recurrent narrowing (re-stenosis) include: women, patients with diabetes, high cholesterol, chronic kidney disease, poorly treated high blood pressure, and (very importantly) those who smoke after their operation or stenting procedure. Accordingly, it is vital that you remember just how important it is to make any lifestyle changes permanent, as well as taking all the medications prescribed by your doctor to actively treat any vascular risk factors which are under your control.

14.13. Do patients who have a stroke due to narrowings in their vertebral arteries need an operation or stent, in addition to medical treatment?

All patients who have a stroke or TIA due to narrowings in their vertebral arteries will benefit from the same lifestyle advice, risk factor control and medications (antiplatelet agents, medicines to lower blood pressure, statins to reduce cholesterol and careful control of diabetes) as described for patients with symptoms due to carotid disease.

Open operations are very rarely performed in symptomatic patients with narrowings in their vertebral arteries and most are treated by medicines alone. The 2023 ESVS guidelines do, however, advise that stenting of vertebral artery narrowings may be considered in patients who have recurrent TIA/stroke despite taking their medications.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.04.011.

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