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European society for vascular surgery (ESVS) 2023 Clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease

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FINAL DRAFT

EUROPEAN SOCIETY FOR VASCULAR SURGERY (ESVS) 2023 CLINICAL PRACTICE GUIDELINES ON THE MANAGEMENT OF ATHEROSCLEROTIC CAROTID AND VERTEBRAL ARTERY DISEASE

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Table of Contents

A. Abbreviations and acronyms

B. What is new in the 2023 guidelines?

C. New Recommendations in the 2023 guidelines

D. Unanswered questions from the 2017 guidelines.

Section 1: Methodology

1.1 Purpose of the Guidelines

1.2 Compliance with AGREE II standards

1.3 Guideline Writing Committee

1.4 Evidence collection

1.5 Studies commissioned for the guidelines

1.6 Recommendations

1.7 Review process

1.8 Audit and update plan

Section 2: Introduction

2.1 Definition of stroke/transient ischaemic attack

2.2 Burden of stroke

2.3 Aetiology of carotid territory ischaemic stroke

2.4 Methods for measuring carotid artery stenosis severity

2.5 Imaging strategies in carotid artery disease

2.6 Role of the multidisciplinary team

Section 3: Management of asymptomatic carotid disease

3.1 Optimal medical therapy

Journal Pre-proof

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3.1.1 Lifestyle measures

3.1.2 Antiplatelet therapy

3.1.2.1 Monotherapy

3.1.2.2 Combination

3.1.2.3 In patients undergoing carotid endarterectomy

3.1.2.4 In patients undergoing carotid artery stenting

3.1.3 Combination antiplatelet therapy and direct oral anticoagulants

3.1.4 Lipid lowering therapy

3.1.5 Management of hypertension

3.1.6 Management of diabetes mellitus

3.1.7 Adherence to medications

3.2 Screening for asymptomatic carotid disease

3.2.1 Is stroke prevention important?

3.2.2 Unheralded stroke and asymptomatic carotid stenoses

3.2.3 Is Duplex ultrasound reliable for diagnosing stenosis severity?

3.2.4 Prevalence of asymptomatic carotid stenoses

3.2.5 Can a 'high risk for carotid stenosis' cohort be identified?

3.2.6 Potential benefits of selective screening

3.2.7 Potential harms associated with screening

3.2.8 Does screening prevent ipsilateral stroke?

3.2.9 Who advocates routine or selective screening?

3.3 Randomised trials: endarterectomy *vs.* best medical therapy

3.3.1 Medical therapy in the randomised trials

3.3.2 Outcomes in the randomised trials

3.4 Important subgroup analyses

3.4.1 Age

3.4.2 Sex

Journal Pre-proof

Journal Pre-proof

3.4.3 Stenosis severity

3.5 Controversy regarding 'modern medical therapy'

3.6 Who is at high risk for stroke on medical therapy?

3.7 Duplex surveillance in asymptomatic patients

3.8 Randomised trials: endarterectomy *vs.* stenting

3.8.1 30 day outcomes in 'average risk for surgery' patients

3.8.2 Long term outcomes in 'average risk for surgery' patients

3.8.3 'High risk for surgery' patients

3.9 Should the 3% threshold for carotid interventions be reduced?

3.10 Carotid revascularisation and cognitive impairment

3.10.1 Do asymptomatic carotid stenoses cause cognitive impairment?

3.10.2 Do carotid interventions improve cognitive function?

Section 4: Management of symptomatic carotid disease

4.1 Symptoms attributable to carotid and vertebral artery disease

4.2 Optimal medical therapy

4.2.1 Lifestyle measures

4.2.2 Antiplatelet therapy

4.2.2.1 Monotherapy

4.2.2.2 Combination

4.2.2.3 Prior to carotid artery stenting

Journal Pre-proof

Journal Pre-proof

4.2.2.4 Prior to carotid endarterectomy

4.2.3 When to prescribe gastric protection medications?

4.2.4 Combination antiplatelet therapy and direct oral anticoagulants

4.2.5 Antiplatelet 'high on treatment platelet reactivity'

4.2.6 Carotid interventions in patients on anticoagulation

4.2.6.1 Assessing peri-operative bleeding risks: CEA

4.2.6.2 Assessing peri-operative bleeding risks: CAS

4.2.6.3 Peri-operative antiplatelet and anticoagulant strategies

4.2.7 Lipid lowering therapy

4.2.7.1 Statins as secondary prevention

4.2.7.2 Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition

4.2.7.3 Lipid targets in stroke/TIA patients.

4.2.7.4 Statins during carotid interventions

4.2.8 Treatment of hypertension

4.2.8.1 Secondary prevention in patients with stroke/TIA

4.2.8.2 Blood pressure management during carotid endarterectomy

4.2.9 Treatment of diabetes mellitus

4.2.10 Adherence to medications

4.3 Randomised trials: Endarterectomy *vs.* medical therapy

4.3.1 30 day and five year outcomes in the randomised trials

4.3.2 Who is at higher risk of stroke on medical therapy?

4.4 Randomised trials: Endarterectomy *vs.* stenting

4.4.1 30 day outcomes

4.4.1.1 Stratified for age

4.4.2 Long term outcomes

4.4.2.1 Late ipsilateral stroke

4.4.2.2 Quality of Life

4.4.2.3 Survival following peri-operative stroke or myocardial infarction

Journal Pre-proof

4.5 Timing of carotid interventions after onset of symptoms

4.5.1 Risk of recurrent stroke over time

4.5.2 Timing of carotid endarterectomy in national registries and meta-analyses

4.5.3 Timing of carotid stenting in national registries and meta-analyses

4.5.4 Comparison of CEA *vs.* CAS in the early time period after symptom onset

4.5.5 TCAR outcomes stratified for timing after symptom onset

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

4.7 Intervening in neurologically unstable patient

4.8 Timing of interventions after intravenous thrombolysis

4.9 Timing of CEA or CAS after mechanical thrombectomy

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

4.11 'High risk for surgery' symptomatic patients

4.11.1 SAPPHIRE defined criteria

4.11.2 Increasing age

4.11.3 Cervical irradiation

4.11.4 Re-stenosis after carotid endarterectomy

4.11.5 Contralateral carotid occlusion

4.12 Managing patients with carotid 'near occlusion'

4.13 Management of free floating thrombus

4.14 Management of carotid webs

4.15 Management of chronic ocular ischaemia syndrome

4.16 Symptomatic patients with > 50% stenosis and atrial fibrillation

Journal Pre-proof

Journal Pre-proof

Section 5: Open Surgical Techniques

5.1 Carotid Endarterectomy

5.1.1 Pre-operative checklist

5.1.2 Staged or synchronous bilateral carotid interventions?

5.1.3 Carotid endarterectomy under general *vs.* locoregional anaesthesia?

5.1.4 Hospital and surgeon volume

5.1.5 Transverse or longitudinal incision?

5.1.6 Antegrade or retrojugular exposure?

5.1.7 Carotid sinus nerve blockade?

5.1.8 Protamine reversal of heparin?

5.1.9 Shunting: routine, never, selective?

5.1.10 Patching: routine, never, selective?

5.1.11 Eversion *vs.* conventional endarterectomy?

5.1.12 Management of coils and kinks

5.1.13 Monitoring and quality control after CEA

5.1.14 Management of high internal carotid artery lesions

5.1.15 Wound drainage

5.1.16 Ward, high dependency or intensive care post-operatively?

Journal Pre-proof

5.2 Carotid Bypass

5.2.1 Indications

5.2.2 Technique

5.2.3 Results

5.3 Extracranial to Intracranial Bypass

Section 6: Carotid Artery Stenting

6.1 Adjuvant medical therapy

6.2 Access routes

Journal Pre-proof

6.2.1 Transfemoral

6.2.2 Transcarotid

6.2.3 Radial or brachial

6.3 Wires, catheters and stent design

6.3.1 carotid stent design

6.4 Pre-dilation and post-dilation

6.5 Cerebral protection devices

6.6 Hospital and individual operator volume

Section 7: Complications following carotid interventions

7.1 Peri-operative

7.1.1 Stroke after carotid endarterectomy

7.1.1.1 Intra-operative

7.1.1.2 Post-operative

7.1.1.3 Predictors of stroke after carotid endarterectomy

7.1.2 Stroke after carotid artery stenting

7.1.2.1 Predictors of stroke after carotid stenting

7.1.3 Haemodynamic instability

7.1.3.1 Post-endarterectomy hypotension

7.1.3.2 Post-stenting hypotension

7.1.3.3 Post-endarterectomy hypertension

7.1.3.4 Post-stenting hypertension

7.1.3.5 Hyperperfusion syndrome

7.1.4 Wound haematoma after carotid endarterectomy

7.1.5 Cranial nerve injury

7.1.6 New post-operative ischaemic brain lesions

7.2 Late complications

7.2.1 Prosthetic patch and stent infection

7.2.2 Re-stenosis after carotid interventions

Journal Pre-proof

7.2.2.1 Pathophysiology

7.2.2.2 DUS criteria for diagnosing re-stenosis severity

7.2.2.3 DUS surveillance after carotid interventions

7.2.2.4 DUS surveillance of contralateral carotid artery

7.2.2.5 Incidence of re-stenosis after carotid interventions

7.2.2.6 Asymptomatic re-stenosis and recurrent ipsilateral symptoms

7.2.2.4 Management of re-stenosis

Section 8: Management of concurrent coronary and carotid disease

8.1 Stroke after cardiac surgery

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

8.3 Screening cardiac surgery patients for asymptomatic carotid stenosis

8.4 Are carotid interventions indicated in cardiac surgery patients?

8.5 What surgical or endovascular options are available?

8.6 Managing patients with unstable coronary artery disease

Section 9: Carotid disease and major non-cardiac surgery

9.1 Incidence of stroke after major non-cardiac surgery

9.2 Prediction of stroke after major non-cardiac surgery

9.3 Timing of major surgery after recent stroke

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

Section 10: Occlusive disease of common carotid and innominate arteries

10.1 Introduction

10.2 Clinical presentation

10.3 Indications for revascularisation

10.4 Endovascular *vs*. open reconstruction

10.5 Open revascularisation: cervical *vs.* transthoracic reconstruction

10.6 Tandem proximal inflow and internal carotid artery disease

Section 11: Management of asymptomatic vertebral artery disease

11.1 Optimal medical therapy

11.2 Screening for asymptomatic vertebral artery disease

11.3 Interventions in patients with asymptomatic vertebral artery disease

Section 12: Management of symptomatic vertebral artery disease

12.1 Aetiology of vertebrobasilar stroke

12.2 Symptoms attributable to vertebral artery disease

12.3 Imaging strategies in vertebral artery disease

12.4 Optimal medical therapy

12.5 Role of vertebral revascularisation in positional vertigo

12.6 Interventions in recently symptomatic patients

12.6.1 Non-randomised studies

12.6.2 Randomised studies

12.6.2.1 Meta-analysis of randomised trials

12.6.3 Endovascular techniques

12.6.3.1 Adjuvant medical therapy

12.6.3.2 Access

12.6.3.3 Wires, catheters, and stent design

12.6.3.4 Cerebral protection devices

12.6.3.5 Pre-dilation

12.6.4 Open surgical techniques

12.6.5 Complications after vertebral artery interventions

12.6.5.1 Open surgery

12.6.5.2 Endovascular intervention

12.7 Surveillance after vertebral artery revascularisation

Section 13: Unanswered questions from the 2023 ESVS guidelines.

Section 14: Information for the Patient.

A. Abbreviations and acronyms

ACAS	Asymptomatic Carotid Atherosclerosis Study	GA	General anaesthesia
		GC	Guidelines Committee
ACE	Aspirin and Carotid Endarterectomy Trial	GWC	Guideline Writing Committee
ACES	Asymptomatic Carotid Emboli Study	HDU	High Dependency Unit
ACS	Asymptomatic carotid stenosis	HR	Hazard ratio
ACSRS	Asymptomatic Carotid Stenosis and Risk of Stroke Study	HRF	High risk feature
		HS	Hyperperfusion syndrome
ACST	Asymptomatic Carotid Surgery Trial (1 &2)	HTPR	High on treatment platelet reactivity
ACT-1	Asymptomatic Carotid Trial-1	ICA	Internal carotid artery
AHA	American Heart Association	ICH	Intracerebral haemorrhage
APRx	Antiplatelet therapy	ICSS	International Carotid Stenting Study
ARR	Absolute risk reduction	IPH	Intraplaque haemorrhage
ARWMC	Age related white matter change	IA	Innominate artery
AF	Atrial fibrillation	ISR	In stent re-stenosis
BA	Basilar artery	ITU	Intensive therapy unit
BD	*Bis die* (twice daily)	iv	Intravenous
BES	Balloon expandable stent	JBA	Juxtaluminal black area
BMS	Bare metal stent	LAA	Large artery atherosclerosis
BMI	Body mass index	LDL-C	Low density lipoprotein cholesterol
BMT	Best medical therapy	LMWH	Low molecular weight heparin
BP	Blood pressure	LRA	Locoregional anaesthesia
CA	Carotid angioplasty	MCA	Middle cerebral artery
CABG	Coronary artery bypass graft	MDT	Multidisciplinary team
CAD	Coronary artery disease	MES	Micro-embolic signals
CAS	Carotid artery stenting	MI	Myocardial infarction

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CAVATAS	Carotid & Vertebral Artery Transluminal Angioplasty Study	MRA	Magnetic resonance angiography
		MRI	Magnetic resonance imaging
CaW	Carotid web	mRS	Modified Rankin Score
CCA	Common carotid artery	MT	Mechanical thrombectomy
CCF	Congestive cardiac failure	NASCET	North American Symptomatic Carotid Endarterectomy Trial
CEA	Carotid endarterectomy		
cCEA	Conventional carotid endarterectomy	NIBL	New ischaemic brain lesion
CEMRA	Contrast enhanced magnetic resonance angiography	NIHSS	National Institute of Health Stroke Score
		OR	Odds Ratio
CETC	Carotid Endarterectomy Trialists Collaboration	PAD	Peripheral arterial disease
		PCA	Posterior cerebral artery
CFA	Common femoral artery	PCSK9	Proprotein convertase subtilisin/kexin type 9
CI	Confidence Interval	PPI	Proton pump inhibitor
CNI	Cranial nerve injury	PSV	Peak systolic velocity
CNO	Carotid near occlusion	PTFE	Polytetrafluoroethylene
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies	QC	Quality control
		QIP	Quality improvement programme
COPD	Chronic obstructive pulmonary disease	RCT	Randomised controlled trial
CoW	Circle of Willis	rTPA	Recombinant Tissue Plasminogen Activator
CPD	Cerebral protection device	RLN	Recurrent laryngeal nerve
CREST	Carotid Revascularisation *vs.* Stenting Trial	RR	Relative risk
CSTC	Carotid Stent Trialists Collaboration	RRI	Relative risk increase
CT	Computerised tomography	RRR	Relative risk reduction
CTA	Computerised tomography angiography	SAPPHIRE	Stenting & Angioplasty with Protection in Patients at High Risk for Endarterectomy
CVR	Cerebral vascular reserve		
DAPT	Dual antiplatelet therapy	SAMMPRIS	Stenting & Aggressive Medical Management for Preventing Recurrent Stroke & Intracranial Stenosis
DBP	Diastolic blood pressure		
DES	Drug eluting stent		
DLS	Dual layer stent	SBP	Systolic blood pressure
DM	Diabetes mellitus	SCS	Symptomatic carotid stenosis
DOAC	Direct oral anticoagulant	SVS	Society for Vascular Surgery (North America)
DSA	Digital subtraction angiography	SPACE	Stent Protected Angioplasty *vs.* Carotid Endarterectomy
DUS	Duplex ultrasound		
DWI	Diffusion weighted imaging	SSEP	Somatosensory evoked potentials

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EAS	European Atherosclerosis Society	TCD	Transcranial Doppler
ECA	External carotid artery	TCAR	Transcarotid artery revascularisation
eCEA	Eversion carotid endarterectomy	TFCAS	Transfemoral carotid artery stenting
ECG	Electrocardiogram	TIA	Transient ischaemic attack
EC-IC	Extracranial intracranial	TOAST	Trial of ORG 10172 in Acute Stroke Treatment
ECST	European Carotid Surgery Trial	TRA	Transradial artery access
EEG	Electroencephalography	TT	Thrombolysis therapy
EJVES	European Journal of Vascular and Endovascular Surgery	UFH	Unfractionated heparin
		USPSTF	US Preventive Services Taskforce
ESC	European Society of Cardiology	VACS	Veterans Affairs Co-operative Study
ESH	European Society of Hypertension	VA	Vertebral artery
ESO	European Stroke Organisation	VAST	Vertebral Artery Stenting Trial
ESVS	European Society for Vascular Surgery	VB	Vertebrobasilar
EVA-3S	Endarterectomy *vs.* Stenting in patients with Symptomatic Severe carotid Stenosis	VISSIT	Vitesse Intracranial Stent Study for Ischaemic Stroke Therapy
FLAIR	Fluid attenuated inverse recovery	VAST	Vertebral Artery Ischaemia Stenting Trial
FFT	Free floating thrombus	VKA	Vitamin K antagonist
		VQI	Vascular Quality Initiative
		VSGNE	The Vascular Surgery Group of New England

B. 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

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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 're-graded' since 2017 and 38 are new. The 2023 ESVS guidelines benefit from 289 new references (240 published between 2017-2022), including 39 primary or secondary analyses from randomised controlled trials (RCTs),[5-43] 71 systematic reviews and/or meta-analyses[44-114] 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 anti-platelet 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

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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 (BMT), 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**).

C. New Recommendations in the 2023 guidelines

No.	CLASS I
11	*For patients with asymptomatic carotid stenosis who are undergoing carotid endarterectomy, lower dose aspirin (75-325mg daily) rather than higher dose aspirin (>325mg 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 – 325mg daily) rather than higher doses (> 325mg 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 is recommended.*

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35	*For symptomatic carotid stenosis patients who do not reach their lipid targets on maximum doses or maximum tolerated doses of statins, ezetimibe (10mg 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 a patient who has 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 has 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 with a peri-operative stroke, it is recommended to differentiate between intra- and post-operative stroke.*
92	*For patients who develop an ipsilateral neurological deficit after flow is restored after 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, urgent diagnostic neurovascular imaging of both carotid arteries and the brain is recommended.*
CLASS IIa	
10	*For patients with >50% asymptomatic carotid stenosis who are intolerant or allergic to aspirin, clopidogrel 75mg daily should be considered. If intolerant or allergic to both aspirin and clopidogrel, dipyridamole monotherapy (200mg 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 undergoing 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 (300-325mg daily for 14 days, followed by 75-162mg daily) should be considered.*

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36	*For symptomatic carotid stenosis patients who are intolerant of, or not achieving target LDL 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 with 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 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 performing the stenting procedure.*
CLASS IIb	
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 symptomatic 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 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.*

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61	*For recently 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 in order to maintain optimal outcomes.*
101	*In selected 'high risk of surgery' 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 III	
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.*

D. '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 for 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*

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ESVS criterion for being 'higher risk for stroke on BMT' 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 antiplatelet 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 three randomised controlled trials (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.*

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Which symptomatic patients are '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 '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 only be considered 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.*

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Section 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 (ie. 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,

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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 scope to go into detail regarding health economics, largely because individual countries have different processes for determining cost acceptability.

1.3 Guideline Writing Committee (GWC)

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 was comprised of 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

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A video conference was held on 6th July 2020, where topics and tasks were allocated. The GWC met monthly (by video conference) to review progress. Search strategies were undertaken for each of the 46 sub-sections, using Medline, Embase and the Cardiosource Clinical Trials and Cochrane databases to December 31st 2020, plus reference checking of cited papers. Hand searches were undertaken of 11 journals between 2017-2020 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 to 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**).

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1.5 Studies commissioned for the guidelines

Four systematic reviews/meta-analyses were commissioned including; (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

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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**).

Table 1: Class of Recommendation

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
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

The letters A, B, C denote evidence levels (**Table 2**), with 'A' being the highest.

Table 2. Levels of evidence.

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 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

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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 amongst 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, pre-defined 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 remain essentially unchanged (compared with 2017), grades of evidence have been revised and the relevant recommendation box is highlighted as having been 're-graded'.

1.7 Review process

There were three rounds of external review, involving 25 reviewers (16 GC members plus 9 external reviewers). Review comments were assessed by the co-chairs, who co-ordinated 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 6th April 2022.

1.8 Audit and Update plan

This guideline will be updated every four years. Vascular centres are encouraged to audit implementations made as a result of the guideline. Audit cycles should be repeated and changes implemented. There are many ways to perform clinical audit and most centres now require they are registered with local audit committees.

Section 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 hrs which is of a non-traumatic, vascular origin.[179] Crescendo TIAs refer to multiple TIAs in a short time period, defined by some as > 2 TIAs in 24 hours,[180] or $\geq$ 3 events in seven days,[181] with full recovery between. Stroke is a sudden onset focal (rather than global) neurological dysfunction, with symptoms lasting > 24 hrs (or causing death < 24 hrs), 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

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1.4 million strokes occur annually in a European population of 715 million.[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] Europeans living with stroke as a chronic condition may increase by 25% from 3.7 million (2015) to 4.6 million (2035), due to an 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 expected to increase to $ 129 billion (€ 114 billion) by 2035.[183]

2.3 Aetiology of stroke

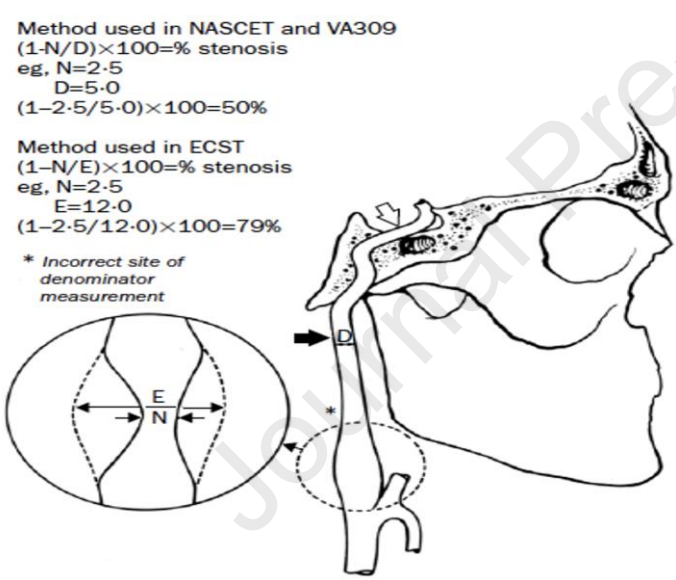
15-20% of strokes are haemorrhagic (intracranial (ICH), subarachnoid), while 20% of ischaemic strokes are vertebrobasilar (VB). The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification for TIA/ischaemic stroke includes five categories: (1) large artery atherosclerosis (LAA): defined as ≥ 50% stenosis or occlusion of an extra- or intracranial artery); (2) cardio-embolic; (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 a 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 cardio-embolic 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 significant increases in antiplatelet (APRx), anti-hypertensive, and statin prescriptions.[186] Between 2002 - 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**).

Figure 1: NASCET and ECST methods for measuring carotid stenosis severity



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

NASCET = North American Symptomatic Carotid Endarterectomy Trial; ECST = European Carotid Surgery Trial.

Reproduced with permission from Rothwell et al. Analysis of pooled data from randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107-16. Table comparing ECST and NASCET stenosis measurements was derived from Donnan GA, Davis SM, Chambers BR, Gates PC. Surgery for prevention of stroke. Lancet 1998;351:1372-3

Both methods used residual lumen diameter as 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

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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 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

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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 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**).

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Table 3: sensitivity and specificity of DUS, CTA and CEMRA, compared with DSA*

		DUS	CTA	CEMRA
Sensitivity	Occlusion	97%	97%	99%
	Stenosis	89%	75-85%	94-95%
Specificity	Occlusion	99%	99%	99.6%
	Stenosis	84%	93-96%	92-93%

** Data derived from Rojoa[91] and Wardlaw[199]. DUS = Duplex ultrasound; CTA = computed tomographic angiography; CEMRA = contrast enhanced magnetic resonance angiography; DSA = digital subtraction angiography.*

Recommendation 1 (Regraded)	Class	Level	References
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.	I	B	199,200

Recommendation 2 (Regraded)	Class	Level	References
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.	I	B	199

Recommendation 3 (Regraded)	Class	Level	References
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	I	B	199

Recommendation 4 (Unchanged)	Class	Level	References
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.	I	C	191

Recommendation 5 (Regraded)	Class	Level	References
For patients with atherosclerotic disease being considered for revascularisation, intra-arterial digital subtraction angiography is not	III	B	199

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recommended, unless there are significant discrepancies on non-invasive imaging.			

2.6 Role of the Multidisciplinary Team (MDT)

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%, $p < .0001$).[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% (CI 95%; 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.* when assessments were undertaken by the operator performing CAS.[203]

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Recommendation 6 (Unchanged)	**Class**	**Level**	**References**
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.	**I**	**C**	201

Recommendation 7 (Unchanged)	**Class**	**Level**	**References**
Independent neurological assessment before and after carotid interventions is recommended to audit peri-procedural risks	**I**	**C**	202,203

Section 3: Management of asymptomatic carotid disease

An asymptomatic carotid artery stenosis (ACS) refers to a stenosis which is 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] whilst 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 significant 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

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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 9 RCTs (*n* = 12 551) evaluated behavioural counselling to promote healthy diets and physical activity. There was a significantly reduced risk of cardiovascular events at 24 months (RRR 0.80; 95% CI 0.73 - 0.87) attributed to significant reductions in BP, LDL-C, fasting glucose, and obesity.[85]

Recommendation 8 (Regraded)	Class	Level	References
For patients with asymptomatic and symptomatic carotid disease, behavioural counselling to promote healthy diet, smoking cessation and physical activity is recommended.	I	B	85,207-210

3.1.2 Antiplatelet therapy

3.1.2.1 Monotherapy

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

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Table 4: Studies evaluating antiplatelet therapy in ACS patients

Study name Stenosis severity	Study Method Follow up	Principle findings
Asymptomatic Cervical Bruit Study[212] 50-100% ACS	**RCT**: 325mg enteric coated aspirin daily (*n* = 188) *vs.* placebo (*n* = 188) Median of 2.3 years	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)

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Asymptomatic Carotid Emboli Study[213] 70-99% ACS	**Observational**: APRx (*n* = 419) *vs.* no APRx (*n* = 58) at baseline Mean of two years	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.

ACS = asymptomatic carotid stenosis; RCT = randomised controlled trial; APRx = antiplatelet therapy; TIA = transient ischaemic attack; MI = myocardial infarction; HR = Hazard ratio; CI = confidence intervals.

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, $p < .0001$).[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, 200mg dipyridamole twice daily (bd) is an alternative,[81] also based on data extrapolation from TIA/stroke patients.[218]

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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 Antiplatelet therapy in ACS patients undergoing CEA

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 significantly lower in patients randomised to 81 - 325 mg aspirin

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(3.7%) *vs.* 650 - 1300 mg (8.2%; *p* = .0002).[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, 200mg dipyridamole monotherapy bd is an alternative.[81]

3.1.2.5 Antiplatelet therapy in ACS patients undergoing CAS

Table 5 summarises two RCTs evaluating APRx (and i.v. heparin) in patients undergoing CAS.

Table 5: RCTs evaluating antiplatelet and i.v. heparin therapy in CAS patients

Study	Method (Stenosis)	Antithrombotic therapy	Main findings
Dalainas[220]	**RCT** (*n*=100; 88 with ACS) (70-99%)	325 mg aspirin daily for seven days pre-CAS + 24 h i.v. heparin post-op, then 325 mg aspirin daily *vs.* 325 mg aspirin daily + 250 mg ticlopidine bd for seven days pre-CAS and 30 days 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]	**RCT** (*n*=47; 9 with ACS) (70-99%)	75 mg aspirin daily + 24 hours i.v. heparin (APTT ratio 1.5-2.5) *vs.* 75 mg aspirin daily + clopidogrel (300 mg stat 6-12 hours pre-op, 75 mg two hours pre-op + 75 mg daily for days 1-28)	Aspirin + heparin associated with significant increase in 30 day ipsilateral amaurosis fugax, TIA, any stroke (25% *vs.* 0%, *p* = .02). No difference in incidence of groin haematoma (17% *vs.* 9%; *p* = .35)

CAS = carotid artery stenting; ACS = asymptomatic carotid stenosis; RCT = randomised controlled trial; APRx = antiplatelet therapy; TIA = transient ischaemic attack; MI = myocardial infarction; HR = Hazard ratio; CI = confidence intervals; APTT = activated partial thromboplastin clotting time.

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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 2 - 4 weeks[223,224] or ≥ 6 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 3-5 days of therapy.[226] In CREST, aspirin 325 mg bd and clopidogrel 75 mg bd 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 BD for ≥ 4 weeks.[227] Patients were not randomised to different APRx regimens in the larger RCTs and ticlopidine is no longer used, due to unfavourable side ef effects.

3.1.3 Combination of Antiplatelet & Direct Oral Anticoagulants (DOACs)

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 bd) plus 100 mg aspirin daily (*n* = 9 152) or 5 mg bd rivaroxaban (*n* = 9 117).[15] After a mean follow up of 23 months, the composite endpoint of stroke, MI or cardiovascular death was 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 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]

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-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 due to insufficient carotid patients being recruited. There was no 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 (Regraded)	**Class**	**Level**	**References**
For patients with >50% asymptomatic carotid stenosis, lower dose aspirin (75-325mg daily) should be considered, mainly for the prevention of late myocardial infarction and other cardiovascular events.	**IIa**	**C**	213,216

Recommendation 10 (New)	**Class**	**Level**	**References ToE**
For patients with >50% asymptomatic carotid stenosis who are intolerant or allergic to aspirin, clopidogrel 75mg daily should be considered. If intolerant or allergic to both aspirin and clopidogrel, dipyridamole monotherapy (200mg twice daily) should be considered.	**IIa**	**C**	81

Recommendation 11 (New)	**Class**	**Level**	**References ToE**

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For patients with asymptomatic carotid stenosis who are undergoing carotid endarterectomy, lower dose aspirin (75-325mg daily) rather than higher dose aspirin (>325mg daily) is recommended.	I	B	219

Recommendation 12 (Unchanged)	Class	Level	References
For patients with asymptomatic carotid stenosis undergoing carotid stenting, combination antiplatelet therapy with aspirin (75-325mg daily) and clopidogrel (75mg daily) is recommended. Clopidogrel (75mg daily) should be started at least three days before stenting or as a single 300mg 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.	I	B	81,221-226

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 significant reductions in stroke in people with a ≤ 10% five year predicted risk of major vascular events (RR 0.76, 95% CI 0.61 - 0.95, *p* = .0012) 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

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hyperlipidaemia who are intolerant of statins or ezetimibe, it is reasonable to consider PCSK9 inhibitors.[18]

Recommendation 13 (Regraded)	Class	Level	References
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.	I	B	111,228,229

Recommendation 14 (New)	Class	Level	References ToE
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.	IIa	C	18,95

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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 anti-hypertensive therapy for stroke prevention in ACS patients, but in a meta-analysis of 61 observational studies (1 million adults), there was a significant relationship between BP and stroke or death. Between 40 - 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 two fold 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 significant reduction in late stroke (RR 0.54; 95% CI 0.45 - 0.65).[234] In

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another RCT, 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 the 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 < 140mmHg/< 80mmHg in non-diabetic patients ≥ 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)	**Class**	**Level**	**References**
For patients with asymptomatic or symptomatic carotid stenoses and hypertension, antihypertensive treatment is recommended.	**I**	**A**	236

3.1.6 Management of Diabetes Mellitus (DM)

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 *vs.* 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 significant 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

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reduce other DM related complications. The Prospective Pioglitazone Clinical Trial in macro–Vascular Events (PROACTIVE) trial (*n* = 5 238) reported that 45mg 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)	**Class**	**Level**	**References**
For diabetic patients with asymptomatic carotid stenoses, optimal glycaemic control is recommended	**I**	**B**	243-246

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.[247,48] 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 Stenoses

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

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to the population in question; (iii) 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 2.1.1 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 due to an ipsilateral 50 - 99% carotid stenosis or occlusion.[185] Stroke in ACS patients has decreased over the last decade (**section 2.3**), attributed to better 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, due to high numbers of false positives. 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%

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ACS, stratified for age and sex. The yield for finding > 70% ACS through unselected screening of patients aged < 80 years would be < 2%,[206] ie. 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]

Table 6: DUS prevalence of > 50% and > 70% ACS in the general population*

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

** Based on data from de Weerd et al[206]. DUS = duplex ultrasound; ACS = asymptomatic carotid stenosis.*

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] Significant predictors included increasing age, male sex, smoking, DM, prior stroke/TIA, CAD, PAD, high BP and raised lipids. Using the highest risk decile

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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 undergo) DUS. Patients randomised to 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 significantly 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 stroke in the general population?

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?

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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 a significant 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 ≥ 2 of: hypertension, hyperlipidaemia, smoking, family history of stroke, or patients with early onset atherosclerosis.[256] The 2021 USPSTF guidelines advise against any form of ACS screening.[105] ESO made no recommendation.[2]

Recommendation 17 (Unchanged)	**Class**	**Level**	**References**
Routine population screening for asymptomatic carotid stenosis is not recommended	**III**	**C**	Expert Opinion

Recommendation 18 (Unchanged)	**Class**	**Level**	**References**
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.	**IIb**	**B**	4,254-258

3.3 Randomised Trials: Endarterectomy *vs.* 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 were included in intention to treat analyses.[195]

3.3.1. BMT in the RCTs

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In VACS, 650 mg aspirin (daily) was taken by 55% of patients, while 27% took lower doses. Anti-hypertensive therapy was less commonly prescribed in VACS, and no-one 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 RCT Outcomes

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 significant reductions in any stroke at five and 10 years,[228] while ACAS reported that CEA conferred significant reductions in ipsilateral and any stroke at five years.[195]

Table 7: Five and ten year outcomes in VACS, ACAS, and ACST-1

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

** Includes strokes occurring after diagnostic angiography; y = years; CEA = carotid endarterectomy; BMT = best medical therapy; 30 day D/S = 30 day death/stroke after CEA; ARR = absolute risk reduction; NNT = number needed to treat to prevent one stroke; stroke/1000 = number of*

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strokes prevented per 1000 CEAs; VACS = asymptomatic Veterans Affairs Carotid Study; ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST-1 = Asymptomatic Carotid Surgery Trial.

3.4 Important subgroup analyses from the RCTs

3.4.1 Effect of age

ACST-1 published outcomes stratified for age (< 65yrs [*n* = 912]; 65 - 74yrs [*n* = 1 558], and > 75yrs [*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 < 5 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 > 5 years and $\geq$ 1 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 significant 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 whilst 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 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 = .427).[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) were 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 due to 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, who they thought to be high risk.[62] If ACAS and ACST-1 data are excluded, patients in cohort studies with 80 - 99% ACS were significantly 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]

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(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 significantly 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 to 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 9 HRFs were already high risk of stroke on BMT criteria in the 2017 guidelines.[165] The incidence of ipsilateral stroke was significantly higher with ACS plus ≥ 1 HRF *vs.* no HRFs (OR 2.0; 95% CI 1.5 - 2.7).[67] HRFs significantly 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 ≥ 1 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 ≥ 1 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

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Stroke (ACSRS) study, where annual stroke rates varied from 0.2 - 8.7% with 50 - 79% ACS and from 0.5 - 10% in patients with 80 - 99% ACS, depending upon 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 gray 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 - 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 > 25% took statins, ipsilateral stroke was 1.2/100 person years *vs.* 2.3/100 person years where < 25% took statins ($p = .009$).[251] Another systematic review (3 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 best 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' meant. 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

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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 grayscale 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 ≥ 1 spontaneous MES during ≥ 1 hour of transcranial Doppler (TCD) monitoring.

Table 8: Clinical/Imaging features associated with an increased risk of late stroke in patients with asymptomatic 50 - 99% stenoses treated medically.

Imaging/Clinical Parameter and stenosis severity Type of study	**Annual rate of ipsilateral stroke**	**OR/HR of increased stroke (95%CI) *P value***
Silent ipsilateral infarction on CT[270] 60-99% stenoses multicentre observational	Yes = 3.6% No = 1.0%	Yes *vs*. No 3.0 (1.46-6.29) *p* = .002
Stenosis progression >20%[271] 50-99% stenoses multicentre observational	regression = 0.0% unchanged = 1.1% progression = 2.0%	Progression *vs*. unchanged 1.92 (1.14-3.25) *p* = .05

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Stenosis progression[272] 70-99% stenoses 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 observational	<40 mm^2 = 1.0% 40-80 mm^2 = 1.4% >80 mm^2 = 4.6%	comparator 2.08 (95% CI 1.05-4.12) 5.81 (95% CI 2.67-12.67)
Juxtaluminal black area on computerised ultrasound plaque analysis[264] 50-99% stenoses multicentre observational	<4 mm^2 = 0.4% 4-8 mm^2 = 1.4% 8-10 mm^2 = 3.2% >10 mm^2 = 5.0%	trend $p < .001$
Intraplaque haemorrhage on MRI[274] 50-99% stenoses meta-analysis		Yes *vs.* No OR 3.66 (2.77-4.95) $p < .01$
Impaired CVR[275] 70-99% stenoses meta-analysis		Yes *vs.* No OR 6.14 (95% CI 1.27-29.5) $p = .02$
Plaque lucency on DUS[276] 50-99% stenoses meta-analysis	predominantly echolucent 4.2% predominantly echogenic 1.6%	echolucent *vs.* echogenic OR 2.61 (95%CI 1.47-4.63) $p = .0$
≥1 spontaneous MES during ≥1 hour TCD monitoring[277] 50-99% stenoses meta-analysis		Yes *vs.* No OR 7.46 (95%CI 2.24-24.89) $P = .001$
Spontaneous embolisation plus uniformly or predominantly	Yes = 8.9% No = 0.8%	Yes *vs.* No OR 10.61 (95%CI 2.98-37.82)

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echolucent plaque[278] 70-99% stenoses multicentre, observational		*P* = .0003
Contralateral TIA/stroke[261] 50-99% stenoses multicentre, observational	Yes = 3.4% No = 1.2%	Yes *vs.* No OR 3.0 (95% CI 1.9-4.73) *P* = .0001

OR/HR = odds ratio/hazard ratio; 95%CI = 95% confidence intervals; 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.

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 9 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% (ie. a minority of ACS patients). The evidence for including plaque morphology features (within the ESVS criteria) is detailed in T**able 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. First, 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] Second, even though there was statistical significance, 4/5 cohort studies which included ACS patients without a history of stroke/TIA were published 25 - 35 years ago, raising questions about generalisability in the modern era of better BMT. In addition, there were only 218 patients with 80 - 99% ACS in these five cohort studies with no prior stroke/TIA. Third, 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 (eg. 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 significant 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 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 DUS surveillance in ACS patients

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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 ≥ 1 clinical or imaging feature making them higher risk of stroke on BMT, might then be considered for CEA or CAS. 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 *vs.* stenting

3.8.1 30 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 significantly higher rates of 30 day any stroke and death/any stroke. Compared with CEA, CAS had significantly lower 30 day MI.[94] There was no significant difference in any other endpoint.

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Table 9: 30 day outcomes in six RCTs comparing CAS with CEA in ACS patients*.

	Death	**Stroke**	**Death/ Stroke**	**Disabling Stroke**	**Death/ Disabling stroke**	**MI**	**Death/ Stroke/MI**
No RCTs *n* =	3 RCTs *n* = 5 313	6 RCTs *n* = 7 030	6 RCTs *n* = 7 030	3 RCTs *n* = 6 257	2 RCTs *n* = 5 076	3 RCTs *n* = 6 257	4 RCTs *n* = 6 393

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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	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	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) *p* =	0.53 (0.17-1.65) 0.27	1.61 (1.18-2.21) 0.003	1.47 (1.09-1.99) 0.011	1.19 (0.61-2.35) 0.61	0.86 (0.46-1.61) 0.63	0.49 (0.26-0.90) 0.024	1.19 (0.89-1.59)

Yellow Box: No significant difference; **Red Box**: Significant benefit favouring CEA; **Green box:** significant benefit favouring CAS

*RCTs = randomised controlled trials; MI = myocardial infarction; CEA = carotid endarterectomy; CAS = carotid artery stenting; OR (95% CI) = odds ratio (95% confidence intervals); p = p value. * Reproduced with permission from Saratzis*[94].

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-220,[224,225,280,]. 30 day any stroke and death/any stroke was significantly higher after CAS, while 30 day MI was significantly higher after CEA.[94] There was no significant difference in other endpoints.

Table 10: 30 day outcomes in four RCTs (comparing CAS with CEA) which randomised > 500 ACS patients *.

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	Death	Stroke	Death/ Stroke	Disabling Stroke	Death/ Disabling stroke	MI	Death/ Stroke/MI
No RCTs **N =**	2 RCTs *n* = 5 078	4 RCTs *n* = 6 659	4 RCTs *n* = 6 659	3 RCTs *n* = 6 259	2 RCTs *n* = 5 078	3 RCTs *n* = 6 259	3 RCTs *n* = 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	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%	17/3494 0.49%	123/3 494 3.52%
CEA	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) ***p* =**	0.33 (0.08-1.34) 0.12	1.61 (1.16-2.23) 0.0046	1.47 (1.07-2.01) 0.017	1.19 (0.61-2.36) 0.60	0.86 (0.42-1.66) 0.63	0.49 (0.26-0.91) 0.023	1.18 (0.89-1.58) 0.25

Yellow Box: No significant difference; **Red Box**: Significant benefit favouring CEA; **Green box:** significant benefit favouring CAS

**Reproduced with permission from Saratzis.[94] RCTs = randomised controlled trials; MI = myocardial infarction; CEA = carotid endarterectomy; CAS = carotid artery stenting; OR (95%CI) = odds ratio (95% confidence intervals); p = p value.*

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 significant 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

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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, ie, CAS was as durable as CEA.

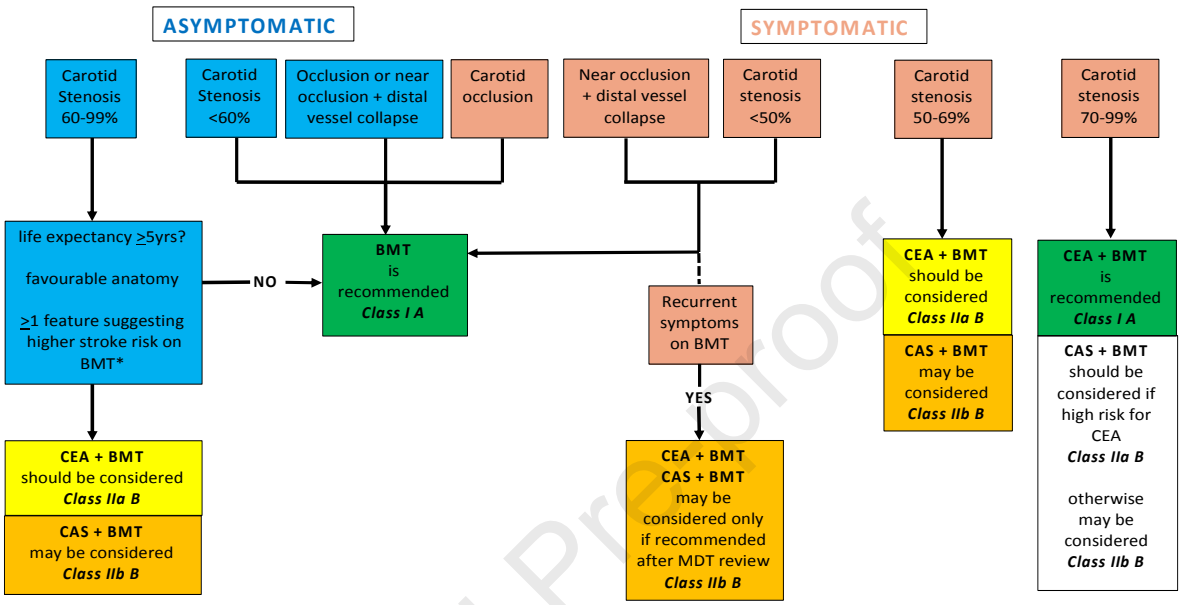
Table 11: Late ipsilateral and any stroke after CEA and CAS (excluding 30 day)

Trial	FU	ipsilateral stroke		any stroke	
		CAS	CEA	CAS	CEA
Lexington[281]	4yrs	0% (avg 0% pa)	0% (avg 0% pa)	0% (avg 0% pa)	0% (avg 0% pa)
Mannheim[222]	26mths	0% (avg 0% pa)	0% (avg 0% pa)	0% (avg 0% pa)	0% (avg 0% pa)
ACT-1[224]	5yrs	2.2% (avg 0.44% pa)	2.7% (avg 0.54% pa)	6.9% (avg 1.38% pa)	5.3% (avg 1.01% pa)
CREST-1[227,280]	5yrs	2.5% (avg 0.50% pa)	2.7% (avg 0.54% pa)	7.1% (avg 1.42% pa)	6.8% (avg 1.36% pa)
CREST-1[227,280]	10yrs	6.9% (avg 0.69% pa)	5.6% (avg 0.56% pa)	13.4% (avg 1.34% pa)	12.5% (avg 1.25% pa)
ACST-2[20]	5yrs	2.1% (avg 0.42% pa)	1.0% (avg 0.20% pa)	5.2% (avg 1.04% pa)	4.5% (avg 0.90% pa)

FU = follow up; CAS = carotid artery stenting; CEA = carotid endarterectomy; avg = average; pa = per annum; yrs = years; mths = months.

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

Figure 2: Management of average risk patients with asymptomatic and symptomatic carotid stenoses.



Green boxes denote Level I recommendations; yellow boxes denote level IIa and IIb recommendations

see **table 8 for Imaging/clinical criteria that confer an increased risk of stroke on BMT. CEA = carotid endarterectomy; CAS = carotid artery stenting; BMT = best medical therapy*

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3.8.3 High risk for CEA 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 ≥ 1 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

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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 more an attempt to define acceptable risk thresholds while the patient remains in hospital (ie. 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)	Class	Level	References
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.	IIa	B	195,204,228, 261,264,270-278

Recommendation 20 (Unchanged)	Class	Level	References
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	IIb	B	222,224,225,261, 264,270-278,280

Recommendation 21 (Unchanged)	Class	Level	References
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*.	IIb	B	223,261,264,270-278,282

** 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 percent 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

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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. A 2013 systematic review reported that 9 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, a significant association does not necessarily mean ACS has an aetiological role, *vs.* 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.

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Ten studies have evaluated the relationship between impaired CVR and cognitive impairment, with 90% reporting ≥ 1 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 *vs.* patients with severe ACS and normal CVR.[288,291-293]

3.10.2 Do carotid interventions improve cognition in ACS patients?

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 ≤ 3 months after CEA or CAS (*vs.* baseline). Assessment of late cognitive function involved assessment ≥ 5 months after CEA or CAS. In 13/21 cohorts, late reassessment was ≥ 1 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]

At late follow up (**Table 12)**, 69% reported no significant change in cognitive function, while in 25%, cognitive scores were mostly unchanged, but 1-2 individual tests were significantly improved. Few patients had significant improvement in late cognitive function (1 cohort; 1.5% of study population) and only one cohort (1.8% of the overall study population) had significant late cognitive impairment.

Table 12: Effect of carotid interventions on cognitive function*

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	EARLY (Baseline *vs.* <3mths)		LATE (Baseline *vs.* >5mths)	
	number of cohorts	**number of patients**	**number of cohorts****	**number of patients**
All domains/tests significantly improved	2/24	91/2 059 (4.4%)	1/21	24/1 554 (1.5%)
Most domains unchanged, 1-2 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 1-2 significantly few 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%)

** Reproduced with permission from Ancetti[46]*

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 had significant 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

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and BMT patients (6.7% *vs.* 6.6%) or in 20 year rates (14.3% *vs.* 15.5%), ie. CEA was not associated with reductions in late dementia *vs.* 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 whom CEA or CAS may be considered in ACS patients (**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)	**Class**	**Level**	**References**
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.	III	B	21,87

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Section 4: Management of symptomatic carotid disease

4.1 Symptoms attributable to carotid and VA 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 (eg. loss/impairment of power, sensation, coordination) *vs.* positive (eg. 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

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posterior communicating artery**.** The severity of symptoms can be scored using the modified Rankin Score (mRS) or National Institute for Health Stroke Scale (NIHSS).[295,296]

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 or blurring, hemianopia
Amaurosis fugax / transient monocular blindness or 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

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	Ataxia

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 Aspirin monotherapy

No adequately powered RCTs have evaluated monotherapy *vs.* combination APRx in SCS patients. However, older RCTs suggest aspirin monotherapy should be started urgently in APRx

naive TIA/ischaemic stroke patients, to reduce recurrent ischaemic stroke, death, or dependency.[297,298] If monotherapy is adopted, 300mg aspirin may be prescribed for days 1-14 to maximally inhibit thromboxane biosynthesis,[299,300] followed by 75 - 325mg daily.

4.2.2.2 Combination antiplatelet therapy

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 *vs.* 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]

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Table 14: Main findings of three RCTs comparing aspirin + dipyridamole antiplatelet therapy with aspirin monotherapy after TIA/ischaemic stroke.

RCT *n* = cohort	Combination antiplatelet strategy	Main findings
ESPS-2[301]	Dipyridamole 200mg bd	**RRR in stroke at two years**

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= 6 602 TIA/ischaemic stroke <3mth % with SCS not clear	*vs.* Aspirin 25mg bd *Vs.* Aspirin 25mg bd + Dipyridamole 200mg bd *Vs.* Placebo	Dipyridamole *vs.* placebo: 16%; $p < .05$ Aspirin *vs.* placebo: 18%; $p < .05$ Aspirin + dipyridamole *vs.* placebo: 37%; $p < .05$ Aspirin + dipyridamole *vs.* dipyridamole: 25%; $p < .05$ Aspirin + dipyridamole *vs.* aspirin: 23%; $p < .05$
ESPRIT*[302] *n* = 2 739 TIA/ischaemic stroke <6mth 9-11% with >50% SCS	Aspirin 30-325mg daily *Vs.* Aspirin 30-325mg daily + Dipyridamole 200mg bd	**Non-fatal stroke/MI/ major bleed/ vascular death at 3yrs** aspirin + dipyridamole *vs.* aspirin (HR 0.80; 95% CI 0.66-0.98) **Non-fatal stroke or MI/ vascular death at 3yrs** Aspirin + dipyridamole *vs.* aspirin (HR 0.78; 95% CI 0.63-0.97)
EARLY[303] *n* = 543 ischaemic stroke <24 hrs: (NIHSS ≤20 + not for thrombolysis) % with SCS not clear	Aspirin 25mg bd + Dipyridamole 200mg MR bd days 1-90 ('Early') *Vs.* Aspirin 100mg/d x 7d; then Aspirin 25mg bd + Dipyridamole 200mg MR bd days 8-90 ('Late')	**Good Functional Outcome (MRS 0 – 1) at 90d:** 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, $p = .2$)

RCT = randomised controlled trial; TIA = transient ischaemic attack; bd = twice daily; MR= modified release; RRR = relative risk reduction; MI = myocardial infarction; mth = months; SCS = symptomatic carotid stenosis

Table 15 details studies evaluating aspirin + clopidogrel on rates of spontaneous MES in SCS patients, which is an important predictor of increased stroke risk.[309] The CARESS RCT reported significant reductions in ongoing micro-embolisation in patients with > 50% SCS who were MES positive at baseline who were randomised to seven days of aspirin + clopidogrel *vs.* 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 *vs.* aspirin + clopidogrel in patients with > 50% SCS.[307] In a prospective audit, starting aspirin + clopidogrel in

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a rapid access TIA clinic after ICH was excluded on CT/MRI was associated with a significant reduction in recurrent TIA/stroke before expedited CEA, plus significant reductions in MES.[308] Sustained embolisation in the early time period after CEA is a predictor of post-operative thrombo-embolic stroke.[309] One study randomised 100 CEA patients established on 150mg aspirin daily (84% SCS), to a single dose of 75mg clopidogrel (*n* = 46) or placebo (*n* = 54) 12 hours before CEA.[310] In comparison with placebo, clopidogrel significantly reduced the odds of having > 20 emboli on TCD in the first three post-operative hours (*p* = .01).

Table 15: Effect of combination aspirin plus clopidogrel in reducing spontaneous embolisation in recently symptomatic patients and in patients undergoing carotid endarterectomy.

Author/Trial Method n= cohort	Combination antiplatelet strategy	Principle findings
Payne[310] RCT *n* = 100 SCS patients with ≥50% stenosis or ≥70% ACS	Aspirin 150mg daily for 4wks pre-op + placebo *vs.* Aspirin 150mg daily for four wks pre-op + single 75mg dose of clopidogrel 12 hours pre-op	During three hours of post-operative TCD monitoring, aspirin + 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* = .01)
CARESS[306] RCT *n* = 107	Aspirin 75mg daily + clopidogrel 300mg on day 1, followed by 75mg Clopidogrel daily until day 7 *vs.* Aspirin 75mg daily	At seven days; aspirin + 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* = .0046)

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>50% SCS + ≥1 MES on TCD at baseline		
AMBDAP[307] RCT *n* = 60 SCS >50%	Aspirin 300mg, then 75mg daily + Dipyridamole 200mg bd for 30 days *Vs.* Aspirin 300mg, then 75mg daily + Clopidogrel 300mg, then 75mg daily for 30 days	At 48 hours, there was a similar reduction in the frequency of micro-embolisation for: Aspirin + Dipyridamole (75.5%) Aspirin + Clopidogrel (77.5%, *p* = .77)
Batchelder[308] observational *n* = 100 SCS patients undergoing CEA <8 days of symptom onset	Aspirin 300mg, then 75mg daily + 75mg Clopidogrel 12 hours pre-op *vs.* Aspirin 300mg, then 75mg daily + 75mg Clopidogrel daily for 48-72 hours pre-op	Starting aspirin + clopidogrel 48-72 hrs 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* = .01) and **Spontaneous embolisation pre-operatively** (5% *vs.* 21%) (OR 0.2; 95% CI 0.09-0.66, *p* = .0047)

RCT = randomised controlled trial; TIA = transient ischaemic attack; SCS = symptomatic carotid stenosis; ACS = asymptomatic carotid stenosis; CEA = carotid endarterectomy; bd = twice daily; RRR = relative risk reduction; wks = weeks; yrs = years.

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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 *vs.* aspirin alone.[25,311,312] A fourth RCT undertook a similar evaluation of aspirin + ticagrelor *vs.* 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.

Table 16: RCTs evaluating the effect of aspirin + clopidogrel or aspirin + ticagrelor *vs.* aspirin monotherapy, in preventing early recurrent stroke.

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RCT n=; cohort	Combination antiplatelet strategy	Main Findings
FASTER[#] [311] *n* = 392 acute minor ischaemic stroke or TIA with initiation of APRx <24 hrs of symptom onset*	All patients received aspirin 81mg/d (162mg x 1 dose if aspirin naive) and were randomised to additional clopidogrel (300mg x 1 dose and then 75mg/d; clopidogrel + simvastatin 40mg/d; simvastatin 40mg/d; or placebo	Aspirin+clopidogrel did not significantly reduce 90d risk of stroke *vs.* aspirin monotherapy (5.1% *vs*. 9.5%, *p* > .05) Symptomatic bleeding higher in the 'clopidogrel' *vs.* 'no clopidogrel' groups (3 *vs.* 0%; *p* = .03
CHANCE [312] *n* = 5 170 acute minor ischaemic stroke or 'high risk' TIA patients in China, with initiation of APRx <24 hrs of symptom onset **	75-300mg aspirin x 1d, 75mg aspirin x 21d, + clopidogrel 300mg stat + clopidogrel 75mg/d days 2-90 *vs.* 75-300mg aspirin x 1d + aspirin75 mg/d days 2-90	**Compared with aspirin, aspirin+clopidogrel was associated with significant reductions in 90 day:** 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* = .01) Ischaemic stroke (7.9% *vs.* 11.4%) HR 0.67; 95% CI 0.56-0.81, *p* < .001) **Compared with aspirin, aspirin+clopidogrel was associated with no significant difference in 90 day:** Moderate or severe bleeding (0.3% *vs.* 0.3%; *p* = .73)
POINT[##] [25] *n* = 4 881 acute minor ischaemic stroke or 'high risk' TIA, with initiation of APRx <12 hrs of symptom onset **	Aspirin 50-325mg/d + clopidogrel 600mg stat + clopidogrel 75mg/d days 2-90 *Vs.* Aspirin 50-325 mg/d x 90d (162mg aspirin/d for 5d and then 81mg/d recommended)	**Compared with aspirin, aspirin+clopidogrel was associated with significant reductions in 90 day:** Stroke/MI/Ischaemic vascular death (5% *vs.* 6.5%) HR 0.75; 95% CI 0.59-0.95, *p* = .02) Ischaemic stroke (4.6% *vs.* 6.3%) HR 0.72; 95% CI 0.56-0.92, *p* = .01 **Compared with aspirin, aspirin+clopidogrel was associated with significant increase in 90 day:** Major bleeding (0.9% *vs.* 0.4%) HR 2.32; 95% CI 1.10-4.87, *p* = .02)

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THALES [24,27] *n* = 11 016 acute minor ischaemic stroke or 'high risk' TIA, with initiation of APRx <24 hrs of symptom onset ***	Aspirin 300-325mg stat and then 75-100mg aspirin days 2-30 + ticagrelor 180mg stat + ticagrelor 90mg BD days 2-30 *vs.* Aspirin 300-325mg stat and 75-100mg aspirin daily days 2-30	**Compared with aspirin, aspirin+ticagrelor was associated with significant reductions in 30 day:** Stroke/death (5.5% *vs.* 6.6%) HR 0.83; 95% CI 0.71-0.96, *p* = .02) Ischaemic stroke (5.0% *vs.* 6.3%) HR 0.79; 95% CI 0.68-0.93, *p* = .004) **Compared with aspirin, aspirin+ticagrelor was associated with significant increase in 30 day:** Severe bleeding: (0.5% *vs.* 0.1%) HR 3.9; 95% CI 1.74-9.14, *p* = .001)

*[#] trial stopped early due to slow enrolment; [##] 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 ≤ 3) or TIA; ** acute minor ischaemic stroke (NIHSS score ≤ 3) or TIA with ABCD² score ≥ 4; *** acute minor ischaemic stroke (NIHSS score ≤ 5) or TIA with ABCD² score ≥ 6, or symptomatic intracranial or extracranial stenosis ≥ 50%. RCT = randomised controlled trial; TIA = transient ischaemic attack; APRx = antiplatelet therapy; RR = Relative Risk; HR = Hazard ratio; 95% CI = 95% confidence intervals; d=day.*

A meta-analysis of the three RCTs comparing aspirin + clopidogrel *vs.* aspirin alone showed that starting aspirin + clopidogrel within 24 hours of the onset of a high risk TIA or minor stroke significantly 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 (ARI 0.2%; RR 1.71, 95% CI 0.92-3.2).[59] Whilst 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 significantly reduce early recurrent stroke, whilst minimising major bleeding complications.[59]

4.2.2.3: Antiplatelet therapy before carotid stenting

Patients with 50 - 99% SCS undergoing CAS are routinely prescribed 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 ≥ 4 - 6 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 *vs.* aspirin monotherapy in CAS patients with a ≥ 50% SCS.

4.2.2.4 Antiplatelet therapy 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, in order 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.

Monotherapy

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Aspirin: Only one RCT has evaluated aspirin *vs.* placebo in CEA patients. 232 patients (215 SCS) were randomised to placebo or aspirin 75mg daily, starting the night before CEA and continuing for six months.[325] Aspirin reduced disabling stroke at seven days *vs.* placebo (1.7% *vs.* 9.6%; p = .01), 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% *vs.* 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 whilst 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 BD is an alternative peri-operative regimen.[81,218]

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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) *vs.* 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 significantly lower in TIA/ischaemic stroke patients of atherosclerotic origin on ticagrelor *vs.* 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) or ticagrelor monotherapy is an option (180 mg loading dose, then 90 mg bd).[24]

Combination therapy

Historically, surgeons have been reluctant to perform CEA in patients on aspirin + clopidogrel, due to 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]. In a SVS vascular quality initiative (VQI) between 2003 - 2014 (*n* = 28 683), 25% of CEA patients were on aspirin + clopidogrel,[137] increasing to 31% between 2010 - 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

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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 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 *vs.* 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 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 = .306) but was 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 *vs.* 23.7% (9/38) on aspirin (p = .0692), 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 *vs.* aspirin alone in patients with recent TIA/ stroke and a 50 - 99% extracranial SCS.

The debate regarding peri-operative monotherapy *vs.* 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 significantly 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 thrombo-embolic stroke.[309] The most important bleeding complication after CEA is neck

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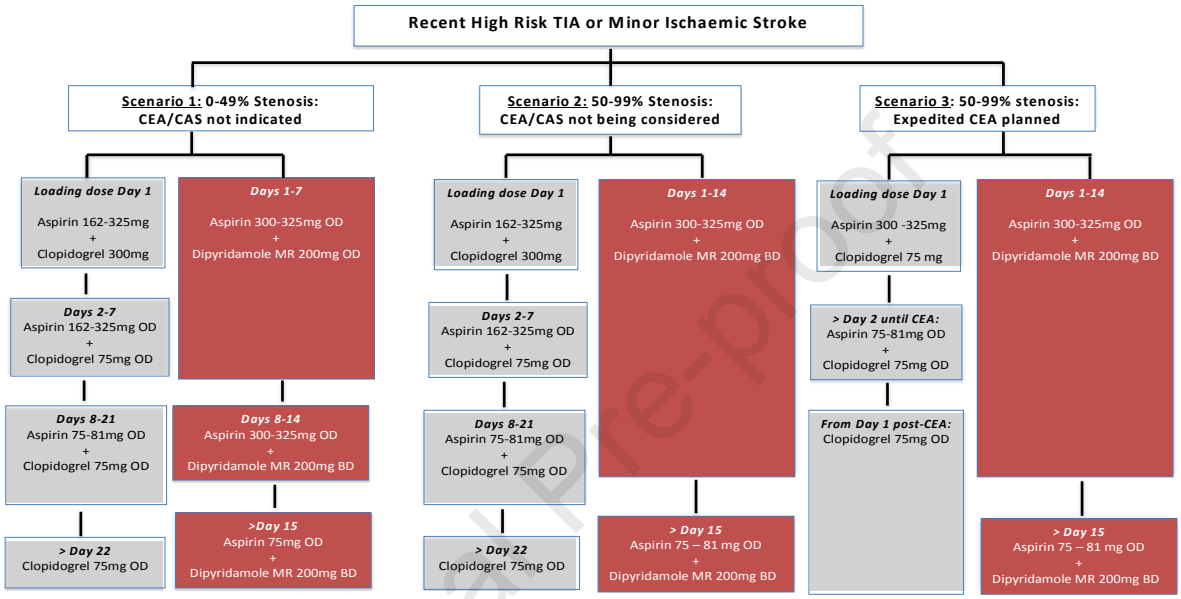
haematoma, which is associated with increased morbidity and mortality.[137] In a 2011 audit of practice between 2003 - 2009 (*n* = 5 264), the Vascular Study Group of New England (VSGNE) registry found no evidence that aspirin + clopidogrel was associated with higher rates of re-exploration for neck 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 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, co-morbidities) 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

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for peri-operative aspirin + clopidogrel combination therapy, aspirin can be stopped on day one after CEA and clopidogrel 75mg daily continued indefinitely, unless contraindicated (**Figure 3**).

Figure 3: Timing, dose and duration of combination antiplatelet therapy in the early phase after onset of TIA or minor ischaemic stroke *.



CEA = carotid endarterectomy; CAS = carotid artery stenting; 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, Elsevier. 2021 (In press)[331].*

The 2021 AHA guidelines made no recommendation regarding combination APRx prior to CEA.[1] The German-Austrian guidelines recommend combination APRx between 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, chronic alcohol use), gastric protection should be considered.[333] If a PPI is indicated, it is recommended to select a PPI which doesn't interact with clopidogrel (eg. pantoprazole).[40,334] If the patient is PPI intolerant or they are ineffective, an H_2 receptor antagonist (eg. famotidine) is an alternative.[335]

Recommendation 23 (New)	**Class**	**Level**	**References ToE**
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*	**I**	**A**	59,301,302, 304,307,

Recommendation 24 (New)	**Class**	**Level**	**References ToE**
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*	**I**	**B**	5,218

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Recommendation 25 (New)	Class	Level	References ToE
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.	I	C	Expert Opinion

Recommendation 26 (UNCHANGED)	Class	Level	References
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.	I	A	81,325,219

Recommendation 27 (New)	Class	Level	References ToE
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*.	IIa	C	59,306, 308,310,

Recommendation 28 (New)	Class	Level	References ToE
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 (300-325mg daily for 14 days, followed by 75-162mg daily) should be considered.	IIa	B	219

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Recommendation 29 (New)	Class	Level	References ToE
For recently symptomatic patients undergoing carotid endarterectomy on aspirin monotherapy, lower dose aspirin (75-325mg daily) rather than higher dose (>325mg daily) is recommended.	I	B	219

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

Recommendation 31 (Regraded)	Class	Level	References
For recently symptomatic patients undergoing carotid stenting, combination antiplatelet therapy with aspirin (75-325mg daily) and clopidogrel is recommended. Clopidogrel (75mg daily) should be started at least three days prior to stenting or as a single 300mg 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 75mg daily) should be continued indefinitely.	I	C	81,221, 226,318

Recommendation 32 (Unchanged)	Class	Level	References
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.	III	A	59,320

Recommendation 33 (Unchanged)	Class	Level	References

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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).	**IIa**	**B**	40,332, 333,334,335

* *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 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 DOACs plus low dose aspirin for secondary stroke prevention as being a knowledge gap to be addressed.[1] No guideline currently recommends low dose rivaoxaban + aspirin in SCS patients.[1-4]

4.2.5 Antiplatelet High On Treatment Platelet Reactivity (HTPR)

In patients with > 50% SCS, the prevalence of antiplatelet HTPR (previously termed antiplatelet resistance) can vary between 9 - 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

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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 *vs.* 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 if *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]

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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

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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 < 3 months, thrombocytopenia (< 50 x 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**).

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4.2.6.1 Assessing peri-operative bleeding risks: CEA

In an SVS-VQI audit (*n* = 28 683), CEA patients undergoing re-exploration for neck haematoma incurred significantly higher in hospital risks *vs.* 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] Accordingly, CEA is classified as a 'high risk of bleeding' operation[343].

4.2.6.2 Assessing peri-operative bleeding risks: CAS

Bleeding complications after CAS are mostly access related and the incidence of re-intervening for bleeding complications in RCTs was ≤ 1%.[48] Care should be taken to minimise access complications in patients on anticoagulants, including using smaller sheaths (≤ 6 Fr) and

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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 anticoagulation and antiplatelet strategies.

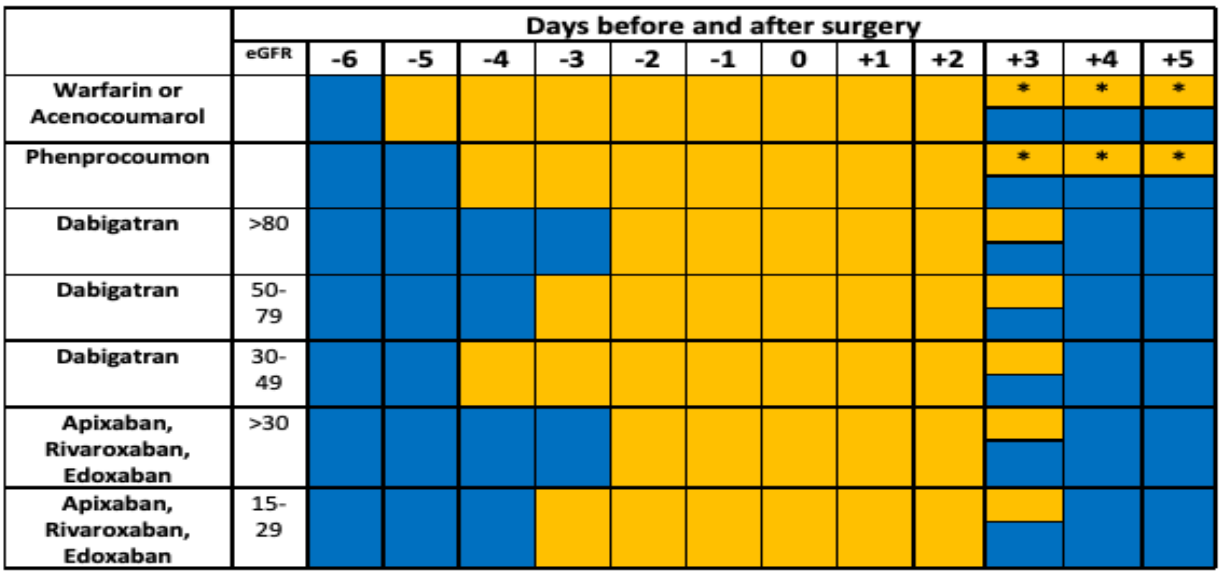
This depends on the procedure (CEA, CAS), thromboembolic risk, bleeding risk, type of anticoagulant (vitamin K antagonist (VKA) or Direct Oral Anticoagulant (DOAC)), renal function and whether bridging anticoagulation is required.

CEA

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 re-starting VKAs and DOACs. Decisions regarding re-starting VKAs/DOACs must take account of post-operative bleeding complications, as well as the patient's ability to swallow. Aspirin 300mg daily should be prescribed as indicated in **Figure 4**.

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Figure 4: Stopping and restarting anticoagulation prior to CEA



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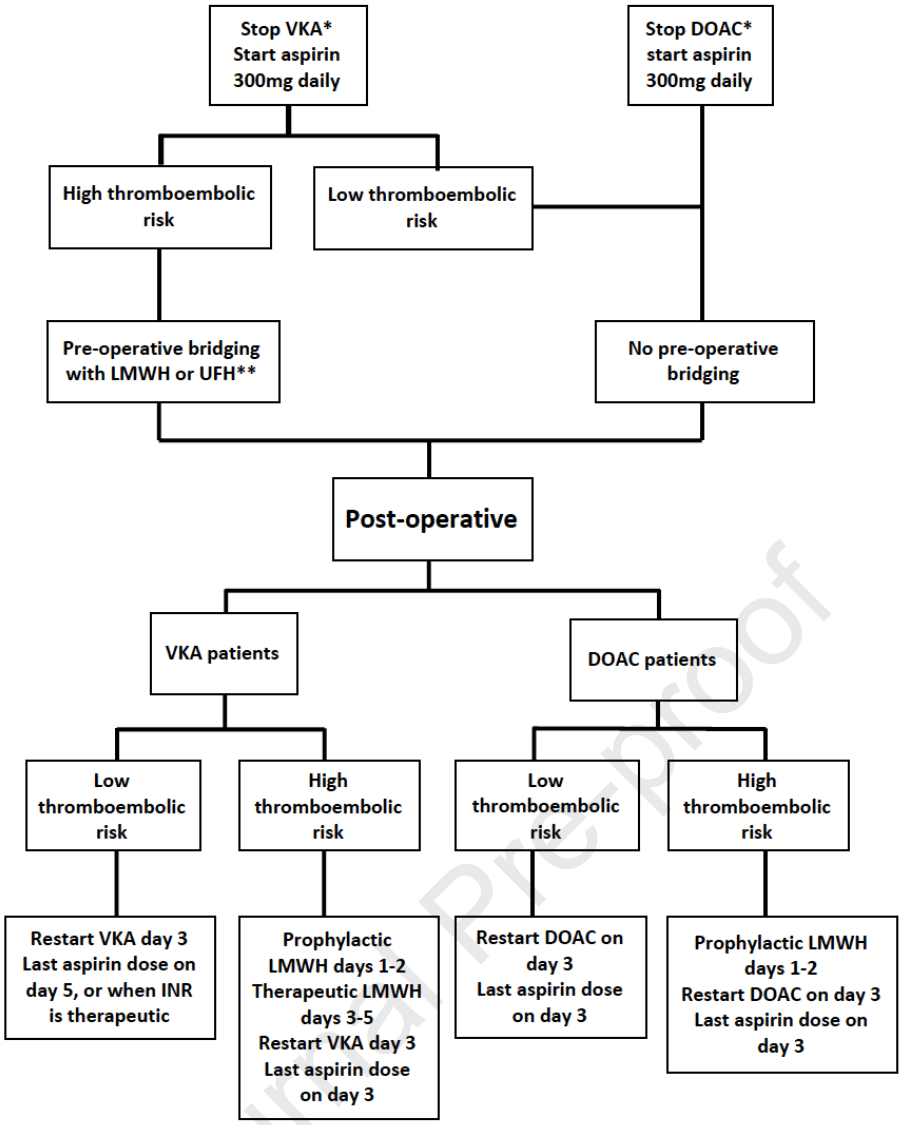
Blue boxes = days for taking anticoagulant; Yellow boxes = days to take 300mg aspirin. If intolerant of, or allergic to aspirin, 75mg of clopidogrel daily or 200mg of dipyridamole modified release monotherapy twice daily are alternatives; eGFR= estimated glomerular filtration rate, measured as mL/min/1.73m.^{2}

** In VKA patients, post-operative aspirin is continued until the International Normalised Ratio is therapeutic (after VKA re-started) or until the patient is started on therapeutic dose low molecular weight heparin or intravenous unfractionated heparin.*

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 significantly 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 high risk of thromboembolism after cessation of VKAs, which would include patients with a recent (≤ 3months) 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 ≥ 24 hours pre-operatively. Intravenous UFH can be stopped 4 - 6 hours before CEA.

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Figure 5: anticoagulation, antiplatelet and bridging strategies in CEA patients



** Stop VKAs and DOACs according to timings in **Figure 4**. ** If pre-operative bridging is being considered, this decision should involve MDT 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.*

VKA = vitamin K antagonist; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; UFH = unfractionated heparin. If intolerant of, or allergic to aspirin, 75mg of clopidogrel monotherapy daily or 200mg of dipyridamole modified release monotherapy twice daily are alternatives.

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]

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In CEA patients whose VKAs have been stopped and who are classed as low thromboembolic risk, VKAs can be restarted on day 3. Aspirin (300mg daily) should be continued until either a last dose on day five 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 re-started 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 three (**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 three, with the last dose of aspirin (300 mg) being taken on day three (**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 three when the DOAC is re-started. In these patients, the last dose of aspirin is taken on day 3.

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CAS

Decisions about anticoagulation and antiplatelet strategies during CAS depend upon whether unit policy is to (i) stent patients whilst 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, *vs.* worries about higher rates of peri-operative ischaemic stroke if antiplatelet therapy is not co-

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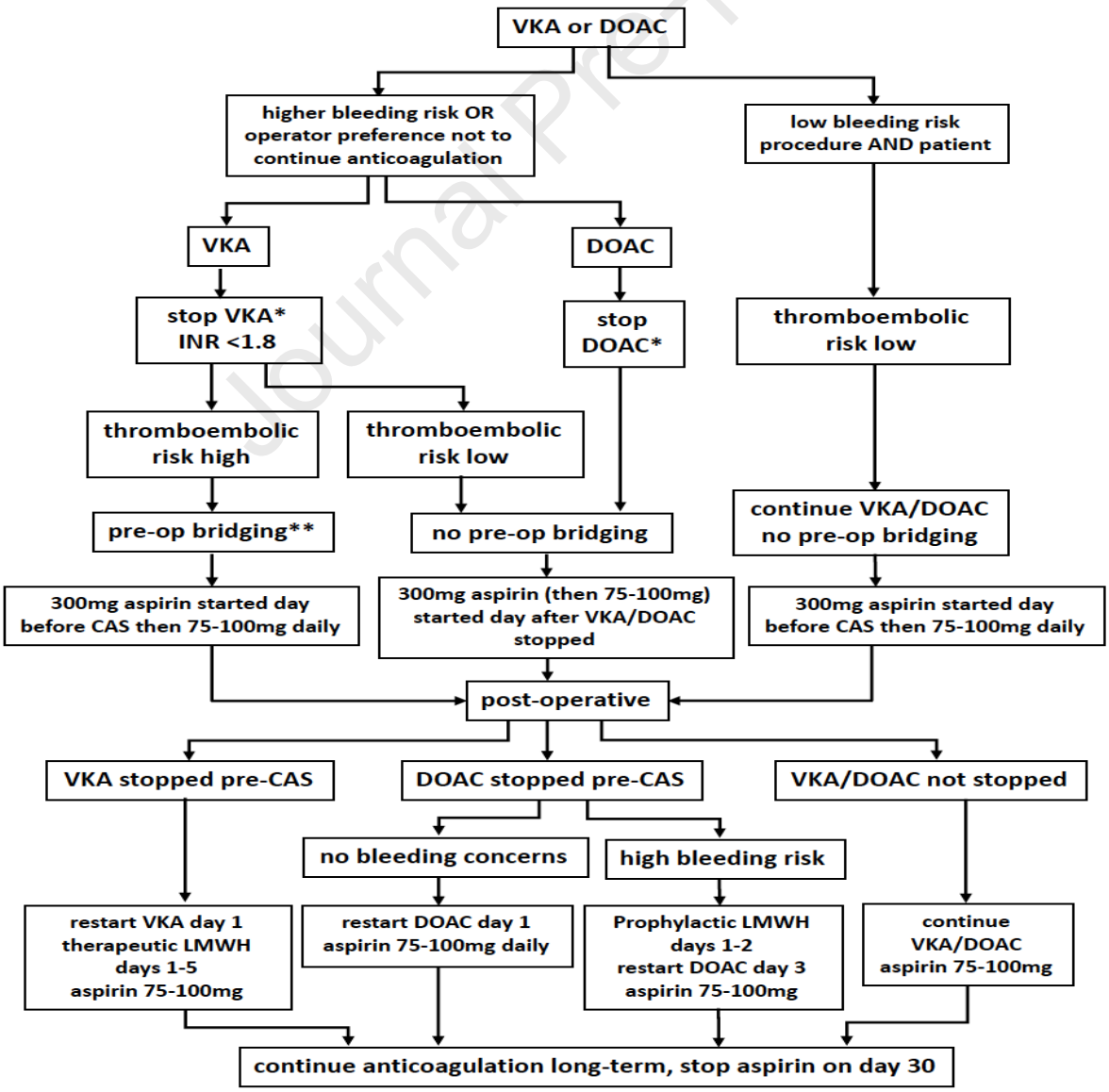
prescribed. Accordingly, individual units will benefit from MDT review, which should ideally include a specialist in coagulation (especially if bridging is being considered) and agreed treatment strategies should be documented in the case notes.

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. Whilst there have been no RCTs in CAS patients, evidence from observational studies suggest that CAS can be performed safely whilst 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 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, whilst 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 *vs.* 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 300mg the day before CAS, then 75 - 100mg 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, 75mg of clopidogrel monotherapy daily or

200mg of dipyridamole modified release monotherapy twice daily are alternatives. After 30 days, antiplatelet therapy is stopped, and anticoagulation continued long term.

Figure 6: anticoagulation and antiplatelet strategies in CAS patients who are taking anticoagulants pre-operatively.



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** Stop VKAs/DOACs according to timings in **Figure 4**. ** If bridging is being considered, this decision should involve MDT 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.*

VKA = vitamin K antagonist; DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin. If intolerant of, or allergic to aspirin, 75 mg clopidogrel monotherapy daily or 200 mg dipyridamole modified release monotherapy twice daily are alternatives.

In some centres, CAS practitioners prefer to stop anticoagulation therapy pre-operatively and then prescribe combination antiplatelet therapy throughout the peri-procedural period, in order 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 re-started.

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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]

Table 17: RCTs evaluating lipid lowering therapy in TIA or minor ischaemic stroke patients

RCT Inclusion criteria	Treatment strategy	Main findings
HPS[348]	40mg Simvastatin daily *vs.* placebo	Simvastatin conferred 20% RR in stroke, non-fatal MI, death from coronary artery disease and/or coronary

3 280 patients with prior TIA (46%), minor ischaemic stroke (63%), prior carotid revascularisation (10%) + cholesterol >3.5mmol/L. Mean interval from symptom onset to randomisation = 4y.		or non-coronary revascularisation in patients with prior cerebrovascular disease *p = .001*). A 19% RR in ischaemic stroke with simvastatin (6.1%) *vs*. placebo (7.5%) was not significant (*p* = .1) with no statistically significant increase in haemorrhagic stroke with simvastatin (1.3% *vs.* 0.7%).
FASTER[311] 392 patients randomised within 24 hours of TIA or minor ischaemic stroke using factorial design	All received aspirin + either Clopidogrel *vs.* placebo and simvastatin *vs.* placebo	No significant differences in the 90 day endpoint of any stroke between those who were *vs.* not taking simvastatin
SPARC [349] 4 731 patients with ischaemic stroke/TIA <6 mths with baseline LDL-C 2.6-4.9mmol/L and no known CAD	80mg Atorvastatin *vs.* placebo	80mg atorvastatin conferred significantly lower fatal/non-fatal stroke at 5yrs (11.2% *vs.* 13.1%; HR 0.84, 95% CI 0.71-0.99, *p = .03*). Significant increase in haemorrhagic stroke with atorvastatin *vs.* placebo (2.3% *vs.* 1.4%; HR 1.66, 95% CI 1.08-2.55, *p = .02*) which didn't negate the benefit of atorvastatin
SPARCL[347] 1 007 SPARCL patients with carotid stenosis (mean 51%) not undergoing CEA or CAS <30d of randomisation.	80mg Atorvastatin *vs.* placebo	80mg atorvastatin associated with significant reductions in (i) any stroke (HR 0.67; 95% CI 0.47-0.94, *p = .02*); (ii) late carotid revascularisation (HR 0.44; 95% CI 0.24-0.79, *p = .006*) and (iii) major coronary events (HR 0.57; 95% CI 0.32-1.0, *p = .05*)
TST Trial[7] 2 860 patients <3mths of ischaemic stroke (MRS 0-3) or <15 days of TIA (patients randomised within median of six days after TIA/stroke).	Aggressive lipid lowering with statins +/- ezetimbe to achieve lower LDL-C target of <1.8mmol/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 (10mg daily). Lower LDL-C target (*vs.* higher target) associated with significant reduction in composite endpoint of any cardiovascular death, stroke, MI, hospitalisation for

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Outcomes in SCS patients not reported.	*vs.* higher LDL-C target of 2.3-2.8mmol/L.	unstable angina requiring urgent CABG or PCI or TIA treated by urgent CEA/CAS at 3.5 years. (8.5% *vs.* 10.9%; HR 0.78, 95% CI 0.61-0.98, *p = .04*).
STARS[30] 98 patients randomised <12hrs of ischaemic stroke.	40mg simvastatin *vs.* placebo (only 4% of simvastatin patients and 15% of placebo patients had LAA).	Independence at 90 days (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 + dyslipidaemia or LDL-C >2.6mmol/L randomised to early statin therapy *vs.* delayed statin therapy.	131 started statin therapy <24hrs (for 12 wks) *vs.* 126 starting statins on day 7 (for 11 wks). (atorvastatin 20mg/day, pitavastatin 4mg/day or rosuvastatin 5mg/day).	At 90 day, 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 naive patients randomised within 48hrs of acute ischaemic stroke. 33-37% had a 50-99% stenosis of a brain supplying artery, but number with extracranial SCS not reported.	Rosuvastatin 20mg (*n*=137) *vs.* placebo *n*=152) over 14 days.	No difference in NIBLs at five or 14 days 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)

RCT = randomised controlled trial; TIA = transient ischaemic attack; 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 C; OR (95% CI) = Odds Ratio with 95% confidence intervals; SCS = symptomatic carotid stenosis; mRS = modified Rankin score; NIBLs = new ischaemic brain lesions; DW-MRI = diffusion weighted magnetic resonance imaging; LAA = large artery atherosclerosis.

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In most RCTs in patients presenting with TIA/stroke (including those with carotid disease), lipid lowering therapy significantly 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 ≥ 2 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 < 4 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 2 weeks or 420 mg every 4 weeks) *vs.* 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/TIA 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 AHA, ESC, and EAS guidelines recommend high dose Atorvastatin 80mg or Rosuvastatin 20mg, unless not tolerated.[1,258] As no RCTs have specifically evaluated lipid lowering targets in SCS

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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),[348, 7,347] or a 50% reduction in LDL-C *vs.* 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 significant increase in haemorrhagic stroke with atorvastatin *vs.* placebo in SPARCL (2.3% *vs.* 1.4%; HR 1.66, 95% CI 1.08 - 2.55, p = .02)[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 (eg. 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)	**Class**	**Level**	**References**
For patients with a symptomatic carotid stenosis, statin therapy is recommended for the long term prevention of stroke, myocardial infarction and other cardiovascular events.	**I**	**B**	347

Recommendation 35 (New)	**Class**	**Level**	**References** **ToE**

Journal Pre-proof

For symptomatic carotid stenosis patients who do not reach their lipid targets on maximum doses or maximum tolerated doses of statins, ezetimibe (10mg daily) is recommended.	I	B	7

Recommendation 36 (New)	**Class**	**Level**	**References ToE**
For symptomatic carotid stenosis patients who are intolerant of, or not achieving target LDL levels on statins, with or without ezetimibe, additional or alternative treatment with PCSK9 inhibitors should be considered	**IIa**	**B**	18

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4.2.7.4 Statins during carotid interventions

In a meta-analysis (7 observational studies; *n* = 610), statin pre-treatment in patients with > 50% SCS was associated with a significantly lower incidence of MES during TCD monitoring *vs.* statin naive patients (RR = 0.67; 95% CI 0.45 - 0.98).[93] In another meta-analysis (6 observational studies; *n* = 7 503), patients taking statins prior to CEA had significantly lower peri-operative mortality (0.2% *vs.* 1.3%) in 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%) in 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 significantly lower mortality (OR 0.30; 95% CI 0.10 - 0.96) and procedural stroke (OR 0.39; 95% CI 0.27 - 0.58) *vs.* 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]

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Recommendation 37 (Unchanged)	Class	Level	References
For patients scheduled to undergo endarterectomy or stenting, it is recommended to commence statin therapy pre-operatively.	I	A	93,100,101

4.2.8 Management of hypertension

4.2.8.1 Secondary prevention in patients with symptomatic carotid stenosis

A Cochrane review (11 RCTs; *n* = 38 742) reported that anti-hypertensive therapy significantly 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 interventions

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, whilst 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).**

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Recommendation 38 (Unchanged)	Class	Level	References
For patients presenting with a transient ischaemic attack or minor ischaemic stroke with hypertension, antihypertensive treatment is recommended	I	A	236

Recommendation 39 (Unchanged)	Class	Level	References
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.	IIa	C	350,351

4.2.9 Management of DM

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 normoglycemia 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%

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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 *vs.* medical therapy

4.3.1 30 day and five year outcomes in the randomised trials

Three RCTs (NASCET, ECST, and the Symptomatic Veterans Affairs Co-operative Study (SVACS)) compared CEA *vs.* 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 significant 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**.

Table 18: individual patient meta-analysis of five year risks of any stroke (including peri-operative stroke/death) from ESCT, NASCET and SVACS RCTs*

	n	**5y risk of any stroke (inc peri-operative)**	**ARR @ 5y**	**RRR @ 5y**		

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stenosis severity (NASCET)		CEA + BMT	BMT			NNT to prevent one stroke @ 5y	strokes prevented per 1 000 CEAs @ 5y
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

(*) data derived from the Carotid Endarterectomy Trialists Collaboration[357-359]

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; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SVACS = Symptomatic Veterans Affairs Carotid Study; ECST = European Carotid Surgery Trial; CNO = chronic near occlusion; y = years.

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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**.

Table 19: Clinical and Imaging features that were predictive of a significant increase in late stroke in patients with 50 - 99% stenoses randomised within ECST and NASCET

CLINICAL FEATURES	IMAGING FEATURES
Increasing Age[357,358,360] ***5y ARR in ipsilateral stroke conferred by CEA*** <65y = 5.6% (NNT18); 65-75y = 8.6% (NNT 12); >75y = 19.2% (NNT 5)	**Irregular *vs.* Smooth Plaques**[358] ***5y ARR in ipsilateral stroke conferred by CEA*** smooth = 8% (NNT 13); irregular = 17% (NNT 6)
Recency of Symptoms[358]	**Increasing Stenosis Severity**[357]

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5y ARR in ipsilateral stroke conferred by CEA <2w=18.5% (NNT 5); 2-4w=9.8% (NNT 10) 4-12w=5.5% (NNT 18); >12w=0.8% (NNT 125)	***5y 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)
Men *vs.* Women[359] ***5y ARR in ipsilateral stroke conferred by CEA*** males = 11% (NNT 9); females = 2.8% (NNT 36)	**Contralateral Occlusion**[358] ***5y ARR in ipsilateral stroke conferred by CEA*** Contralat occlusion = 24% (NNT 4); no occlusion = 13% (NNT 8)
Hemispheric *vs.* Ocular Symptoms[358] ***5y ARR in ipsilateral stroke conferred by CEA*** ocular = 5% (NNT 20); TIA = 15% (NNT 7); stroke = 18% (NNT 6)	**Tandem intracranial disease**[362] ***3y 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)
Cortical *vs.* Lacunar Stroke[361] ***3y ARR in ipsilateral stroke conferred by CEA*** non-lacunar stroke 15% (NNT 7); lacunar stroke 9% (NNT 11)	**No recruitment of collaterals**[363] ***2y ARR in ipsilateral stroke*** conferred by CEA collaterals recruited = 5% (NNT 20); no recruitment = 19% (NNT 5)
Increasing Medical co-morbidities[189] ***2y risk of ipsilateral stroke on BMT*** 0-5 co-morbidities = 17%; 6 = 23%; 7+ = 39% ***2y risk of ipsilateral stroke with CEA*** 0-5 co-morbidities = 11%; 6 = 6%; 7+ = 8%	

NASCET = North American Symptomatic Carotid Endarterectomy Trial; ECST = European Carotid Surgery Trial; 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.

4.4 Randomised trials: Endarterectomy *vs.* stenting

4.4.1 30 day outcomes

10 RCTs compared CEA *vs.* CAS (not CA) in 5 797 SCS patients. A meta-analysis of 30 day outcomes is detailed in **Table 20.** CAS (almost exclusively TFCAS) was associated with

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significantly higher rates of any stroke, death/any stroke, death/disabling stroke and death/any stroke/MI *vs.* CEA.[48]

Table 20: Meta-analysis of 30 day outcomes in 10 RCTs* comparing CAS *vs.* CEA **

	Death	Stroke	Death/ Stroke	Disabling Stroke	Death/ Disabling Stroke	MI	Death/ Stroke/MI
	9 RCTs *n*=4 257	9 RCTs *n*=5 535	10 RCTs *n*=5 797	6 RCTs *n*=4 855	5 RCTs *n*=3 534	6 RCTs *n*=3 980	6 RCTs *n*=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)

Yellow boxes *indicate no statistically significant difference.* ***Red boxes*** *indicate a statistically significant result favouring CEA*

** CREST-1; EVA-3S; ICSS; Kuliha; Naylor; Brooks; Steinbauer; SPACE-1; SAPPHIRE; Wallstent; RCTs = randomised controlled trials; MI = myocardial infarction; CEA = carotid endarterectomy; CAS = carotid artery stenting; OR (95%CI) = odds ratio (95% confidence intervals).*

*** 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;58:479-493.*

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 significantly higher rates of 30 day stroke, death/stroke and death/stroke/MI *vs.* CEA.[48] All other endpoints were similar.

Table 21: Meta-analysis of 30 day outcomes after CAS *vs.* CEA in four RCTs which randomised more than 500 symptomatic patients*

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

Yellow boxes = no statistically significant difference. Red boxes = statistically significant result favouring CEA.

*RCTs = randomised controlled trials; MI = myocardial infarction; CEA = carotid endarterectomy; CAS = carotid artery stenting; OR (95% CI) = odds ratio (95% confidence intervals). *CREST-1; EVA-3S; ICSS; 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;58:479-493.*

4.4.1.2 30 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 between increasing age and higher 30 day death/stroke after CAS, but not CEA (**table 22**).[169]

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Compared with CEA **(column 3, table 22)**, CAS patients aged > 70 years incurred significantly higher rates of death/stroke. Below 70 years, CAS had similar outcomes to CEA.

Table 22: Age and 30 day rates of death/stroke after CEA and CAS in symptomatic patients randomised within ICSS, CREST, EVA-3S, SPACE*

	CAS		CEA		CAS *vs.* CEA HR (95% CI) ***
Age - y	30 day death/stroke	HR (95% CI)	30 day death/stroke	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 derived from Howard [169]*

** *All HR age based calculations compared against age < 60 years*

*** *age based HR calculation for CAS compared with CEA. If HR is < 1.0, CAS is associated with significantly lower peri-operative death/stroke. If HR is > 1.0, CAS is associated with significantly higher rates of peri-operative stroke/death.*

CAS = carotid artery stenting; CEA = carotid endarterectomy; HR (95% CI) = hazard ratio (95% confidence intervals).

4.4.2 Long term outcomes in RCTs

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 *vs.* 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 *vs.* 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 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 = .01), 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 < .05). 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 MI

The relevance of peri-operative MI (especially non-ST elevation MI with troponin elevation) has

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been a source of controversy since its inclusion in the 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 significantly higher mortality *vs.* 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 due to deaths occurring in the first 90 days (HR 14.41; 95% CI 5.33-38.94, $p < .0001$). 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 significantly higher mortality at 10 years *vs.* 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, $p < .0001$).[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 significantly more likely to suffer major cardiac events at 12 months *vs.* patients receiving intensified BMT (HR 2.8; 95% CI 1.05-24.2, $p = .04$).[369]

4.5 Timing of 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 - 8% at 48 hours, 4 - 17% at 72 hours, 8 - 22% at 7 days and 11 - 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).

Table 23: Risk of stroke in the early time period after TIA onset in patients with 50 - 99% SCS

	n	**48 hours**	**72 hours**	**7 days**	**14 days**	**5 years**
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%	

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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. * timing relates to time from randomisation; ** timing relates to time from TIA onset; BMT = best medical therapy; SCS = symptomatic carotid stenosis; TIA = transient ischaemic attack.*

However, early recurrent stroke in a CSTC meta-analysis of four RCTs (4 754 SCS patients randomised to and then 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) 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 significantly 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] *vs.* 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 24: Proportion of patients undergoing CEA in national audits within 0 - 2, 3 - 7, 8 – 14, and > 15 days after onset of symptoms

National Audit	0-2 days	3-7 days	8-14 days	≥15 days
Sweden[382] *n* = 2 596	148/2 596 (6%)	804/2 596 (31%)	677/2 596 (26%)	967/2 596 (37%)
UK[380] *n* = 23 235	780/23 235 (3%)	5 126/23 235 (22%)	6 292/23 235 (27%)	11 037/23 235 (48%)
Germany[381] *n* = 56 279	5 198/56 279 (9%)	19 117/56 279 (34%)	16 205/56 279 (29%)	15 759/56 279 (28%)

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 significant 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]

Table 25. 30 day death/stroke after CEA, stratified for delay from symptom onset

National Audit	0-2 days % (95%CI)	3-7 days % (95%CI)	8-14 days % (95%CI)	≥15 days % (95%CI)

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Sweden[382] *n* = 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] *n* = 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] *n* = 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)

A 2021 meta-analysis (3 RCTs, 68 observational cohorts (*n* = 232 952)) reported that when CEA was performed within 2 days of symptom onset (*vs.* days 3 - 14), there were significantly 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 7 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.

Table 26: Proportion of patients undergoing CAS in national audits within 0 - 2, 3 - 7, 8 – 14, and ≥ 15 days after onset of symptoms

National Audit	0-2 days	3-7 days	8-14 days	≥15 days
Sweden[383]	13/323 (4.0%)	85/323 (26.3%)	80/323 (24.8%)	145/323 (44.9%)

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Germany[156]	550/4 717 (11.6%)	1 579/4 717 (33.4%)	1 244/4 717 (26.3%)	1 344/4 717 (28.4%)

Table 27: Procedural death/stroke rates after CAS, stratified for delay from symptom onset to CAS in national audits of practice

National Audit	**0-2 days**	**3-7 days**	**8-14 days**	**≥15 days**
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%)

** 30 day death/stroke; ** in hospital death/stroke*

In the German Statutory Quality Assurance database, performing CAS 3 - 7 days after symptom onset was not associated with reduced in hospital death/stroke *vs.* when CAS was performed in ≤ 2 days. Performing CAS 8 - 14 days after symptom onset was associated with significantly lower in hospital death/stroke *vs.* patients undergoing CAS within two days of symptom onset (OR 0.36; 0.20 - 0.67, p = .001).[156] In a 2021 meta-analysis (3 RCTs, 68 observational cohorts (n = 232 952)), two studies evaluated outcomes when CAS was performed within 2 days *vs.* 3 - 14 days of the index symptom[52]. Compared with CAS interventions at 3 - 14 days, CAS within 2 days was not associated with significant increases in 30 day stroke (OR 1.36; 95% CI 0.84 - 2.04), but there was a significantly higher risk of death (OR 2.77; 95% CI 1.39 - 5.52). Two studies compared outcomes when CAS was performed within seven days *vs.* 8-14 days.[52] CAS was associated with significantly higher rates of 30 day stroke (OR 1.8; 95% CI 1.14 - 2.84) if performed within 7 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]

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4.5.4 Comparison of CEA with CAS 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] Amongst patients treated within seven days of symptom onset, patients undergoing TFCAS were significantly more likely to suffer an adverse 30 day outcome, compared with patients undergoing CEA (**table 28**).

Table 28: 30 day outcomes following CAS *vs.* CEA, stratified for timing after symptom onset in a meta-analysis of symptomatic patients randomised in CREST, ICSS, EVA-3S and SPACE*

	30 day outcomes		OR (95%CI)	*p*
	CEA	CAS		
ANY STROKE/DEATH				
≤7 days	3/226 (1.3%)	24/287 (8.4%)	6.51 (2.00-21.21)	0.002
>7 days	65/1 819 (3.6%)	129/1 806 (7.1%)	2.00 (1.49-2.67)	< .0001
ANY STROKE				
≤7 days	3/226 (1.3%)	23/287 (8.0%)	6.27 (1.92-20.44)	0.002
>7days	62/1 819 (3.4%)	122/1 806 (6.8%)	1.98 (1.47-2.67)	< .0001
FATAL/DISABLING STROKE				
≤7 days	1/226 (0.4%)	9/287 (3.1%)	8.29 (1.07-64.28)	0.04
>7 days	26/1 819 (1.4%)	46/1 806 (2.5%)	1.77 (1.10-2.85)	0.02

** Based on data from Rantner et al[170]. CEA = carotid endarterectomy; CAS = carotid artery stenting; OR (95%CI) = odds ratio (95% confidence intervals)*

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

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undergoing TFCAS within 8 - 14 days of their most recent symptom also had significantly higher rates of 30 day death/stroke (8.1%) *vs.* 3.4% after CEA (OR 2.42; 95% CI 1.0 - 5.7, p = .04).[384]

4.5.5: TCAR 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, *vs.* 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 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 significantly 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 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]

Table 29. In hospital rates of stroke and death/stroke in 2 608 patients undergoing TCAR, stratified for timing after most recent neurological event*.

	<2 days ***n* = 144**	**3-14 days** ***n* = 928**	**>14 days** ***n* = 1 536**
In hospital stroke	5.6% OR 2.8; 95% CI 1.3-6.2, p = .01	2.5% OR 1.3; 95%CI 1.3-6.4, p = .4	2.0% (reference group for calculating OR)**

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In hospital stroke/ death	6.5% OR 2.9; 95% CI 1.3-6.4, *p* = .01	2.9% OR 1.2; 95% CI 0.7-2.1, *p* = .48	2.3% (reference group for calculating OR)**

** based on data from Cui et al[118]. **OR (95%CI) calculated by comparing outcomes against those performed > 14 days.*

OR (95%CI) = Odds Ratio (95% confidence intervals); TCAR = Transcarotid artery revascularisation.

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 in symptomatic patients be modified?

Guidelines since 1998 advise that the 30 day risk of stroke/death when performing CEA in patients reporting ipsilateral carotid territory symptoms < 6 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 (ie. easier to audit). RCTs suggest that 19 - 24% of peri-operative strokes and deaths occur after the 8th 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**).

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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)	**Class**	**Level**	**References**
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%.	**I**	**A**	357-359

Recommendation 41 (Unchanged)	**Class**	**Level**	**References**
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%.	**IIa**	**A**	357-359

Journal Pre-proof

Recommendation 42 (Unchanged)	Class	Level	References
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.	I	A	169

Recommendation 43 (Unchanged)	Class	Level	References
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%.	IIb	A	169

Recommendation 44 (Unchanged)	Class	Level	References
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.	I	A	358,359

Recommendation 45 (Unchanged)	Class	Level	References
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.	I	A	170,384

4.7 Intervening in neurologically unstable patients

Patients with a disabling stroke (mRS $\geq$ 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, due to 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 $\geq$ 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 LWMH 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)	Class	Level	References
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.	I	C	388,389

Recommendation 47 (Unchanged)	Class	Level	References
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.	IIa	C	80,392-394

4.8 Timing of CEA and CAS after intravenous thrombolytic therapy (TT)

In the absence of advanced imaging techniques, i.v. TT is recommended in selected patients with acute ischaemic stroke, provided it is started within 4.5 h 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)

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severe persistent neurological deficit (modified Rankin score ≥ 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 30: Peri-operative outcomes in pooled series undergoing CEA or CAS after TT*

	CEA (*n* = 2 076)	**CAS** (*n* = 481)
Stroke/death	5.2% (95% CI 3.3-7.5)	14.9% (95% CI 11.9-18.2)
ICH	3.4% (95% CI 1.7-5.6)	5.5% (95% CI 3.7-7.7)
Haemorrhage	neck: 3.8% (95% CI 2.9-4.9)	local: 4.9% (95% CI 0.09-16.2)

*CEA = carotid endarterectomy; CAS = carotid artery stenting; 95% CI = 95% confidence intervals; TT = thrombolysis; ICH = intracranial haemorrhage. * Data derived from Kakkos[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 significantly higher rates of ICH and neck haematoma in patients undergoing CEA (*vs.* no TT), while TT was associated with significantly higher stroke/death and ICH in patients undergoing CAS (*vs.* no TT).[66]

Table 31. Peri-operative outcomes for case control studies in CEA and CAS patients who did (did not) have TT.

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	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 (95% CI 2.12-33.95)
Intracranial haemorrhage	2.2%	0.1%	7.82 (4.07-15.2)	5.4%	0.7%	7.48 (95% CI 4.69-11.92)
Neck haematoma	3.6%	2.3%	1.65 (1.17-2.33)			

Data derived from Kakkos et al.[66] CEA = carotid endarterectomy; CAS = carotid artery stenting; OR 95% CI = Odds Ratio and 95% confidence intervals; TT = thrombolysis.

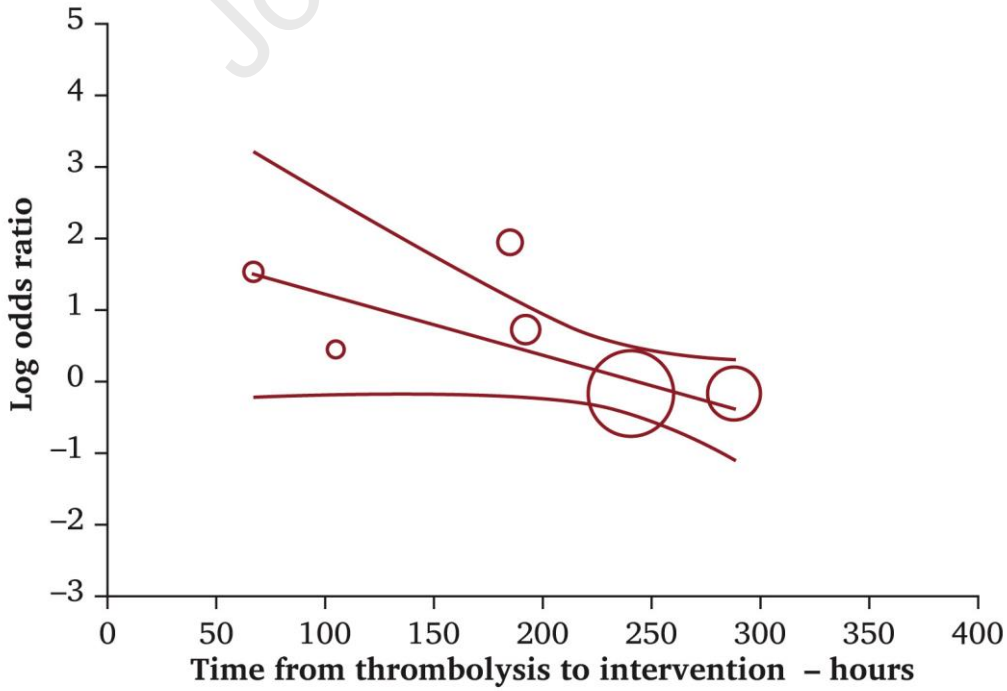
Thrombolysis is associated with complex haematological changes that may make CEA and CAS patients prone to ICH or neck haematoma formation. The half life of i.v. recombinant tissue plasminogen activator (rtPA) is five minutes (Tenecteplase 24 minutes), but fibrinogen and plasminogen levels only revert to > 80% of pre-TT levels ≥ 24 hours after rtPA treatment.[403] Recombinant tPA increases circulating fibrin degradation products and levels > 200 mg/L may be associated with a five fold 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 significantly higher rates of post-operative stroke and ICH if CEA was performed early after TT, which then declined to levels comparable to those in non-TT patients

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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 = .02); ie. performing CEA early after TT was associated with significantly 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]

Figure 7. Regression of Log Odds Ratio on time (hours) of peri-operative death/stroke in patients with stroke undergoing CEA after thrombolysis or without thrombolysis*.



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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 re-starting 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]

Recommendation 48 (Unchanged)	**Class**	**Level**	**References**
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	**I**	**C**	399

Recommendation 49 (New)	**Class**	**Level**	**References** **ToE**

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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.	IIa	B	66,157

Recommendation 50 (Unchanged)	Class	Level	References
For patients undergoing early carotid interventions after thrombolysis, active treatment of post-interventional hypertension is recommended to reduce the risks of parenchymal haemorrhage.	I	C	402

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4.9 Carotid interventions after mechanical thrombectomy (MT)

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 significantly 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 significantly higher probability of successful reperfusion *vs.* MT alone (OR 40.63; 95% CI 30.3 - 70.06), as well as significantly better clinical outcomes (39.5% *vs.* 29.3%; $p < .001$) and

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lower mortality rates (17.1% *vs.* 27.1%; $p < .001$). MT + CAS was associated with similar complication rates (23.9%) *vs.* 18.1% (p = ns) in patients undergoing MT alone.[124]

There is, however, no consensus and a survey of clinicians treating acute stroke patients reported that 59% would perform MT + CAS, while 41% wouldn't.[409] Whilst 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 significantly shorter flow restoration times with an intracranial first strategy (53 mins *vs.* 72 mins, $p < .001$).[124] Few registries have reported outcomes following staged CEA after MT. In an audit of 63 consecutive cases from

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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 > 3000 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]

Whilst 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)	**Class**	**Level**	**References ToE**
For a patient with acute ischaemic stroke undergoing intracranial mechanical thrombectomy with a tandem 50-99% carotid stenosis and a small area of	**IIb**	**C**	Expert Opinion

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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.			

4.10 Patients with < 50% stenoses who may benefit from intervention?

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 (eg. 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.

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

Recommendation 53 (Unchanged)	**Class**	**Level**	**References**
For selected patients experiencing recurrent transient ischaemic attacks or minor stroke, despite best medical therapy and who have a <50% stenosis, carotid endarterectomy may be considered but only following neurovascular work up and multidisciplinary team review	**IIb**	**C**	415-417

4.11 'High risk of surgery' symptomatic patients

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

4.11.1 SAPPHIRE defined high risk criteria

In SAPPHIRE, high risk of CEA criteria included carotid territory symptoms within 180 days and a 50 - 99% stenosis plus more than one of: significant 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 of 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% *v.s* 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 of CEA patients (173 with $\geq$ 1 physiological high risk criterion; 293 with $\geq$ 1 anatomical risk criterion) with 424 propensity matched patients with no high risk criteria. There were no significant differences in 30 day death/stroke/MI after CE.[420]

4.11.2 Increasing age

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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 due to 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 *vs.* 3.5% after CEA (p = .77).[422] CNI after CEA was 9.2% *vs.* 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 significantly 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 of 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 significant increase in peri-operative stroke/death

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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 significantly between CAS and CEA, but the adjusted risk of any stroke/death over two years was significantly higher after CAS (adjusted HR 1.42; 95% CI 1.08 - 1.86, p = .011). In SCS patients, CAS was associated with 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 significantly higher after CAS *vs.* CEA (adjusted HR 1.94; 95% CI 1.18 - 3.19, p = .009).[151]

Recommendation 54 (New)	**Class**	**Level**	**References ToE**
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.	**IIa**	**B**	72,151,422

Recommendation 55 (Unchanged)	**Class**	**Level**	**References**
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%.	**IIa**	**B**	223,282, 315,316

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 significant 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 significantly 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 cross over 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] 30 day death/stroke was 1.8% after CEA, 2.2% after CAS and 4.9% with BMT. BMT was associated with significantly higher 30 day death/stroke *vs.* 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 *vs.* BMT and found no 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 *vs.* 11% in patients

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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 significant 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. Post-operatively, 1/17 (5.8%) died due to 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)	**Class**	**Level**	**References**
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.	**III**	**B**	357

Recommendation 57 (New)	**Class**	**Level**	**References ToE**
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	**IIb**	**C**	78,110, 126,423

4.13 Management of free floating thrombus

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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, $p < .0001$)[49] and a significant proportion (47%) are hypercoagulable due to 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 *vs.* no anticoagulation (HR 1.21; 95% CI 0.35 - 4.23, p = .76), nor interventions <3 days *vs.* >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 significantly higher rates of silent ischaemia, TIA or stroke/death (HR 14.79; 95% CI 3.41 - 64.25) $p < .0001$).[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 (eg. 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

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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)	**Class**	**Level**	**References ToE**
For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus within the carotid artery, therapeutic anticoagulation is recommended.	**I**	**C**	49,54

Recommendation 59 (New)	**Class**	**Level**	**References ToE**
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.	**IIb**	**C**	Expert Opinion

Recommendation 60 (New)	**Class**	**Level**	**References ToE**
For patients presenting with recent carotid territory symptoms and evidence of free floating thrombus, intravenous thrombolysis is not recommended.	**III**	**C**	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 due to 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 *vs.* 0.7% in those with a known source of embolism.[427] Logistic regression analysis showed a 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% 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 due to large vessel occlusion and no CaW had recurrent ipsilateral stroke by two years, *vs.* 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)	**Class**	**Level**	**References** **ToE**

Journal Pre-proof

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.	**IIb**	**C**	19,69,241, 426,427

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 due to 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 neo-vascularisation, 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 significant increases in peak systolic velocity in the ipsilateral ophthalmic artery, with improvement in ocular ischaemic symptoms

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in 93%.[83] No other international guidelines have provided any recommendations regarding the optimal management of ocular ischaemia syndrome.

Recommendation 62 (New)	Class	Level	References ToE
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.	IIa	C	83,431

4.16 Symptomatic patients with > 50% carotid 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 ten patients with > 50% carotid stenosis will have AF and vice versa. Not all strokes in AF patients are cardio-embolic. 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, *vs.* 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 cardio-embolic source) and a

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pragmatic approach is required. This is greatly aided by MDT involvement. Investigations should aim to determine whether the TIA/ischaemic stroke was probably cardio-embolic (ie. 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 cardio-embolic 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

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minutes of TCD monitoring within seven days of TIA/stroke onset had ongoing ipsilateral MCA embolisation.[433] Bilateral embolisation, however, suggests a cardio-embolic 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 cardio-embolism. 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 cardio-embolism was the likeliest aetiology) but then suffers recurrent event(s) in the territory ipsilateral to the 50 - 99% carotid stenosis whilst 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)	**Class**	**Level**	**References ToE**
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	**I**	**C**	Expert opinion

Journal Pre-proof

multidisciplinary team review is recommended to determine whether urgent carotid revascularisation or anticoagulation alone is indicated.			

Recommendation 64 (New)	**Class**	**Level**	**References ToE**
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.	**I**	**C**	Expert opinion

Section 5: Open surgical techniques

5.1 Carotid endarterectomy

5.1.1 Pre-operative check list

Responses to key questions should be documented in the casenotes prior to CEA. The aim is to minimise morbidity/mortality and lessen medicolegal 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 CEA under general (GA) *vs.* locoregional anaesthesia (LRA)?

There is controversy whether to perform CEA under LRA or 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 *vs.* 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 commoner 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

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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 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* = .00001) and lower mortality (OR 0.72; 95% CI 0.59 - 0.90, *p* = .003) in observational studies.[60] However, there were no 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 significantly higher complication rates (OR 2.13; *p* = .006) *vs.* 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. Intra-operative DUS may enable safer infiltration of LRA, with visualisation of the cervical transverse processes and VAs. ESVS recommendations regarding LRA *vs.* GA are the same as in the SVS and German-Austrian guidelines.[3,4]

Recommendation 65 (Unchanged)	Class	Level	References
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.	IIa	B	58,70,70, 130,149,436

5.1.4 Hospital and surgeon volumes

Interpretation of data is confounded by inter-study heterogeneity regarding presentation (symptomatic *vs.* asymptomatic), urgency (emergency *vs.* elective) and non-standardised definitions of low *vs.* high volume surgeons or hospitals (actual numbers *vs.* quintiles). A meta-analysis of 25 studies (900 000 USA based CEAs) reported significant 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 significant 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 peri-operative 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

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CEAs. High volume surgeons (≥ 30 CEAs/year) had significantly lower 30 day stroke/death (1.3%) than 4.1% in surgeons performing < 30 CEAs/year. 30 day death/stroke was significantly higher when CEA was performed by non-vascular surgeons *vs.* 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 significant inverse association between operator volume and in hospital stroke/death, which was 2.2% for the lowest three volume quintiles (≤ 17 CEAs per year), *vs.* 1.76% in surgeons with the two highest volume quintiles (≥ 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, 7/9 studies showed a significant 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, 7/8 studies reported that specialist vascular training was associated with lower death/stroke after CEA *vs.* non-vascular training, but only in low volume surgeons. For high volume surgeons, specialty had no impact.[445] In a Canadian study ($n = 14\,301$), 30 day stroke was significantly higher when CEA was performed by non-vascular surgeons (3.6%), than 2.5% by vascular surgeons (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 ≥ 800 000. At the time, it was advised that each vascular unit should perform ≥ 50 CEAs per year.[158] However, the UK has seen a 25% decline in CEA numbers in symptomatic patients between 2011 - 2017 and a 65% decline in ACS patients, which was not associated with parallel increases in CAS

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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 *vs.* 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)	**Class**	**Level**	**References ToE**
For patients undergoing carotid endarterectomy, it is recommended that the operation be performed by trained vascular surgeons, rather than by surgeons from other specialties.	**I**	**B**	133,444, 445

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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

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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 mobilizing 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)	Class	Level	References
For patients undergoing carotid endarterectomy, decisions regarding carotid exposure (antegrade, retrojugular) should be left to the operating surgeon	IIa	B	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)	Class	Level	References
For patients undergoing carotid endarterectomy, routine carotid sinus nerve blockade is not recommended.	III	A	451,452

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 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% C I0.49 - 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 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 significantly 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 significant 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)	**Class**	**Level**	**References**
For patients undergoing carotid endarterectomy, protamine reversal of heparin should be considered.	**IIa**	**B**	154, 453,454

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. Whilst 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 (6 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 included 5683 CEA procedures performed within 14 days of symptom onset showed no difference in peri-operative stroke rates following routine *vs.* 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)	**Class**	**Level**	**References**
For patients undergoing carotid endarterectomy, decisions regarding shunting (routine, selective, never) should be considered at the discretion of the operating surgeon.	**IIa**	**C**	146, 162,455

Journal Pre-proof

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]

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A meta-analysis of 10 RCTs (*n* = 2 157) observed that routine patching (*vs.* routine primary closure) was associated with 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* = .0011)). 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 significant differences regarding peri-operative death, fatal stroke, death/stroke and CNI.[456,457] An SVS-VQI registry reported significantly 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) *vs.* 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 significantly lower one year re-stenosis rates *vs.* primary closure.[122]

Routine patching (*vs.* routine primary closure) was associated with 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)	**Class**	**Level**	**References**
For patients undergoing conventional carotid endarterectomy, routine patch closure is recommended, rather than routine primary arteriotomy closure.	**I**	**A**	73, 456,457

Recommendation 72 (Unchanged)	**Class**	**Level**	**References**

Journal Pre-proof

For patients undergoing carotid endarterectomy, the choice of patch closure material should be considered at the discretion of the operating surgeon.	IIa	A	73

5.1.11 Eversion (eCEA) *vs.* conventional (cCEA) 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 reanastomosed 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 significantly more post-CEA hypertension than cCEA (OR 2.75; 95% CI 1.82 - 4.16). Conversely, cCEA was associated with significantly 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 restenoses (OR 0.40; *p* = .001). In 20 observational studies, eCEA (*vs.* cCEA) was associated with significant reductions in 30 day death (OR 0.46; *p* < .0001), stroke (OR 0.58; *p* < .0001), death/stroke (OR 0.52; *p* < .0001) and late re-stenosis (OR 0.49; *p* = .032). However, when eCEA outcomes were compared with patched CEA in observational studies, there were no significant differences in 30 day death, stroke or death/stroke,[86] suggesting cCEA provides equivalent outcomes to eCEA, provided the

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arteriotomy is patched. ESVS recommendations regarding eCEA *vs.* cCEA, are similar to SVS guidelines.[4] The German-Austrian guidelines advise that the choice of eCEA *vs.* cCEA should be left to the operating surgeon.[3]

Recommendation 73 (Unchanged)	Class	Level	References
For patients undergoing carotid endarterectomy, eversion endarterectomy or patched endarterectomy is recommended over routine primary arteriotomy closure.	I	A	86

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

Journal Pre-proof

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 *vs.* 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, *vs.* 5.5% with BMT (p = .02). Late stroke was 0% after surgery, *vs.* 6.6% with BMT (p = .01). ESVS recommendations regarding treatment of coils/kinks are similar to SVS guidelines.[4]

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

Recommendation 76 (Unchanged)	Class	Level	References
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.	IIb	B	460

5.1.13 Monitoring and quality control (QC) after CEA

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 significantly 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 = .0001).[71] ESVS recommendations regarding monitoring

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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)	Class	Level	References ToE
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.	IIa	B	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 it cannot be done once CEA is underway. 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)	Class	Level	References
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.	I	C	Expert Opinion

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 significantly higher rates of re-exploration, *vs.* no drains (OR 1.24; 95% CI 1.03 - 1.49, p = .02),[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)	Class	Level	References ToE
For patients undergoing carotid endarterectomy, selective wound drainage should be considered	IIa	B	89, 153

5.1.16 Ward, high dependency or intensive care after CEA?

Patients benefit from 3 - 6 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 (4 - 6 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 2 - 3 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, re-stenosis 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.

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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 to CEA. Late prosthetic graft infection was rare (3/987; 0.3%)**.**

Table 32: Thirty day and late outcomes following carotid bypass

author	*n*	conduit type	30 day death/stroke	primary patency	late infection
Ricco[465]	198	PTFE	1/198 (0.5%)	98% @ 10y	none
Dorafshar[466]	31	PTFE	1/31 (3.2%)	90% @ 4 y	1/31
Roddy[478]	22	PTFE	0/22 (0.0%)	95% @ 2y	none
Veldenz[469]	51	PTFE	1/51 (1.9%)	96% @ 2y	none
Illuminati [472]	66	PTFE	0/66 (0%)	93% @5y	none
Ricco [473]	42	PTFE (31), GSV (11)	0/42 (0%)	n/a	none
Stilo [474]	13	PTFE (7), GSV (6)	0/13 (0%)	100% @41m	n/a
Koncar[471]	292	Polyester	19/292 (6.5%)	96% @ 32m	2/292
Dorafshar[466]	10	GSV	1/10 (10%)	80% @ 4y	n/a
Lauder[467]	50	GSV	3/50 (6.0%)	83% @ 3y	n/a
Branchereau[470]	212	GSV	14/212 (6.6%)	92% @10y	n/a

PTFE = polytetrafluoroethylene; GSV = greater saphenous vein

5.3. Extracranial to intracranial (EC-IC) bypass.

The rationale for 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 (2 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, *vs.* 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)	**Class**	**Level**	**References**
For recently symptomatic patients with an extracranial atherosclerotic internal carotid artery occlusion, extracranial to intracranial bypass surgery is not recommended.	**III**	**A**	475,476

Section 6. Carotid Artery Stenting

6.1 Adjuvant medical therapy

Most operators administer 5000iu i.v. heparin to prevent thrombosis, plus 0.6 - 1.2mg atropine (0.6mg glycopyrrolate) before balloon inflation to prevent hypotension, bradycardia, or asystole.[477,478]

Recommendation 81 (Regraded)	**Class**	**Level**	**References**
For patients undergoing carotid artery stenting, intravenous atropine or glycopyrrolate is recommended prior to balloon inflation to prevent hypotension, bradycardia or asystole	**I**	**C**	477,478

6.2 Access

6.2.1 Transfemoral

Access in RCTs comparing CEA *vs.* 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 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 of 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%. 30 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 significantly higher in hospital TIA/stroke/death *vs.* TCAR (OR 2.1; 95% CI 1.08 - 4.08, p = .03).[148] However, only 33% of the TCAR cohort were symptomatic, *vs.* 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 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)

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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 and 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 significantly 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)	**Class**	**Level**	**References ToE**
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.	**IIa**	**B**	35,64,148, 481-483

6.3 Wires, catheters and stent design

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Access to the CFA, brachial or RA is secured and a .035" hydrophilic guide wire used to access the CCA. 6 - 8 Fr long sheaths 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 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).

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

	open	closed	hybrid
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

There are conflicting data regarding open *vs.* closed cell stents. Two small RCTs reported no outcome differences,[484,485] although NIBLs were commoner with open cell stents (p = .02).[485] A CSTC meta-analysis (n = 1 557) reported that open cell stents incurred significantly higher 30 day stroke/death (10.3%) *vs.* 6% with closed cell (RR 1.7; 95% CI 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-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

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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* = .02).[123] In a meta-regression analysis (*n* = 46 728), open cell stents were associated with significantly higher 30 day death/stroke and NIBLs (RR 1.25; *p* = .03), 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% *vs.* distal filter protection (*p* < .0001), while DLS reduced MES by 13% - 29% *vs.* 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% with single layer stents (*p* = .001).[487]

Recommendation 83 (New)	**Class**	**Level**	**References ToE**
For patients undergoing carotid artery stenting, decisions regarding stent design (open cell, closed cell) should be considered at the discretion of the operator.	**IIa**	**B**	53,123, 141

Recommendation 84 (New)	**Class**	**Level**	**References ToE**

Journal Pre-proof

For patients undergoing elective carotid artery stenting, dual layer mesh covered stents may be considered.	IIb	C	486

6.4 Pre- 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 due to 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 (6 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 *vs.* double dilation was associated with significantly fewer neurological events (RR 0.67; 95% CI 0.47 - 0.97, *p* = .03), as was less aggressive pre-dilation (balloon diameter < 5 mm) *vs.* > 5mm 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 *vs.* CAS with pre- and/or post-dilation (OR 1.15; 95% CI 0.72183, *p* = .55).[131]

Recommendation 85 (New)	**Class**	**Level**	**References ToE**
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.	IIa	C	113

Journal Pre-proof

Recommendation 86 (New)	Class	Level	References ToE
For patients undergoing carotid artery stenting, post-dilatation is not recommended when the residual stenosis is <30%, in order to reduce haemodynamic instability.	III	B	113

6.5 Cerebral protection devices (CPDs)

The role of 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 amongst 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 amongst 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)	Class	Level	References
For patients undergoing carotid artery stenting, cerebral protection systems should be considered	IIa	C	224,316, 490

Recommendation 88 (New)	Class	Level	References ToE
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.	IIa	B	108,131, 141,224, 316,490

Recommendation 89 (Unchanged)	Class	Level	References
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.	III	C	491

6.6 Hospital and individual operator volumes

Low volume hospitals (< 20 CAS/year) had a 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 of CEA registry, a lifetime experience of 72 procedures was required to achieve 30 day death/stroke rates < 3% in non-octogenarian ACS patients.[493] 30 day mortality in Centre for Medicare and Medicaid beneficiaries was higher if practitioners performed < 6 CAS/year, *vs.* > 24 (OR 1.9; 95% CI 1.4 - 2.7, p < .001).[494] In a single

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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), whilst < 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 30 day death /stroke was not influenced by lifetime CAS experience,[496] but 30 day death/stroke was significantly higher with lower volume operators (≤ 3.2 CAS/year) *vs.* 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 significantly higher peri-operative stroke/death rates with lower volume CAS operators (2.63% for operators doing < 11 annual cases) *vs.* 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)	**Class**	**Level**	**References ToE**
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.	**IIb**	**C**	128,492,498

Journal Pre-proof

Section 7: Complications after carotid interventions

7.1 Peri-operative period

7.1.1 Stroke after carotid endarterectomy

7.1.1.1 Intra-operative stroke

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 1 - 2 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 *vs.* 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 stroke

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 commonest 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 CEA

In ECST, predictors included (i) female sex (10.4% *vs.* 5.8%, *p* = .0001); (ii) PAD (12.0% *vs.* 6.1%, *p* = .0001); (iii) pre-operative SBP (< 120 mmHg = 3.4%; 121 - 159 = 6.5%; 160 - 180 = 7.7%; > 180 mmHg = 13.0%, *p* = .04) and (iv) presentation (retinal (3.2%), hemispheric stroke (6.3%), TIA (9.1%) *p* = .006).[352] Predictive features in NASCET were (i) hemispheric *vs.* retinal events (6.3% *vs.* 2.7%; OR 2.3; 95% CI 1.1 - 5.0); (ii) left *vs.* right CEA (6.7% *vs.* 3.0%; OR 2.3, 95% CI 1.4 - 3.6); (iii) contralateral occlusion (9.4% *vs.* 4.4%; OR 2.2, 95% CI 1.1 - 4.5); (iv) ipsilateral CT/MR infarct (6.3% *vs.* 3.5%; OR 1.8; 95% CI 1.2 - 2.8) and (v) irregular *vs.* 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 +10mmHg; 95% CI 1.02 - 1.66, *p* = .04), but unrelated to CEA method or GA *vs.* 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)	**Class**	**Level**	**References ToE**
For patients experiencing a peri-operative stroke, it is recommended to differentiate between an intra-operative and a post-operative stroke.	**I**	**C**	502

Recommendation 92 (New)	**Class**	**Level**	**References ToE**
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.	**I**	**C**	502

7.1.2 Stroke after carotid artery stenting

Journal Pre-proof

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 due to 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 due to 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 5mg bolus, followed by slow infusion (maximum dose 20mg), 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 5mg abciximab followed by an i.v. bolus of 5mg abciximab has been effective in treating distal embolisation during CAS.[508] While no RCTs have addressed the treatment of acute stroke due to 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.

Journal Pre-proof

Recommendation 93 (New)	Class	Level	References ToE
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.	I	C	Expert opinion

7.1.2.1 Predictors of stroke after CAS

A Delphi consensus identified anatomic 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 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 (≥ 60° *vs.* < 60°; OR 4.1, 95% CI 1.7 - 10.1, p = .002).[32]

In a CSTC meta-analysis (**section 2.3.5**), CAS incurred significantly higher rates of death/stroke (*vs.* CEA) in the first 7 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 =

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.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 ≥ 7 on CT/MRI had higher rates of peri-operative stroke, *vs.* 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 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 significant 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

Journal Pre-proof

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* = .03).[113] Meta-analysis of 27 observational studies (*n* = 4204) suggested no differences in peri-operative stroke in CAS patients with orwithout 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 due to 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 *vs.* norepinephrine/phenylephrine (*p* = .04). 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

Journal Pre-proof

to carotid bulb denervation.[524] In a meta-analysis of six observational studies, patients undergoing eCEA were significantly more likely to require vasodilator therapy in the early post-operative period *vs.* cCEA (OR 2.75; 95% CI 1.82 - 4.16).[458] However, evidence suggests that (in the long term) there is no 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, $p < .0001$). 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

Journal Pre-proof

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 (ie. 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 ≥ 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 commoner after CAS than CEA,[63,134] possibly because CAS is associated with intraprocedural 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

Journal Pre-proof

management of post-intervention hypotension, hypertension and HS are similar to the 2021 SVS and German-Austrian guidelines.[3,4]

Recommendation 94 (Unchanged)	Class	Level	References
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.	IIa	C	517,518

Recommendation 95 (Unchanged)	Class	Level	References
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.	I	C	Expert Opinion

Recommendation 96 (Unchanged)	Class	Level	References
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.	I	C	Expert Opinion

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

7.1.4 Neck 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

Journal Pre-proof

haematoma requiring re-exploration.[48] In GALA, the incidence of haematoma needing re-operation was 2.6% under GA *vs.* 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 significantly higher in hospital risks *vs.* 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)	Class	Level	References
For a patient who develops a post-operative neck haematoma associated with stridor or tracheal deviation, immediate re-exploration is recommended.	I	C	Expert Opinion

7.1.5 Cranial nerve injury (CNI)

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% resolved in less than one year. CNI impacted on swallowing at 2 - 4 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

Journal Pre-proof

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 ischaemic brain lesions (NIBLs)

In ICSS, a subgroup (*n* = 161) underwent DWI-MRI pre-operatively, with a second MRI scan 1 - 3 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 ≥ 1 NIBL at the first post-operative scan (OR 5·21; 95% CI 2·78 - 9·79, $p < ·0001$). At 1 month, there were persisting FLAIR-MRI changes in 28/86 CAS patients (33%) *vs.* 6/75 (8%) after CEA (OR 5.93; 95% CI 2.25 - 15.62, $p = .0003$).[537] In a meta-analysis (two RCTs, 18 observational studies), NIBLs were commoner after CAS *vs.* CEA (40% *vs.* 12%; OR 5.17, 95% CI 3.31 - 8.06, $p < .00001$).[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 *vs.* filter CPDs was associated with significantly 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 *vs.* 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 *vs.* 8.8% in patients without NIBLs (HR 2.85; 95% CI 1.05 - 7.72, $p = .04$).[167] NeuroVISION also reported increased rates of stroke/TIA at one year in patients with NIBLs (HR 4.13; 95% CI

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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 9 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 > 6 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, due to 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

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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 9 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 reinfection.[74] ESVS

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recommendations regarding patch infection are similar to SVS and German-Austrian guidelines[3,4].

Recommendation 99 (Unchanged)	Class	Level	References
For patients with prosthetic patch infection or carotid stent infection excision and autologous venous reconstruction is recommended.	I	C	74,542

Recommendation 100 (Unchanged)	Class	Level	References
For patients with carotid patch or stent infection, excision and prosthetic reconstruction is not recommended.	III	C	74,542

Recommendation 101 (New)	Class	Level	References ToE
In selected high risk of surgery or emergency patients with suspected prosthetic patch infection, insertion of a covered stent may be considered, as part of the three stage EndoVAC technique	IIb	C	74,541,545

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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

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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 DUS criteria for diagnosing re-stenosis

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 $\geq$ 2.5) for diagnosing > 50% re-stenosis and $\geq$ 300cm/sec (end diastolic velocity $\geq$ 90 cm/sec; ICA/CCA ratio $\geq$ 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 DUS 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 re-do 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 significant EEG/SSEP changes during carotid clamping, or MCAV < 15cm/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 DUS 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 ≥ 1 clinical or imaging feature that make them higher risk of stroke on BMT, would then be considered for a carotid intervention (**section 3.3.5**).

7.2.2.5 Incidence of re-stenosis

In a Cochrane review (9 RCTs; *n* = 5 477), CAS had 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 eversion CEA[43]. At five years, the cumulative incidence of re-stenosis ≥ 50% was 25.9%, 37.2% and 30% respectively. Primary arteriotomy closure incurred a 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 significant difference in re-stenosis rates between patched and eversion CEA.[43]

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Table 34. Meta-analyses of rates of re-stenosis > 70% after CEA and CAS

Author	Procedure	No RCTs	No non-RCTs	*n*	Mean FU	Re-stenosis >70% or occlusion
Kumar[555]	any CEA	11		4 249	47mths	5.8% (95% CI 4.1-8.2)
	patched CEA	5		1 078	32mths	4.1% (95% CI 2.0-8.4)
	CAS or CA	6		2 916	60mths	10.3% (95% CI 6.4-16.4)
	CAS	5		2 716	62mths	10.0% (95% CI 6.0-16.3)
Xin[109]	CEA	15	12		6mths	2.04%
	CAS	15	12		6mths	4.12%
	CEA *vs.* CAS			20 479		OR 0.49 (95% CI 0.29-0.86) *p* = .013
Xin[109]	CEA	15	12	1 578	120mths	8.4%
	CAS	15	12	1 610	120mths	10.2%
	CEA *vs.* CAS					OR 0.92 (95% CI 0.42-2.04)
Li[75]	CEA	8		3 136	48mths	8.0%
	CAS	8		3 869	48mths	11.3%
	CAS *vs.* CEA					OR 1.48 (95% CI 0.93-2.35) *p*=0.10
Jung[65]	CEA	8		2,798	>10yrs	7.1%
	CAS	8		2,757	>10yrs	9.9%
	CEA *vs.* CAS					OR (0.68 (95% CI 0.48-0.97)

RCTs = randomised controlled trials; FU = follow up; CEA = carotid endarterectomy; CAS = carotid artery stenting; 95% CI = 95% confidence intervals; mths = months; yrs = years.

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 7 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% *vs.* 2% without re-stenosis > 70% (OR 0.87; 95% CI

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0.24 - 3.21, p = .8339).[555] By contrast, > 70% asymptomatic re-stenosis after CEA was associated with a significantly higher risk of ipsilateral stroke (5.2%) at three years *vs.* 1.2% without re-stenosis > 70% (OR 4.77; 95% CI 2.29 - 9.92).[555]

Table 35: meta-analysis of late ipsilateral stroke in CEA and CAS patients with and without an asymptomatic re-stenosis > 70% in RCTs*

Procedure	Mean follow up (mths)	Stroke ipsilateral to >70% re-stenosis or occlusion**	Stroke ipsilateral to re-stenosis <70%	OR (95% CI)
Any CEA 7 RCTs*** (n = 2 810)	37	7/135 5.2%	40/2704 1.2%	4.77 (95%CI 2.29-9.92)
CAS 4 RCTs**** (n = 1 964)	50	1/125 0.8%	37/1839 2.0%	0.87 (0.24-3.21)

** Data derived from Kuma; [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; Mths = months; CEA = carotid endarterectomy; CAS = carotid artery stenting; RCTs = randomised controlled trials; OR (95% CI) = odds ratio (95% confidence intervals).*

7.2.2.7 Management of re-stenosis

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 re-do 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.

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 2 - 3 peri-operative strokes,[556] and 85% of late ipsilateral strokes would still occur in patients with re-stenosis < 70%.

Re-do endarterectomy or stenting?

Once a decision has been made to re-intervene, options include surgery (re-do 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 *vs.* 2% after CAS (*p* = ns). Permanent CNI was 3.3% after redo CEA *v.s* 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% *vs.* 1.4% after redo CAS (*p* = .91), while death/stroke was 4.5% after CEA *vs.* 1.9% after redo CAS (*p* = .09).[116]

Recommendation 102 (Regraded)	**Class**	**Level**	**References**
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.	I	B	357

Recommendation 103 (Regraded)	**Class**	**Level**	**References**

Journal Pre-proof

For patients experiencing a late ipsilateral stroke or transient ischaemic attack in the presence of an ipsilateral <50% re-stenosis, medical therapy is recommended	I	B	357

Recommendation 104 (Unchanged)	Class	Level	References
For carotid endarterectomy patients with an asymptomatic 70-99% re-stenosis, re-intervention may be considered following multidisciplinary team review.	IIb	A	555

Recommendation 105 (Unchanged)	Class	Level	References
For carotid stent patients who develop an asymptomatic re-stenosis >70%, medical management is recommended.	I	A	555

Recommendation 106 (Unchanged)	Class	Level	References
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.	I	C	Expert Opinion

Recommendation 107 (Unchanged)	Class	Level	References
For carotid endarterectomy patients who develop significant electrophysiological changes during carotid clamping, or whose mean middle cerebral artery velocities fell below 15cm/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.	I	C	Expert Opinion

Recommendation 108 (Unchanged)	Class	Level	References
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.	I	C	Expert Opinion

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 of 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% restenoses be treated medically, unless they are progressive or symptomatic. The SVS also advised that CEA and CAS patients with late re=stenoses should be treated as if they had primary atherosclerosis.[4]

Section 8 Management of concurrent coronary & carotid disease

8.1 Stroke after cardiac surgery

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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 7 - 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%, *vs.* 18% with post-operative stroke, *vs.* 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 *vs.* 9% after post-operative stroke *vs.* 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 *vs.* bilateral disease, symptomatic *vs.* asymptomatic stenoses and stenoses *vs.* occlusion.

CABG patients with prior TIA/stroke or carotid occlusion have the highest rates of post-operative stroke. D'Agostini 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 significant 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 ($p < .0001$), while carotid stenoses were not significantly predictive ($p = .1271$).[55] The evidence suggests no causal relationship between unilateral ACS and post-CABG stroke in most cases, ie. 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**).

Table 36: Prevalence of post-CABG stroke and its association with age and prevalence of carotid and aortic arch disease.

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

*M = male; F = female; CABG = coronary artery bypass graft, * prevalence of carotid stenosis based on population screening (**section 2.2.2.4**) rather than screening in CABG patients*

8.3 Screening cardiac surgery patients for ACS

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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 = .6) or 30 day mortality (OR 1.28; 95% CI 0.97 - 1.69, p = .08), *vs.* 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 significantly higher peri-operative stroke (10.3%) *vs.* 1.4% after isolated CABG in patients with confirmed or presumed normal ICAs (p = .008), plus 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 > .05).[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

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with CABG *vs.* isolated CABG followed by deferred CEA. 30 day mortality was 1% in each group, while 30 day death/stroke was 4% (deferred CEA) *vs.* 1% (staged/synchronous CEA) (p = ns). 90 day death/stroke was 9% for deferred CEA *vs.* 1% for staged/synchronous CEA (p = .02). The authors concluded that prophylactic CEA was potentially beneficial in CABG patients with unilateral 70 - 99% ACS in order 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 *vs.* CABG alone. Patients undergoing synchronous CEA + CABG had a 30 day stroke/death rate of 18.5% *vs.* 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. 30 day death/stroke ranged from 6 - 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]

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

Procedure	*n*	Death	Stroke	MI	Death/ stroke	Death/ stroke/MI
Staged CEA then CABG (all)						
Brener 1996[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 2015[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 + 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 2015[575]	17 469	4.0%	4.3%	3.6%	7.9%	
Giannopoulos 2019[58]	16 712	4.0%	3.0%	5.0%		
Synchronous CEA + CABG (symptomatic)						
Naylor 2003[576]	514	5.8%	6.8%	1.9%	7.6%	8.1%
Synchronous CEA + CABG (asymptomatic)						
Naylor 2003[576]	925	3.6%	3.7%	2.2%	4.5%	4.5%
Synchronous CEA + CABG (off bypass)	324	1.5%			2.2%	3.6%
Fareed 2009[571]						
Synchronous CEA + CABG						

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(pre-bypass)						
Naylor 2003[576]	5 386	4.5%	4.5%	3.6%	8.2%	11.5%
Synchronous CEA + CABG (on bypass)						
Naylor 2003[576]	844	4.7%	2.1%	2.9%	8.1%	9.5%
Same day CAS + CABG (all)						
Paraskevas 2016[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 2016[577]	2 196	4.8%	5.4%	4.2%	8.5%	11.0%
Giannopoulos 2019 [58]	985	2.0%	3.0%	5.0%		

** synch = synchronous; 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*

Table 38: 30 day procedural risks after CEA + CABG stratified for treatment strategy in administrative dataset registries

Procedure	Registry	*n*	Death	Stroke	Death/ stroke
Staged CEA + 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%

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Staged or synchronous CEA + 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 + 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%	

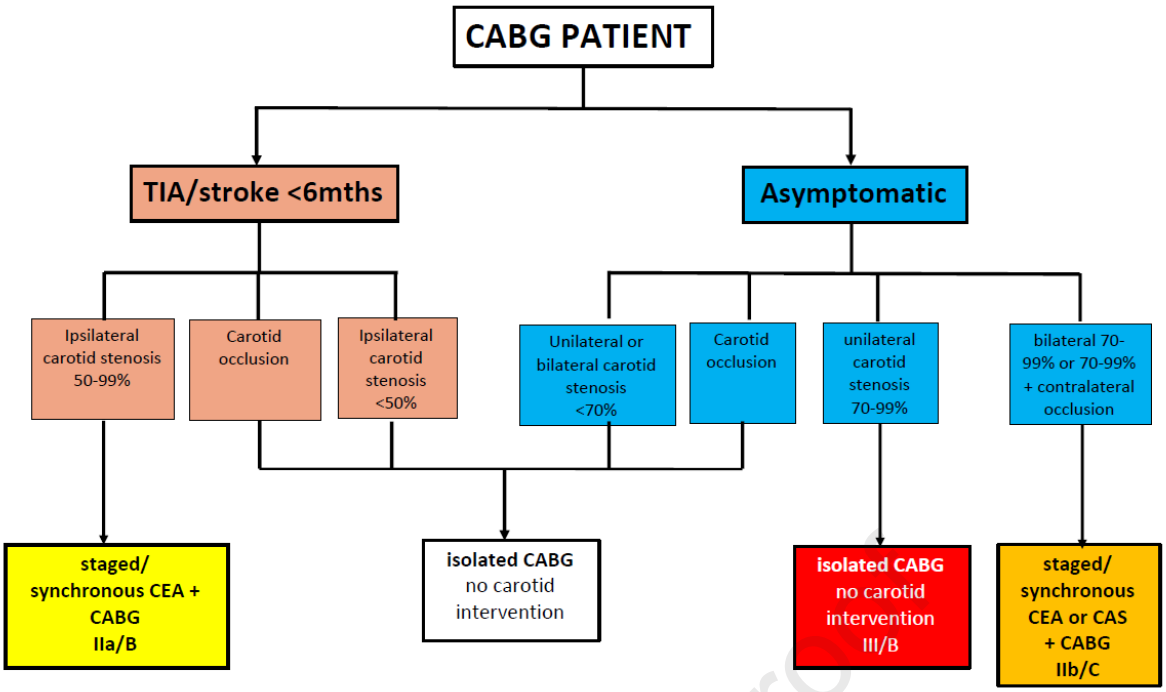
*n = number of cases; CEA = carotid endarterectomy; CAS = carotid artery stenting; CABG = coronary artery bypass graft; NIS = National Inpatient Sample; STS ACSD = Society of Thoracic Surgeons Adult Cardiac Surgery Database; * = prior stroke or transient ischaemic attack*

A 2017 meta-analysis of 31 observational studies included 2 727 patients undergoing staged orsame day CAS-CABG, reported a 30 day death/stroke rate of 7.9%.[577] 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 significantly different, but patients undergoing synchronous CEA + CABG incurred significantly 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 *vs.* 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**.

Figure 8. Managing CABG patients with symptomatic and asymptomatic carotid disease.



CABG = coronary artery bypass graft; TIA = transient ischaemic attack; CEA = carotid endarterectomy; CAS = carotid artery stenting.

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. 30 day death/stroke/MI was 15% after CAS *vs.* 22% after CEA. CARE did not differentiate between staged or synchronous CEA + CABG, regional practice variations existed and 60% of interventions involved ACS patients.[582]

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

Recommendation 110 (Unchanged)	**Class**	**Level**	**References**
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	**IIa**	**C**	557,566

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informed of the increased risks associated with coronary artery bypass if they have concurrent carotid disease.			

Recommendation 111 (Unchanged)	**Class**	**Level**	**References**
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	**IIa**	**B**	557,559

Recommendation 112 (Unchanged)	**Class**	**Level**	**References**
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.	**IIa**	**B**	570,574, 577,579

Recommendation 113 (Unchanged)	**Class**	**Level**	**References**
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.	**III**	**B**	558,567, 568

Recommendation 114 (Unchanged)	**Class**	**Level**	**References**
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.	**IIb**	**C**	558

Recommendation 115 (Unchanged)	**Class**	**Level**	**References**
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	**IIa**	**C**	58,125

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therapy during coronary bypass, individual patient characteristics, symptom status and local expertise.			

The German-Austrian guidelines made no recommendation regarding CABG patients with a unilateral 70 - 99% ACS, whilst 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]

Section 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, in order to prevent peri-operative stroke.

9.1 Incidence of stroke after major non-cardiac surgery

The incidence of peri-operative stroke depends upon 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.

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

Author	Population	*n*	Stroke risk
Axelrod[583]	major vascular surgery	5 296 aortic operations 7 299 lower limb bypasses 7 442 major amputations	0.5% 0.4% 0.6%

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Sharifpour[584]	major vascular surgery	8 077 major amputations 21 962 lower limb bypasses 7 888 open aortic 9 823 EVAR	0.7% 0.5% 0.8% 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 hip replacement lung resection	131 067 201 235 39 339	0.7% 0.2% 0.6%
Huang[590]	Caesarian 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.*

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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.

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)

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Sharifpour[584]	major vascular surgery	each one yr increase in age cardiac history *vs.* none female sex *vs.* male history of stroke *vs*. no stroke acute/chronic renal failure *vs.* no history	1.02 (1.01-1.04) 1.4 (1.1-1.9) 1.5 (1.1-1.9) 1.7 (1.3-2.3) 2.0 (1.4-3.0
Kikura[587]	general, orthopaedic, thoracic, non-carotid vascular	age >70 yrs *vs* <70 yrs diabetes *vs.* no diabetes coronary disease *vs.* none CCF *vs.* no CCF AF *vs.* no AF prior stroke *vs.* no stroke	23.6 (9.6-58.1) 2.2 (1.4-3.3) 2.3 (1.3-4.1 1.7 (1.1-2.7) 5.5 (2.8-10.9) 7.1 (4.6-11)
Bateman[589]	hemicolectomy, hip replacement, lung resection	renal impairment *vs.* none AF *vs.* no AF prior stroke *vs.* no stroke valvular heart disease *vs.* none CCF *vs.* no CCF Diabetes *vs.* no diabetes	3.0 (2.5-3.5) 2.0 (1.7-2.3) 1.6 (1.3-2.1) 1.5 (1.3-1.9) 1.4 (1.2-1.7) 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 history of stroke *vs.* none history of TIA *vs.* none on dialysis *vs.* not on dialysis hypertension *vs.* no COPD *vs.* no COPD Smoking *vs.* non smoking	3.6 (2.3-5.8) 2.9 (2.3-3.8) 1.9 (1.3-2.6) 2.3 (1.6-3.4) 2.0 (1.6-2.6) 1.8 (1.4-2.4) 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 months *vs.* no stroke stroke 3-6 months *vs.* no stroke	67.6 (52.3-87.4) 24.0 (15.0-38.4) 10.4 (6.2-17.4)

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		stroke 6-12 months *vs.* no stroke	

BMI = body mass index; OR (95% CI) = odds ratio (95% confidence intervals); CCF = congestive cardiac failure; AF = atrial fibrillation; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease; ENT = Ear, Nose and Throat operations.

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 3 - 6 months had elapsed and 1.8% where 6 - 12 months had elapsed *vs.* 0.1% in patients with no history of stroke.[585]

9.4 Is there a role for prophylactic CEA or CAS?

Patients undergoing major non-cardiac surgery with 3 - 4 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 $\geq$ 5 risk factors, peri-operative stroke increased to 1.9%,[591,592] emphasising the 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 antiplatelet 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) *vs.* 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 < 6 months of, 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)	**Class**	**Level**	**References**
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.	I	B	585

Recommendation 117 (Unchanged)	**Class**	**Level**	**References**
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.	I	B	357,585

Recommendation 118 (Unchanged)	**Class**	**Level**	**References**

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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	I	B	585

Recommendation 119 (Unchanged)	**Class**	**Level**	**References**
For asymptomatic patients undergoing non-cardiac surgery procedures, routine carotid imaging is not recommended.	III	B	583,584

Recommendation 120 (Unchanged)	**Class**	**Level**	**References**
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	I	B	591,593

Recommendation 121 (Unchanged)	**Class**	**Level**	**References**
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	III	B	590,593

Recommendation 122 (Unchanged)	**Class**	**Level**	**References**
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	III	B	586,594

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

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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]

Section 10: Disease of the 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 *vs.* 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 commoner 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 *vs.* open surgical 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

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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 significant 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 *vs.* transthoracic

Options include bypass via a transthoracic route (median sternotomy or trapdoor incision), or an extra-thoracic (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 *vs.* 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 significantly better long term patency.[90,599]

10.6 Tandem proximal inflow and internal carotid artery disease

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Tandem disease refers to lesions affecting the IA or proximal CCA in the presence of significant 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)	**Class**	**Level**	**References**
For asymptomatic patients with proximal common carotid artery or innominate artery stenoses/occlusions, open or endovascular interventions are not recommended.	**III**	**C**	Expert Opinion

Recommendation 124 (Unchanged)	**Class**	**Level**	**References**
For symptomatic patients with proximal common carotid artery or innominate stenoses, open retrograde angioplasty and stenting should be considered.	**IIa**	**C**	90,596

Section 11. Management of asymptomatic vertebral artery disease

11.1 Optimal medical therapy

No RCTs have evaluated the effect 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 VA 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 VA 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)	Class	Level	References
For patients with asymptomatic vertebral artery atherosclerotic lesions, open or endovascular interventions are not recommended.	III	C	600

Section 12. Management of symptomatic vertebral artery disease

12.1 Aetiology of vertebrobasilar (VB) stroke

About 20% of ischaemic strokes are VB, mostly due to cardio-embolism, 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 commoner with sub-Saharan or East-Asian ethnic origins. A haemodynamic aetiology was thought to be the commonest 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 VA disease

Bing recently symptomatic refers to VB symptoms in the preceding 6 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 VA 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)	Class	Level	References

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For patients with suspected vertebrobasilar ischaemia, computed tomographic angiography or contrast enhanced magnetic resonance angiography is recommended as the first line vascular imaging modality.	I	B	604,606

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 over diagnosed, 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)	**Class**	**Level**	**References**
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.	III	C	608-610

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%) *vs.* extracranial VA stenoses (1.3%).[612]

12.6.2 Randomised studies

12.6.2.1 meta-analysis of RCTs: VA stenting *vs.* BMT

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]

Table 41: main findings of meta-analysis of three RCTs comparing VA stenting with BMT alone*

	30 day death or stroke		**HR (95% CI) Stent *vs.* BMT**	**Cumulative 5 year 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 derived from Markus et al[77]. Stenting for symptomatic vertebral artery stenosis: a preplanned pooled individual patient data analysis. The Lancet Neurology. 2019;18:666-73. BMT = best medical therapy; HR (95% CI =*

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hazard ration (95% confidence intervals); yrs = years; EC = extracranial; VA = vertebral artery IC = intracranial stenosis.

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 significant differences between extracranial and intracranial stenting (1% *vs.* 16%; $p < .0001$). At five years, there were no differences in stroke rates between stenting and BM.[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-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). The $p_{interaction}$ 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 significantly 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)	**Class**	**Level**	**References** **ToE**

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For patients presenting with a vertebrobasilar territory transient ischaemic attack or stroke and a 50-99% vertebral artery stenosis, routine stenting is not recommended.	III	A	77

Recommendation 129 (Unchanged)	Class	Level	References
For patients with recurrent vertebrobasilar territory symptoms (despite best medical therapy) and a 50-99% extracranial vertebral artery stenosis, revascularisation may be considered.	IIb	B	29,77, 613,614

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 4.2.2.3** and **4.3.7.4)**.

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

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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 = .01) 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 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.

Table 42. 30 day morbidity and mortality rates after vertebral artery reconstructions

Author	Operation	*n*	% Symp	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%

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Hanel[620]	proximal VA	29		0.0%	0.0%	0.0%	0.0%	0.0%
Ramirez[621]	all VA ops VA ops only VA + carotid	74 39 35	82%	4.1%	4.1% 2.6% 5.7%	0.0%	2.6%	6.8% 5.1% 8.5%
Coleman[622]	distal VA ops VA ops only VA + carotid	41 35 6	91%	0.0% 0.0% 0.0%	2.4% 0.0% 33%			2.4% 0.0% 33%
Mert[623]	Proximal VA VA + carotid	43 11	100%	2.3%	4.7% 18%	4.7% 18%	0%	7% 18%

VB = vertebrobasilar; VA = vertebral artery.

Recommendation 130 (Unchanged)	Class	Level	References
For patients with combined carotid and vertebral artery disease, synchronous carotid and vertebral artery revascularisations are not recommended.	III	C	617,619, 621,622

12.6.5.2 Endovascular Interventions

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 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**).

In stent re-stenosis (ISR) after VA stenting

Table 43 summarises four systematic reviews on ISR after VA stenting.

Table 43: Meta-analyses on in stent re-stenosis after VA stenting

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Author	Years	*n*	BMS *n*	DES *n*	Mean follow up	Mean ISR %	ISR BMS	ISR DES
Eberhardt[612]	1966-2005	313			12mth	25.7%		
Stayman[625]		980	340	196	24mth		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	14mth DES 20mth BMS	24.4%	33.6%	15.5%

BMS = bare metal stent; DES = drug eluting stent; ISR = in stent re-stenosis

Risk factors for ISR include intracranial stenosis, ostial stenosis, stenosis > 10 mm, smaller stent size, BMS *vs.* 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 significantly lower with DES *vs.* BMS (OR 0.38; 95% CI 0.19 - 0.75, *p* = .01),[627] a finding corroborated in another study, where DES were associated with significantly lower ISR rates (18% at one year) *vs.* 31% with BMS (OR 2.6; *p* = .02).[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 significantly different in

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patients undergoing repeat interventions *vs.* BMT, with recurrent re-stenoses developing in 33%. The rate of recurrent ISR was higher (50%) in patients undergoing balloon angioplasty alone *vs.* 22% with redo stenting (p = .009).[174] Patients with recurrent VB symptoms after stenting should probably be considered for re-do stenting (having ensured all were on optimal BMT). However, there are no data to guide practice in patients who with an asymptomatic > 70% re-stenosis after VA stenting.

Recommendation 131 (Unchanged)	**Class**	**Level**	**References**
For patients undergoing vertebral artery stenting, drug eluting stents should be considered in preference to bare metal stents	**IIa**	**C**	615,616, 626-628

12.6.7 Surveillance after VA 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

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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)	Class	Level	References
For patients undergoing vertebral artery interventions, serial surveillance with catheter angiography is not recommended.	III	B	615,625

Recommendation 133 (Unchanged)	Class	Level	References
For patients who have undergone an open or endovascular vertebral artery intervention, serial non-invasive imaging surveillance may be considered.	IIb	C	256,612

Section 13. Unanswered questions from 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 there was 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 6 months) be reduced?

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

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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 (eg. 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 of 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 re-stenoses after VA stenting?

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REFERENCES

1. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364-e467.

2. Bonati LH, Kakkos S, Berkefeld J, de Borst GJ, Bulbulia R, Halliday A et al. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. Eur Stroke J 2021;6:I-XLVII.

3. Eckstein HH, Berkefeld J, Dorfler A et al. S3-Leitline zur Diagnostik, Therapie und Nachsorge der extracraniellen Carootisstenose Langfassung, Kurzfassung und Leitlinienreport. https://www.awmf.org/fileadmin/user_upload/Leitlinien/004_D_Ges_fuer_Gefaesschirurgie/004-028ke_extracranial-carotid-stenosis-diagnosis-treatment-aftercare_2021-04.pdf (accessed 31st January 2022).

4. AbuRahma AF, Avgerinos E, Chang RW, Darling RC, Duncan AA, Forbes TL et al. Society for Vascular Surgery Clinical Practice Guidelines for Management of Extracranial Cerebrovascular Disease. J Vas Surg 2022;75:26S-98S.

5. Amarenco P Albers GW, Denison H, Easton JD, Evans SR, Held P, Hill MD et al. Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. Lancet Neurol 2017;16:301–310.

6. Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M et al on behalf of the THALES Steering Committee and Investigators. Ticagrelor added to aspirin in acute non-severe ischemic stroke or transient ischemic attack of atherosclerotic origin. Stroke 2020;51:3504-3513.

7. Amarenco P, Kim JS, Labreuche J, Charles H, Abtam J, Bejot Y et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med. 2020;382:9-19.

8. Amarenco P, Hobeaunu C, Labreuche J, Charles H, Giroud M, Meseguer E et al. Carotid atherosclerosis evolution when targeting a LDL-C concentration <70mg/dL after an ischemic stroke of atherosclerotic origin. Circulation 2020;142:748-757.

9. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P et al. COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219-229.

10. Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce L et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med, 2012;367:817-25.

11. Bosch J, Eikelboom JW, Connolly SJ, Bruns NC, Larius V, Yuan F. et al. Rationale, Design and Baseline Characteristics of Participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. Can J Cardiol 2017;33:1027-1035.

12. Brott TG, Calvet D, Howard G, Gregson J, Algra A, Becquemin J-P et al. Long term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: A preplanned pooled analysis of individual patient data. Lancet Neurol 2019;18:348-56.

13. de Waard DD, de Borst GJ, Bulbulia R, Huibers A, Halliday A. Diastolic Blood Pressure is a Risk Factor for Peri-procedural Stroke Following Carotid Endarterectomy in Asymptomatic Patients. Eur J Vasc Endovasc Surg. 2017;53:626-631.

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14. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS et al. Peri-operative bridging anticoagulation in patients with atrial fibrillation. NEJM 2015;373:823-833.

15. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319-1330.

16. Fisch U, von Felten S, Wiencierz A, Jansen O, Howard G, Hendrikse J, et al. Risk of stroke before revascularisation in patients with symptomatic carotid stenosis: A pooled analysis of randomised controlled trials. Eur J Vasc Endovasc Surg 2021;61:881-887

17. Fox AJ, Eliasziw M, Rothwell PM, Schmidt MH, Warlow CP, Barnett HJ. Identification, prognosis and management of patients with carotid artery near occlusion. AJNR 2005;26:2086-94.

18. Giugliano RP, Pedersen TR, Saver JL, Sever PS, Keech AC, Bohula EA, for FOURIER Investigators. Stroke Prevention with the PCSK9 (Proprotein Convertase Subtilisin-Kexin Type 9) Inhibitor Evolocumab Added to Statin in High-Risk Patients with Stable Atherosclerosis. Stroke. 2020;51:1546-1554.

19. Gugliemi V, Compagne KCJ, Sarrami AH, Sluis WM, van den Berg YB, van der Slujis PM et al. Assessment of recurrent stroke risk in patients with a carotid web. JAMA Neurol 2021;78:826-833.

20. Halliday A, Bulbulia R, Bonati LH, Chester J, Cradduck-Bamford A, Peto R et al on behalf of the ACST-2 Collaborative Group. Second Asymptomatic Carotid Surgery Trial (ACST-2): A randomised comparison of carotid artery stenting vs carotid endarterectomy. Lancet 2021;398:1065-1073.

21. Halliday A, Sneade M, Bjorck M, Pendlebury ST, Bulbulia R, Parish S et al. Effect of carotid endarterectomy on 20-year incidence of recorded dementia: A randomised trial. Eur J Vasc Endovasc Surg (IN PRESS: doi.org/10.1016/j.ejvs.2021.12.041)

22. Heo JH, Song D, Nam HS, Kim EY, Kim YD, Lee KY et al for the EUREKA Investigators. Effect and Safety of Rosuvastatin in Acute Ischemic Stroke. J Stroke. 2016;18:87-95.

23. Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W et al. Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients with Acute Ischemic Stroke: The SHINE Randomized Clinical Trial. JAMA. 2019;322:326-335.

24. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med 2016; 375:35-43.

25. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ et al. Clopidogrel and aspirin in acute ischaemic stroke and high-risk TIA. N Engl J Med. 2018;379:215-225.

26. Johnston SC, Elm JJ, Easton JD, Farrant M, Barsan WG, Kim AS et al. Clopidogrel and aspirin after acute transient ischemic attack and minor ischemic stroke: A secondary analysis from the POINT randomized trial. Circulation 2019;140:658-664.

27. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelman A, James S et al. on behalf of the THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. NEJM 2020;383:207-217.

28. Jones MR, Howard G, Roubin GS, Blackshear JL, Cohen DJ, Cutlip DE et al. Periprocedural stroke and myocardial infarction as risks for long-term mortality in CREST. Circulation Cardiovasc Qual Outcomes 2018;11:e004663.

29. Markus HS, Larsson SC, Kuker W, Schulz UG, Ford I, Rothwell PM, et al. Stenting for symptomatic vertebral artery stenosis: The Vertebral Artery Ischaemia Stenting Trial. Neurology. 2017;89:1229-36.

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30. Montaner J, Bustamante A, García-Matas S, Martínez-Zabaleta M, Jiménez C, de la Torre J. Combination of Thrombolysis and Statins in Acute Stroke Is Safe: Results of the STARS Randomized Trial (Stroke Treatment with Acute Reperfusion and Simvastatin). Stroke. 2016;47:2870-2873.

31. Montorsi P, Caputi L, Galli S, Ravagnani PM, Teruzzi G, Annoni A, et al. Carotid Wallstent Versus Roadsaver Stent and Distal Versus Proximal Protection on Cerebral Microembolization During Carotid Artery Stenting. JACC Cardiovasc Interv 2020;13:403-414.

32. Müller MD, Ahlhelm FJ, von Hessling A, Doig D, Nederkoorn PJ, Macdonald S, et al. Vascular Anatomy Predicts the Risk of Cerebral Ischemia in Patients Randomized to Carotid Stenting Versus Endarterectomy. Stroke. 2017;48:1285-1292.

33. Müller MD, Gregson J, McCabe DJH, Nederkoorn PJ, van der Worp HB, de Borst GJ, et al. Stent Design, Restenosis and Recurrent Stroke After Carotid Artery Stenting in the International Carotid Stenting Study. Stroke 2019;50:3013-3020.

34. Näslund I, Ng N, Lundgren A, Fharm E, Gronlund C, Johansson H et al. Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. Lancet 2019;393:133-142.

35. Ruzsa Z, Nemes B, Pintér L, Berta B, Tóth K, Teleki B, et al. A randomised comparison of transradial and transfemoral approach for carotid artery stenting: RADCAR (RADial access for CARotid artery stenting) study. EuroIntervention. 2014;10:381-91.

36. Weimar C, Bilbilis K, Rekowski J, Holst T, Feyersdorf F, Breuer M et al. Safety of Simultaneous Coronary Artery Bypass Grafting and Carotid Endarterectomy Versus Isolated Coronary Artery Bypass Grafting: A Randomized Clinical Trial. Stroke 2017;48:2769-2775.

37. Yoshimura S, Uchida K, Daimon T, Takashima R, Kimura K, Morimoto T. Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients with Acute Ischemic Stroke: ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient). Stroke. 2017;48:3057-3063.

38. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA 2015; 313:1240–1248.

39. Bonati LH, Gregson J, Dobson J, McCabe DJH, Nederkoorn PJ, van der Worp HB et al. Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study *ICSS): Secondary analysis of a randomised trial. Lancet Neurol 2018;17:587-96.

40. Arbel Y, Birati EY, Finkelstein A, Halkin A, Kletzel H, Abramowitz Y et al. Platelet inhibitory effect of clopidogrel in patients treated with omeprazole, pantoprazole, and famotidine: a prospective, randomized, crossover study. Clinical Cardiology 2013, 36,342–346.

41. Blanco M, Nombela F, Castellanos M, Rodriguez-Yáñez M, García-Gil M, Leira R et al. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology. 2007 Aug 28;69:904-910.

42. Nolde JM, Cheng SF, Richards T, Schlaich MP. No evidence for long-term blood pressure differences between eversion and conventional carotid endarterectomy in two independent study cohorts. Eur J vasc Endovasc Surg 2022;63:33-42.

43. Cheng SF, Richards T, Gregson J, Brown MM, de Borst GJ, Bonati LH on behalf of the International Carotid Stenting Study Investigators. Long term restenosis rate after carotid endarterectomy: Comparison of three surgical techniques and intra-operative shunt use. Eur J Vasc Endovasc Surg 2021;62:513-521.

44. AbuRahma AF. Predictors of Perioperative Stroke/Death after Carotid Artery Stenting: A Review Article. Ann Vasc Dis 2018;11:15–24

Journal Pre-proof

45. Abreu P, Nogueira J, Rodrigues FB, Nascimento A, Carvalho M, Marreiros A et al. Intracerebral haemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularisation: A systematic review and meta-analysis. Acta Neurochir (Wien) 2017;159:2089-2097.

46. Ancetti S, Paraskevas KI, Faggioli G, Naylor AR. Effect of carotid interventions on cognitive function in patients with asymptomatic carotid stenosis: A systematic review. Eur J Vasc Endovasc Surg (IN PRESS).

47. Barkat M, Hajibandeh S, Hajibandeh S, Torella F, Antoniou GA. Systematic Review and Meta-analysis of Dual Versus Single Antiplatelet Therapy in Carotid Interventions. Eur J Vasc Endovasc Surg. 2017;53:53-67.

48. 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;58:479-493.

49. Bhatti AF, Leon LR Jr, Labropoulos N, Rubinas TL, Rodriguez H, Kalman PG, et al. Free-floating thrombus of the carotid artery: literature review and case reports. J Vasc Surg. 2007;45:199-205.

50. Chang XL, Zhou HQ, Lei CY, Wu B, Chen YC, Hao ZL, et al. Association between asymptomatic carotid stenosis and cognitive function: a systematic review. Neurosci Biobehav Rev 2013;37:1493–9.

51. Coelho A, Prassaparo T, Mansilha A, Kappelle J, Naylor R, de Borst GJ. Critical Appraisal on the Quality of Reporting on Safety and Efficacy of Transcarotid Artery Stenting With Flow Reversal. Stroke. 2020;51:2863-2871.

52. Coelho A, Peixoto J, Mansilha A, Naylor AR, de Borst GJ. Timing of carotid intervention in symptomatic carotid stenosis: A systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2022;63:3-23.

53. de Vries EE, Meershoek AJA, Vonken EJ, den Ruijter HM, van den Berg JC, de Borst GJ. ENDORSE Study Group. A meta-analysis of the effect of stent design on clinical and radiologic outcomes of carotid artery stenting. J Vasc Surg 2019;69:1952-1961.

54. Fridman S, Lownie SP, Mandzia J. Diagnosis and management of carotid free-floating thrombus: A systematic literature review. Int J Stroke. 2019;14:247-256.

55. Gaudino M, Rahouma M, Di Mauro M, Ynagawa B, Abouarab A, Demetres M et al. Early versus Delayed Stroke After Cardiac Surgery: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2019;8;e012447.

56. Giannopoulos S, Texakalidis P, Jonnalagadda AK, Karasavvidis T, Giannopoulos S, Kokkinidis DG. Revascularization of radiation-induced carotid artery stenosis with carotid endarterectomy vs. carotid artery stenting: a systematic review and meta-analysis. Cardiovasc Revasc Med 2018;19:638-44.

57. Giannopoulos S, Texakalidis P, Charisis N, Jonnalagadda A, Chaitidis N, Giannopoulos S et al. Synchronous Carotid Endarterectomy and Coronary Artery Bypass Graft versus Staged Carotid Artery Stenting and Coronary Artery Bypass Graft for Patients with Concomitant Severe Coronary and Carotid Stenosis: A Systematic Review and Meta-analysis. Ann Vasc Surg 2020;62:463-47.

58. Hajibandeh S, Hajibandeh S, Antoniou SA, Torella F, Antoniou GA. Meta-analysis and trial sequential analysis of local vs general anaesthesia for carotid endarterectomy. Anaesthesia 2018;73:1280–1289.

59. Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: Systematic review and meta-analysis. BMJ 2018;363:k5108.

Journal Pre-proof

60. Harky A, Chan JSK, Kot TKM, Makar R, Chandrasekar R, Dimitri S. General Anesthesia Versus Local Anesthesia in Carotid Endarterectomy: A Systematic Review and Meta-Analysis. J Cardiothorac Vasc Anesth 2020;34:219-34.

61. Hellegering J, Uyttenboogaart M, Bokkers RPH, El Moumni M, Zeebregts CJ, van der Laan MJ. Treatment of the extracranial carotid artery in tandem lesions during endovascular treatment of acute ischemic stroke: a systematic review and meta-analysis. Ann Trans Med. 2020;8:1278.

62. Howard DPJ, Gaziano L, Rothwell PM on behalf of the Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: A population-based cohort study, systematic review and meta-analysis. Lancet Neurol 2021;20:193-202.

63. Huibers AE, Westerink J, de Vries EE, Hoskam A, den Ruijter HM, Moll FL. Et al. Cerebral hyperperfusion syndrome after carotid artery stenting: A systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2018;56:322-333.

64. Jaroenngarmsamer T, Bhatia KD, Kortman H, Orru E, Krings T. Procedural success with radial access for carotid artery stenting: systematic review and meta-analysis. J Neurointerv Surg. 2020;12:87-93.

65. Jung JM, Choi JY, Kim HJ, Suh SI, Seo WK. Long term durability and outcomes of carotid stenting and carotid endarterectomy. J Neurointerv Surg. 2017;9:750-755.

66. Kakkos SK, Vega de Ceniga M, Naylor AR. A Systematic Review and Meta-analysis of Periprocedural Outcomes in Patients Undergoing Carotid Interventions Following Thrombolysis. Eur J Vasc Endovasc Surg 2021;62:350-357.

67. Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, Saqqur A, Jickling GC. Prevalence of high-risk plaques and risk of stroke in patients with asymptomatic carotid stenosis: A meta-analysis. JAMA Neurol 2020;77:1-12.

68. Katsanos AH, Filippatou A, Manios E, Deftereos S, Parissis J, Frogoudaki A, et al. Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials. Hypertension. 2017;69:171-179.

69. Kim SJ, Noguira RG, Haussen DC. Current understanding and gaps in research of carotid webs in ischemic strokes. A review. JAMA Neurol 2019;76:355-361.

70. Knappich C, Kuehnl A, Haller B, Salvermoser M, Algra A, Becquemin JP, et al. Associations of Perioperative Variables With the 30-Day Risk of Stroke or Death in Carotid Endarterectomy for Symptomatic Carotid Stenosis. Stroke 2019;50:3439-3448.

71. Knappich C, Lang T, Tsantilas P, Schmid S, Kallmayer M, Haller B, et al. Intraoperative completion studies in carotid endarterectomy: systematic review and meta-analysis of techniques and outcomes. Ann Transl Med 2021:9:1201.

72. Kokkinidis DG, Chaitidis N, Giannopoulos S, Texakalidis P, Haider MN, Aronow HD et al. Presence of carotid occlusion is associated with increased peri-procedural stroke risk following CEA but not for CAS: A meta-analysis and meta-regression analysis of 43 studies and 96,658 patients. J Endovasc Ther 2020;27:334-344.

73. Lazarides MK, Christaina E, Argyriou C, Georgakarakos E, Tripsianis G, Georgiadis GS, et al. Network meta-analysis of carotid endarterectomy closure techniques. Eur J Vasc Endovasc Surg 2021;61:181-90.

74. Lejay A, Koncar I, Diener H, Vega de Ceniga M, Chakfé N. Post-operative infection of prosthetic material or stents involving the supra-aortic trunks: a comprehensive review. Eur J Vasc Endovasc Surg 2018;56:885-900.

75. Li Y, Yang JJ, Zhu SH, Xu B, Wang L. Long-term efficacy and safety of carotid artery stenting versus endarterectomy: A meta-analysis of randomized controlled trials. PLoS One. 2017;12:e0180804.

Journal Pre-proof

76. Lim ST, Murphy SJX, Thijs V, Fernandez-Cadenas I, Montaner J, Marquardt L, et al. Platelet function/reactivity testing and prediction of risk of recurrent vascular events and outcomes after TIA or ischemic stroke: Systematic review and meta-analysis. J Neurol 2020;267:3021-3037.

77. Markus HS, Harshfield EL, Compter A, Kuker W, Kappelle LJ, Clifton A, et al. Stenting for symptomatic vertebral artery stenosis: a preplanned pooled individual patient data analysis. The Lancet Neurology. 2019;18:666-73.

78. Meershoek AJA, de Vries EE, Veen D, den Ruijter HM, de Borst GJ for the NEON study group Meta-analysis of the outcomes of treatment of internal carotid artery near occlusion. Br J Surg 2019;106:665-671.

79. Müller MD, Lyrer P, Brown MM, Bonati LH. Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis. Cochrane Database Syst Rev. 2020: CD000515.

80. Munster AB, Franchini AJ, Qureshi MI, Thapar A, Davies AH. Temporal trends in safety of carotid endarterectomy in asymptomatic patients: A systematic review. Neurology 2015;85:365-372.

81. Murphy SJX, Naylor AR, Ricco JB, Sillesen H, Kakkos S, Halliday A, et al. Optimal Antiplatelet Therapy in Moderate to Severe Asymptomatic and Symptomatic Carotid Stenosis: A Comprehensive Review of the Literature. Eur J Vasc Endovasc Surg. 2019;57:199-211.

82. Nana PN, Brotis AG, Spanos KT, Kouvelos GN, Matsagkas MI, Giannoukas AD. A systematic review and meta-analysis of carotid artery stenting using the transcervical approach. Int Angiol 2020;39:372-380.

83. Nana P, Spanos K, Antoniou G, Kouvelos G, Vasileiou V, Tsironi E, Giannoukas A. The effect of carotid revascularization on the ophthalmic artery flow: systematic review and meta-analysis. Int Angiol. 2021;40:23-28.

84. Noubiap JJ, Agbaedeng TA, Tochie JN, Nkeck JR, Ndoadoumgue AL, Fitzgerald JL et al. Meta-analysis comparing the frequency of carotid artery stenosis in patients with atrial fibrillation and vice versa. Am J Cardiol 2021;138:72-79.

85. O'Connor EA, Evans CV, Rushkin MC, Redmons N, Lin JS. Behavioural counselling to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2020;324:2076-2094.

86. Paraskevas KI, Robertson V, Saratzis A, Naylor AR. An updated review and meta-analysis of outcomes following eversion vs. conventional carotid endarterectomy in randomised controlled trials and observational studies. Eur J Vasc Endovasc Surg 2018;55:465-473.

87. Paraskevas KI, Faggioli G, Ancetti S, Naylor AR. Asymptomatic carotid stenosis and cognitive impairment: A systematic review. Eur J Vasc Endovasc Surg 2021;61:888-899.

88. Phillips P, Poku E, Essat M, Woods HB, Goka EA, Kaltenthaler EC, et al. Systematic review of carotid artery procedures and the volume-outcome relationship in Europe. Br J Surg 2017:104:1273-83.

89. Rivolta N, Piffaretti G, Corazzari C, Bush RL, Dorigo W, Tozzi M, et al. To drain or not to drain following carotid endarterectomy; a systematic review and meta-analysis. J Cardiovasc Surg (Torino) 2021;62:347-53

90. Robertson V, Poli F, Saratzis A, Divall P, Naylor AR. A Systematic Review of Procedural Outcomes in Patients with Proximal Common Carotid or Innominate Artery Disease with or Without Tandem Ipsilateral Internal Carotid Artery Disease. Eur J Vasc Endovasc Surg. 2020;60:817-827.

Journal Pre-proof

91. Rojoa DM, Lodhi AQD, Kontopodis N, Ioannou CV, Labropoulos N, Antoniou GA. Ultrasonography for the diagnosis of extracranial carotid occlusion: Diagnostic test accuracy meta-analysis. VASA 2020;49:195-204.

92. Rots ML, Meershoek AJA, Bonati LH, den Ruijter HM, de Borst GJ. Predictors of new ischaemic brain lesions on diffusion weighted imaging after carotid stenting and endarterectomy: A systematic review. Eur J Vasc Endovasc Surg 2019;58:163-74

93. Safouris A, Katsanos A, Kerasnoudis A, Krogias C, Kinsella J, Sztajzel R et al. Statin pre-treatment and micro-embolic signals in large artery atherosclerosis: A systematic review and meta-analysis. Stroke 2018;49:1992-1995.

94. Saratzis A, Naylor AR. 30-day outcomes after carotid interventions: An updated meta-analysis of randomised controlled trials in asymptomatic patients. Eur J Vasc Endovasc Surg 2022;63:157-8

95. Schmidt AF, Carter JL, Pearce LS, Wilkins JT, Overington JP, Hingorani AD et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020:CD011748.

96. Song P, Fang Z, Wang H, Cai Y, Rahmini K, Fowkes GR et al. Global and regional prevalence, burden and risk factors for carotid atherosclerosis: A systematic review, meta-analysis and modelling study. Lancet Global Health 2020:8::e721–29.

97. Sorrentino S, Nguyen P, Salerno N, Polimeni A, Sabatino J, Makris A et al. Standard Versus Ultrasound-Guided Cannulation of the Femoral Artery in Patients Undergoing Invasive Procedures: A Meta-Analysis of Randomized Controlled Trials. J Clin Med. 2020;9:677.

98. Stabile E, de Donato G, Musialek P, Deloose K, Nerla R, Sirignano P, et al. Use of Dual-Layered Stents for Carotid Artery Angioplasty: 1-Year Results of a Patient-Based Meta-Analysis. JACC Cardiovasc Interv 2020;13:1709-1715.

99. Subramnian A, Delaney S, Murphy SJX, Smith DR, Offiah C, McMahon J et al. Platelet biomarkers in patients with atherosclerotic extracranial carotid artery stenosis: A systematic review Eur J Vasc Endovasc Surg 2021 (in press).

100. Texakalidis P, Giannopoulos S, Kokkinidis D, Jabbour P, Reavey-Cantwell J, Rangel-Castilla L. Outcome of carotid artery endarterectomy in statin users versus statin-naïve patients: A systematic review and meta-analysis. World J Surg 2018;116:444-450.

101. Texakalidis P, Giannopoulos S, Jonnalagadda AK, Chitale RV, Jabbour P, Armstrong EJ et al. Pre-operative use of statins in carotid artery stenting: A systematic review and meta-analysis. J Endovasc Ther 2018;25:624-31.

102. Texakalidis P, Giannopoulos S, Jonnalagadda AK, Kokkinidis DG, Machinis T, Reavey-Cantwell J. et al. Carotid Artery Endarterectomy versus Carotid Artery Stenting for Restenosis After Carotid Artery Endarterectomy: A Systematic Review and Meta-Analysis. World Neurosurg 2018;115:421-429.

103. Texakalidis P, Tzoumas A, Giannopoulos S, Jonnalagadda AK, Jabbour P, Rangel-Castilla L, et al. Risk Factors for Restenosis After Carotid Revascularization: A Meta-Analysis of Hazard Ratios. World Neurosurg. 2019;125:414-424.

104. Traenka C, Engelter ST, Brown MM, Dobson J,Frost C,Bonati LH. Silent brain infarcts on diffusion-weighted imaging after carotid revascularisation: a surrogate outcome measure for procedural stroke? A systematic review and meta-analysis. Eur Stroke J. 2019; 4: 127-143.

105. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, et al. Screening for asymptomatic carotid artery stenosis: US Preventive Services Task Force recommendation statement. JAMA 2021;325:476-481.

106. Varetto G, Trevisan A, Barile G, Gibello L, Spalla F, Frola E, et al. Carotid Pseudoaneurysm After Eversion Endarterectomy: A Case Report and Review of the Literature. Vasc Endovascular Surg 2018;52:309-312

Journal Pre-proof

107. Wilson MP, Murad MH, Krings T, Pereira VM, O'Kelly C, Rempel J, et al. Management of tandem occlusions in acute ischemic stroke - intracranial versus extracranial first and extracranial stenting versus angioplasty alone: A systematic review and meta-analysis. J Neurointerv Surg. 2018;10:721-728.

108. Wodarg F, Turner EL, Dobson J, Ringleb PA, Mali WP, Fraedrich G, et al. Carotid Stenosis Trialists' Collaboration. Influence of stent design and use of protection devices on outcome of carotid artery stenting: a pooled analysis of individual patient data. J Neurointerv Surg 2018;10:1149-1154.

109. Xin WQ, Li MQ, Li K, Li QF, Zhao Y, Wang WH, et al. Systematic and Comprehensive Comparison of Incidence of Restenosis Between Carotid Endarterectomy and Carotid Artery Stenting in Patients with Atherosclerotic Carotid Stenosis. World Neurosurg. 2019;125:74-86.

110. Xue S, Tang X, Zhao G, Tang H, Cai L et al. A systematic review and updated meta-analysis for carotid near occlusion. Ann Vasc Surg 2020;66:636-645.

111. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database Syst Rev. 2018:CD012502.

112. Zhang AJ, Dhruv P, Choi P, Bakker C, Koffel J, Anderson D, et al. A systematic literature review of patients with carotid web and acute ischemic stroke. Stroke 2018;49:2872-2876.

113. Ziapour B, Schermerhorn ML, Iafrati MD, Suarez LB, TourSavadkohi S, Salehi P. A systematic review and meta-analysis of predilation and post-dilation in transfemoral carotid artery stenting. J Vasc Surg. 2020;72:346-355.e1.

114. Zonneveld TP, Richard E, Vergouwen MD, Nederkorn PJ, de Haan R, Roos YB et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. Cochrane Database Syst Rev. 2018:CD007858).

115. Arhuidese I, Obeid T, Nejim B, Locham S, Hicks CW, Malas MB. Stenting versus endarterectomy after prior ipsilateral carotid endarterectomy. J Vasc Surg. 2017;65:1-11.

116. Arhuidese IJ, Nejim B, Chavali S, Locham S, Obeid T, Hicks CW, et al. Endarterectomy versus stenting in patients with prior ipsilateral carotid artery stenting. J Vasc Surg. 2017;65:1418-1428.

117. Beyer-Westendorf J, Gelbricht V, Förster K, Ebertz F, Köhler C, Werth S, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 2014;35:1888-96.

118. Cui CL, Dakour-Aridi H, Eldrup-Jorgensen J, Schermerhorn ML, Siracuse JJ, Malas MB. Effects of timing on in-hospital and 1-year outcomes after transcarotid artery revascularisation. J Vasc Surg 2021;73:1649-1657.

119. de Carlo C, Tanious A, Boitano LT, Mohebali J, Stone DH, Clouse WD et al. Addition of common carotid intervention increases the risk of stroke and death after carotid artery stenting for asymptomatic patients. J Vasc Surg 2021;74:1919-1928.

120. de Geus SWL, Farber A, Levin S, Carlson SJ, Cheng TW, Tseng JF, Siracuse JJ. Perioperative Outcomes of Carotid Interventions in Octogenarians. Ann Vasc Surg. 2020 Oct;68:15-21.

121. den Brok MGHE, Kuhrij LS, Roozenbeek R, van der Ligt A, Hilkens PHE, Dippel DWJ et al. Prevalence and risk factors of symptomatic carotid stenosis in patients with recent TIA or ischaemic stroke in the Netherlands. Eur J Stroke 2020;5:271-77.

Journal Pre-proof

122. Edenfield L, Blazick E, Eldrup-Jorgensen J, Hawkins R, Aranson N, Nolan B. Outcomes of carotid endarterectomy in the Vascular Quality Initiative based on patch type. J Vasc Surg 2020;71:1260-7.

123. Faateh M, Dakour-Aridi H, Mathlouthi A, Locham S, Naazie I, Malas M. Comparison of Open and Closed-Cell Stent Design Outcomes after Carotid Artery Stenting in The Vascular Quality Initiative. J Vasc Surg 2021;73:1639-1648.

124. Feil K, Herzberg M, Dorn F, Tiedt S, Kupper C, Thunstedt DC et al. Tandem lesions in anterior circulation stroke: Analysis of the German Stroke Registry- Endovascular treatment. Stroke 2021;52:1265-1275.

125. Feldman D, Swaminathan RV, Geleris JD, Okin P, Minutello RM, Krishnam U. et al. Comparison of Trends and In-Hospital Outcomes of Concurrent Carotid Artery Revascularization and Coronary Artery Bypass Graft Surgery: The United States experience (2004-2012). JACC Cardiovasc Interv 2017;13:286-98.

126. García-Pastor A, Gil-Núñez A, Ramírez-Moreno JM, González-Nafría N, Tejada J, Moniche F et al. Stroke Project of the Spanish Cerebrovascular Diseases Study Group. Early risk of recurrent stroke in patients with symptomatic carotid near-occlusion: results from CAOS, a multicenter registry study. Int J Stroke 2017; 12: 713–719.

127. GBD16 Stroke Collaborators. Global, regional and national burdens of stroke, 1990-2016: A systematic analysis for the Global Burden of Disease Study of 2016. Lancet Neurol 2019;18:439-58.

128. Giurgius M, Horn M, Thomas SD, Shishehbor MH, Beiles CB, Mwipatayi BP, et al. The relationship between carotid revascularization procedural volume and 4149 perioperative outcomes in Australia and New Zealand. Angiology 2021;72:715-723.

129. González García A, Moniche F, Escudero-Martínez I, Mancha F, Tomasello A, Ribó M et al. Clinical Predictors of hyperperfusion syndrome Following carotid stenting: Results from a national prospective multicenter study JACC Cardiovasc Interv. 2019;12:873-882.

130. Grieff AN, Dombrovskiy V, Beckerman W, Ventarola D, Truong H, Huntress L, et al. Anesthesia Type is Associated with Decreased Cranial Nerve Injury in Carotid Endarterectomy. Ann Vasc Surg 2021;70:318-325.

131. Hicks CW, Nejim B, Obeid T, Locham SS, Malas MB. Use of a primary carotid stenting technique does not affect perioperative outcomes. J Vasc Surg. 2018;67:1736-1743.

132. Hung CS, Yeh CF, Lin MS, Chen YH, Huang CC, Li HY, Kao HL. Impact of hospital volume on long-term neurological outcome in patients undergoing carotid artery stenting. Catheter Cardiovasc Interv. 2017;89:1242-1249.

133. Hussain MA, Mamdani M, Tu JV, Saposnik G, Salata K, Bhatt DL, et al.: Association between operator specialty and outcomes after carotid artery revascularization. J Vasc Surg 2018; 67: 478-89.

134. Hussain MA, Alali AS, Mamdani M, Tu JV, Saposnik G, Salata K et al. Risk of intracranial hemorrhage after carotid artery stenting versus endarterectomy: a population-based study. J Neurosurg. 2018;129:1522-1529.

135. Johal AS, Loftus IM, Boyle JR, Naylor AR, Waton S, Heikkila K, Cromwell DA. Changing patterns of carotid endarterectomy between 2011 and 2017 in England: A population based cohort study. *Stroke* 2019;50:2461-2468.

136. Johal AS, Naylor AR, Perwani AD, Li Q, Birmpili P, Waton S, O'Neill R, Boyle JR, Cromwell DA. Carotid endarterectomy following intravenous thrombolysis in the UK. Eur J Vasc Endovasc Surg 2021;62:9-15.

Journal Pre-proof

137. Jones DW, Goodney PP, Conrad MF, Nolan BW, Rzucidlo EM, Powell RJ et al. Dual antiplatelet therapy reduces stroke but increases bleeding at the time of carotid endarterectomy. J Vasc Surg 2016;63:1262-12671.

138. Jonsson M, Arp E, Bjorses, Holmin S, Ijas P, Martinez-Majander. Carotid endarterectomy after intracranial endovascular thrombectomy for acute ischaemic stroke in patients with carotid artery stenosis. Eur J Vasc Endovasc Surg 2022 (in press) doi.org/10.1016/j.ejvs.2021.10.034

139. Kochar A, Harrison JK, Hughes GC, Thourani VH, Mack MJ, Matsouaka RA et al. Stroke and cardiovascular outcomes in patients with carotid disease undergoing Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv 2018;11:e006322.

140. Kjorstad KE, Baksaas ST, Halbakken E, Hasselgard T, Jonung T, Jorgensen GT et al. The National Norwegian Carotid Study: Time from onset of symptom onset to surgery is too long resulting in additional neurological events. Eur J Vasc Endovasc Surg 2017;54:415-422.

141. Knappich C, Kuehnl A, Tsantilas P, Schmid S, Breitkreuz T, Kallmayer M, et al. The Use of Embolic Protection Devices Is Associated With a Lower Stroke and Death Rate After Carotid Stenting. JACC Cardiovasc Interv 2017;10:1257-1265.

142. Kuhrij LS, Meershoek AJA, Karthaus EG, Vahl AC, Hamming JF, Nederkoorn PJ, et al. Factors Associated with Hospital Dependent Delay to Carotid Endarterectomy in the Dutch Audit for Carotid Interventions. Eur J Vasc Endovasc Surg 2019;58:495-501.

143. Institut fur Qualitatssicherung und Transparenz im Gesundheitswesen (IQTiG). Karotis-Revaskularisation. https://iqtig.org/qs-verfahren/qs-karotis/ (accessed 16th February 2022).

144. Lawaetz M, Sandholt B, Eilersen EN, Petersen C, Torslev K, Shilenok D et al. Low risk of neurological recurrence while awaiting carotid endarterectomy: Results from a Danish multicentre study. Eur J Vasc Endovasc Surg 2021;62:160-66.

145. Lehtola H, Airaksinen KEJ, Hartikainen P, Hartikainen JEK, Palomaki A Nuotio AP et al. Stroke recurrence in patients with atrial fibrillation: Concomitant carotid artery stenosis doubles the risk. Eur J Neurol 2017;24:719-725.

146. Levin SR, Farber A, Goodney PP, Schermerhorn ML, Patel VI, Arinze N, et al. Shunt intention during carotid endarterectomy in the early symptomatic period and perioperative stroke risk. J Vasc Surg 2020;72:1385-94.

147. Liang P, O'Donnell TFX, Cronenwett JL, Malas MB, Eldrup-Jorgensen J, Kashyap VS. Vascular Quality Initiative Risk Score for 30-day Stroke or Death Following TransCarotid Artery Revascularization. J Vasc Surg. 2021;73:1665-1674

148. Malas MB, Dakour-Aridi H, Wang GJ, Kashyap VS, Motaganahalli RL, Eldrup-Jorgensen J, et al. Transcarotid artery revascularization versus transfemoral carotid artery stenting in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg. 2019;69:92-103.

149. Malik OS, BrovmanEY, Urman RD. The Use of Regional or Local Anesthesia for Carotid Endarterectomies May Reduce Blood Loss and Pulmonary Complications. J Cardiothorac Vasc Anesth 2019;33:935-942.

150. Marmor RA, Dakour-Aridi H, Naazie I, Mathlouthi A, Al-Nouri O, Malas M. Outcomes of dual antiplatelet therapy for patients undergoing carotid endarterectomy. J Am Coll Surg 2020;231:s350-s351.

151. Nejim B, Dakour Aridi H, Locham S, Arhuidese I, Hicks C et al. Carotid artery revascularization in patients with contralateral carotid artery occlusion: Stent or endarterectomy? J Vasc Surg. 2017;66:1735-1748.

152. Schermerhorn ML, Liang P, Dakour-Aridi H, Kashyap VS, Wang GJ, Nolan BW, et al. In-hospital outcomes of transcarotid artery revascularization and carotid endarterectomy in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg. 2020;71:87-95.

Journal Pre-proof

153. Smolock CJ, Morrow KL, Kang J, Kelso RL, Bena JF, Clair DG. Drain placement confers no benefit after carotid endarterectomy in the Vascular Quality Initiative. J Vasc Surg 2020;72:204-8.

154. Stone DH, Giles KA, Kubilis P, Suckow BD, Goodney PP, Huber TS, et al. Protamine reduces serious bleeding complications associated with carotid endarterectomy in asymptomatic patients without increasing the risk of stroke, myocardial infarction, or death in a large national analysis. Eur J Vasc Endovasc Surg 2020;60:800-7.

155. Stroke Alliance for Europe: The burden of stroke in Europe. www.strokeeurope.eu (accessed 4th February 2020).

156. Tsantilas P, Kuehni A, Kallmayer M, Knappich C, Schmid S, Breitkreuz T et al. Risk of stroke or death is associated with the timing of carotid artery stenting for symptomatic carotid stenosis: A secondary data analysis of the German Statutory Quality Assurance Database. J Am Heart Assoc 2018;27:e007983.

157. Vellimana AK, Washington CW, Yarborough CK, Pilgram TK, Hoh BL, Derdeyn CP et al. Thrombolysis is an independent risk factor for poor outcome after carotid revascularisation. Neurosurg 2018; 83: 922-30.

158. https://www.vsqip.org.uk/content/uploads/2013/10/UK-Carotid-Endarterectomy-Audit-Round-5-Report.pdf (accessed 5th September 2021).

159. https://www.vascularsociety.org.uk/_userfiles/pages/files/Document%20Library/Service-Specification.pdf (accessed 14th September 2021).

160. Vascular Society of Great Britain and Ireland Provision of Services for People with Vascular Disease 2021. https://www.vascularsociety.org.uk/_userfiles/pages/files/Resources/FINAL%20POVS.pdf (accessed 19th December 2021)

161. Wang GJ, Beck AW, DeMartino RR, Goodney PP, Rockman CB, Fairman RM. Insight into the cerebral hyperperfusion syndrome following carotid endarterectomy from the national Vascular Quality Initiative. J Vasc Surg. 2017;65:381-389.

162. Wiske C, Arhuidese I, Malas M, Patterson R. Comparing the efficacy of shunting approaches and cerebral monitoring during carotid endarterectomy using a national database. J Vasc Surg 2018;68:416-25.

163. Zhu F, Bracard S, Anxionnat R, Derelle AL, Tonnelet R, Liao L et al. Impact of emergent cervical carotid stenting in tandem occlusion strokes treated by thrombectomy: Review of the TITAN Collaboration. Front Neurol 2019;10:206.1-6.

164. Zhu F, Anadani M, Labreuche J, Spiotta A, Turjman F, Piotin M. et al. Impact of Antiplatelet Therapy During Endovascular Therapy for Tandem Occlusions: A Collaborative Pooled Analysis. Stroke. 2020;51:1522-1529.

165. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A et al. Management of atherosclerotic carotid and vertebral artery disease: 2017 Clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:3-86.

166. NeuroVISION Investigators. Peri-operative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): A prospective cohort study. Lancet 2019;394:1022–9.

167. Gensicke H, van der Worp HB, Nederkoorn PJ, Macdonald S, Gaines PA, van der Lugt A, et al. Ischemic brain lesions after carotid artery stenting increase future cerebrovascular risk. J Am Coll Cardiol 2015;65:521-9.

168. Werner M, Bausback Y, Bräunlich S, Ulrich M, Piorkowski M, Friedenberger J, et al. Anatomic variables contributing to a higher periprocedural incidence of stroke and TIA in carotid artery stenting: single center experience of 833 consecutive cases. Catheter Cardiovasc Interv. 2012;80:321-8.

Journal Pre-proof

169. Howard G, Roubin GS, Jansen J, Halliday A, Fraedrich G, Eckstein H-H. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. Lancet 2016;387:1305-11.

170. Rantner B, Kollertis B, Roubin GS, Ringleb PA, Jansen O, Howard G, Hendrickse J et al. Early Endarterectomy Carries a Lower Procedural Risk Than Early Stenting in Patients With Symptomatic Stenosis of the Internal Carotid Artery Results From 4 Randomized Controlled Trials. Stroke 2017;48:1580-1587

171. Moore WS, Popma JJ, Roubin GS, Voeks JH, Jones M, Howard G et al. Carotid angiographic characteristics in the CREST trial were major contributors to periprocedural stroke and death differences between carotid artery stenting and carotid endarterectomy. J Vasc Surg. 2016;63:851-7

172. Kokkosis AA, Macdonald S, Jim J, Shah R, Schneider PA. Assessing the suitability of the carotid bifurcation for stenting: Anatomic and morphologic considerations. J Vasc Surg. 2021;74:2087-2095.

173. Ederle J, Davagnanam I, van der Worp HB, Venables GS, Lyrer PA, Featherstone RL, et al. Effect of white-matter lesions on the risk of periprocedural stroke after carotid artery stenting versus endarterectomy in the International Carotid Stenting Study (ICSS): a prespecified analysis of data from a randomised trial. Lancet Neurol 2013;12:866-72.

174. Qiu Z, Liu J, Huang R, Liu D, Dai Z, Luo M, et al. Incidence, risk, and treatment of binary restenosis after vertebral artery stenting. Catheter Cardiovasc Interv. 2020;96:404-409.

175. Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaides AN Fernandes e Fernandes J et al on behalf of the ESVS Guidelines Collaborators. ESVS Guidelines. Invasive treatment for carotid stenosis: Indications and techniques. Eur J Vasc Endovasc Surg 2009;37:S1-S19

176. https://www.agreetrust.org/agree-ii/ (accessed 25th January 2022).

177. https://www.escardio.org/static-file/Escardio/Guidelines/About/CPG%20and%20ESC%20Guidelines%20Process%20-%20Version%202020%20for%20web.%20pptx.pdf (accessed 25th September 2021).

178. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A. et al. Updated Definition of Stroke for the 21st Century. A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064-89.

179. Bamford J. Clinical examination in diagnosis and subclassification of stroke. Lancet 1992; 339: 400-402.

180. Dorigo W, Pulli R, Nesi M, Alessi Innocenti A, Pratesi G, et al. Urgent carotid endarterectomy in patients with recent/crescendo transient ischaemic attacks or acute stroke. Eur J Vasc Endovasc Surg. 2011;41:351-7

181. Karkos CD, McMahon G, McCarthy MJ, Dennis MJ, Sayers RD, London NJ et al. The value of urgent carotid surgery for crescendo transient ischemic attacks. J Vasc Surg. 2007;45:1148-54.

182. https://datatools.ahrq.gov (accessed 25th January 2022).

183. RTI International. *Projections of Cardiovascular Disease Prevalence and Costs: 2015–2035: Technical Report [report prepared for the American Heart Association]*RTI International; November 2016. RTI project No. 021480.003.001.001

184. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL et al. Classification of subtype of acute ischaemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke therapy. Stroke 1993;24:35-41.

185. Flaherty ML, Kissela B, Khoury JC, Alwell K, Mooman CJ, Woo D et al. Carotid artery stenosis as a cause of stroke. Neuroepedemiol 2013;40:36-41.

Journal Pre-proof

186. Rosales JS, Alet MJ, Pujol Lereis VA, Ameriso SF. Fall in the proportion of atherothrombotic strokes during the last decade. J Stroke Cerebrovasc Dis (2021 in press) doi.org/10.1016/j.jstrokecerbrovascdis.2020.105257.

187. Hackam DG, Spence JD. Decline in the severity of carotid atherosclerosis and associated risk factors from 2002-2014. Stroke 2018;49:2786-2788.

188. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991;337:1235-43.

189. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. N Engl J Med 1991;325:445-53.

190. Donnan GA, Davis SM, Chambers BR, Gates PC. Surgery for prevention of stroke. Lancet 1998;351:1372-3.

191. Walker J., Naylor A.R. Ultrasound based diagnosis of 'carotid stenosis >70%': An audit of UK practice. Eur J Vasc Endovasc Surg 2006;31:487-90.

192. 193 Johansson E, Fox AJ. Carotid near-occlusion: a comprehensive review: Part 1 – definition, terminology, and diagnosis. Am J Neuroradiol 2016; 37: 2–10.

193. Bartlett ES, Walters TD, Symons SP, Fox AJ. Diagnosing carotid stenosis near occlusion by using CT angiography. AJNR 2006;27:632-637.

194. Johansson E, Gu T, Fox AJ. Defining carotid near-occlusion with full collapse: A pooled analysis. Neuroradiol 2022;64:59-67.

195. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421-8.

196. Oates C, Naylor AR, Hartshorne T, Charles SM, Humphries K, Aslam M, Khodabaksh P. Reporting carotid ultrasound investigations in the United Kingdom Eur J Vasc Endovasc Surg 2009;37:251-261.

197. Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth EI et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis: Society of Radiologists in Ultrasound Consensus Conference. Radiology 2003;229:340-6.

198. Arning C, Widder B, von Reutern GM, Stiegler H, Gortler M. Revision of DEGUM ultrasound criteria for grading internal carotid artery stenoses and transfer to NASCET measurement. Iltraschall Med 2010;31:251-7.

199. Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. Health Technol Assess 2006;10:1–182.

200. Patel SG, Collie DA, Wardlaw JM, Lewis SC, Wright AR, Gibson RJ, et al. Outcome, observer reliability, and patient preferences if CTA, MRA, or Doppler ultrasound were used, individually or together, instead of digital subtraction angiography before carotid endarterectomy. J Neurol Neurosurg Psychiatry. 2002;73:21-8.

201. Bazan HA, Caton G, Talebinejad S, Hoffman R, Smith TA, Vidal G, et al. A stroke/vascular neurology service increases the volume of urgent carotid endarterectomies performed in a tertiary referral center. Ann Vasc Surg 2014;28:1172-1177.

202. Rothwell PMR, Warlow CP. Is self-audit reliable?. Lancet 1995;346:1623.

Journal Pre-proof

Journal Pre-proof

203. Theiss W, Hermanek P, Mathias K, Ahmadi R, Heuser L, Hoffmann FJ, Kerner R, Leisch F, Sievert H, von Sommoggy S. Pro-CAS: a prospective registry of carotid angioplasty and stenting. Stroke 2004;35:2134-2139.

204. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491–502

205. Yu E, Malik VS, Hu FB, Cardiovascular disease prevention by diet modification: JACC Health Promotion series. J Am Coll Cardiol 2018;72:914-26.

206. De Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH. Prevalence of asymptomatic carotid artery stenosis in the general population: An individual participant data meta-analysis. Stroke 2010;41:1294-1297

207. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso Study. Stroke 2012;43:1818-23.

208. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989;298:789-94.

209. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. Stroke 2003;34:2475-81.

210. Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. Stroke 2010;41:418-26.

211. Lobelo F, Rohm Young D, Sallis R, Garber MD, Billinger SA, et al. Routine Assessment and Promotion of Physical Activity in Healthcare Settings: A Scientific Statement from the American Heart Association. American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Cardiovascular Surgery and Anesthesia; and Stroke Council. Circulation. 2018;137:e495-e522

212. Cote R, Battista RN, Abrahamowicz M, Langlois Y, Bourque F, Mackey A. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. The Asymptomatic Cervical Bruit Study Group. Ann Intern Med. 1995;123:649-55.

213. King A, Shipley M, Markus H. The effect of medical treatments on stroke risk in asymptomatic carotid stenosis. Stroke. 2013;44:542-6.

214. Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. Stroke 2003;34:2310-22.

215. Giannopoulos A, Kakkos S, Abbott A, Naylor AR, Richards T, Mikhailidis DP, et al. Long-term mortality in patients with asymptomatic carotid stenosis: implications for statin therapy. Eur J Vasc Endovasc Surg 2015;50:573-82.

216. Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849-1860.

217. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348:1329-39.

218. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicyclic acid in the prevention of stroke. J Neurol Sci 1996;143:1-13.

Journal Pre-proof

219. Taylor DW, Barnett HJ, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Lancet. 1999;353:2179-84.

220. Dalainas I, Nano G, Bianchi P, Stegher S, Malacrida G, Tealdi DG. Dual antiplatelet regime versus acetyl-acetic acid for carotid artery stenting. Cardiovasc Intervent Radiol. 2006;29:519-21.

221. McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. Eur J Vasc Endovasc Surg. 2005;29:522-7.

222. Mannheim D, Karmeli R. Prospective randomized trial comparing endarterectomy to stenting in severe asymptomatic carotid stenosis. J Cardiovasc Surg. 2017;58:814-7.

223. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. N Engl J Med. 2008;358:1572-9.

224. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med 2016;374:1011-20.

225. Eckstein HH, Reiff T, Ringleb P, Jansen O, Mansmann U, Hacke W for the SPACE 2 Investigators. SPACE-2: A Missed Opportunity to Compare Carotid Endarterectomy, Carotid Stenting, and Best Medical Treatment in Patients with Asymptomatic Carotid Stenoses. Eur J Vasc Endovasc Surg. 2016;51:761-5.

226. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation 1999;100:1667-1672.

227. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. N Engl J Med. 2016;374:1021-31.

228. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J et al: 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010; 376:1074–84.

229. Cholesterol Treatment Trialists Collaboration. The effects of lowering LDL-Cholesterol with statin therapy in people at low risk of vascular disease Meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.

230. Ogata A, Oho K, Matsumoto N, Masuoka J, Inoue K, Koguchi M, et al. Stabilization of vulnerable carotid plaques with proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab. Acta Neurochir (Wien). 2019; 161 :597-600.

231. Mathiesen EB, Joakimsen O, Bonaa KH. Prevalence of and risk factors associated with carotid artery stenosis: the Tromso Study. Cerebrovasc Dis 2001;12:44-51.

232. Sutton-Tyrrell K, Wolfson SK, Jr., Kuller LH. Blood pressure treatment slows the progression of carotid stenosis in patients with isolated systolic hypertension. Stroke 1994;25:44-50.

233. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. for the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. The Lancet 2002;360:1903–13.

234. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665.

Journal Pre-proof

235. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, et al Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA* 2015;313:1325-1335.

236. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021-3104.

237. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. Stroke. 2012;43:1212–1217.

238. Scholtes VP, Peeters W, van Lammeren GW, Howard DP, de Vries JP, de Borst GJ, et al. Type 2 diabetes is not associated with an altered plaque phenotype among patients undergoing carotid revascularization. A histological analysis of 1455 carotid plaques. Atherosclerosis. 2014;235:418-23.

239. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–591.

240. Colhoun H, Betteridge D, Durrington P, Hitman G. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised. Lancet 2004;364:685–96.

241. Zhang C, Zhou YH, Xu CL, Chi FL, Ju HN. Efficacy of intensive control of glucose in stroke prevention: a meta-analysis of data from 59197 participants in 9 randomized controlled trials. PLoS One. 2013;8:e54465.

242. Wilcox R, Kupfer S, Erdmann E on behalf of the PROactive Study Investigators. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: Results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10). Am Heart J 2008;155:712-7.

243. https://www.nice.org.uk/guidance/NG28 (accessed 16th October 2021)

244. https://www.nice.org.uk/guidance/NG17 (accessed 16th October 2021)

245. https://abcd.care/position-papers (accessed 16th october 2021).

246. https://professional.diabetes.org/content-page/practice-guidelines-resources (accessed 16th October 2021)

247. Kirkpatrick AC, Vincent AS, Guthery L, Prodan CI. Cognitive impairment is associated with medication nonadherence in asymptomatic carotid stenosis. Am J Med. 2014;127:1243-6.

248. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487-97.

249. Luebke T, Brunkwall J. Development of a microsimulation model to predict stroke and long-term mortality in adherent and non-adherent medically managed and surgically treated octogenarians with asymptomatic significant carotid artery stenosis. World Neurosurg 2016;92:513-20.

250. Wilson J, Jungner G. Principles and practice of screening for disease. Geneva: WHO;1968 http://www.who.int/entity/bulletin/volumes/86/4/07-050112/en/. Accessed 23rd February 2021.

251. Hadar N, Raman G, Moorthy D, Asymptomatic Carotid Artery Stenosis Treated with Medical Therapy Alone: Temporal Trends and Implications for Risk Assessment and the Design of Future Studies. Cerebrovasc Dis 2014;38:163-73.

252. Jonas DE, Feltner C, Amick HR, Sheridan S, Zheng ZJ, Watford DJ et al. Screening for Asymptomatic Carotid Stenosis; A Systematic review

Journal Pre-proof

and Meta-analysis for the US Preventive taskforce. Evidence Synthesis no 111. AHRQ Publication no. 13-05178-EF-1 Rockville, MD: Agency for Healthcare Research and Quality; 2014.

253. Sillesen H, Sartori, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. Eur Heart J Cardiovasc Imag 2018;19:1042-50

254. Poorthuis MHF, Sherliker P, Morris DR, Massa MS, Clarke R, Staplin N et al. Development and internal validation of a risk score to detect asymptomatic carotid stenosis. Eur J Vasc Endovasc Surg 2021;61:365-373.

255. Poorthuis MHF, Morris DR, de Borst GJ., Bots ML, Greving JP, Visseren FLJ, et al. Detection of Asymptomatic Carotid Stenosis in Patients with Lower Extremity Arterial Disease: development and external validations of a risk score Br J Surg 2021; 108:960-967

256. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ ASNR/CNS/SAIP /SCAI/SIR/SNIS/SVM/SVS guidelines on the management of patients with extracranial carotid and vertebral artery disease. J Am Coll Cardiol. 2011;57:1002-44.

257. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V et al. 2019 ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255-323

258. Mach F, Baigent C, Catapano AL, Koskinas KC, Patel RS, Manuela C et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019;290:140-205.

259. Hobson R, Weiss D, Fields W, Goldstone J, Moore W, Towne J for the Veterans' Affairs Cooperative Study Group. Efficacy of Carotid Endarterectomy for Asymptomatic Carotid Stenosis. N Eng J Med 1993;328:221-227.

260. Rothwell PM, Goldstein LB. Carotid Endarterectomy for Asymptomatic Carotid Surgery Trial. Stroke 2004;35;2425-2427.

261. Nicolaides A.N., Kakkos S.K., Griffin M., Sabetai M., Dhanjil S., Tegos T. et al Severity of Asymptomatic carotid Stenosis and Risk of Ipsilateral Hemispheric Ischaemic Events: Results from ACSRS. Eur J Vasc Endovasc Surg 2005;30:275-284.

262. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002;106:1368-1373.

263. Naylor AR. Time to rethink management strategies in asymptomatic carotid disease. Nat Rev Cardiol 2012;9:116-24.

264. Kakkos SK, Griffin MB, Nicolaides AN, Kyriacou E, Sabetai MM, Tegos T et al. The size of the juxta-luminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. J Vasc Surg 2013;57:609-18

265. Veith FJ, Bell PRF. How Many of You Can Read But Still Not See? A Comment on a Recent Review of Carotid Guidelines. Eur J Vasc Endovasc Surg 2016;51:471-2.

266. Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? Eur J Vasc Endovasc Surg. 2009;37;625-32.

267. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S. et al. Guidelines for the Primary Prevention of Stroke A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754-3832.

268. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-3337.

Journal Pre-proof

269. Aboyans V, Ricco J-B, Bartelink M-L, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the diagnosis and treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:305-368.

270. . Kakkos SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M et al. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. J Vasc Surg 2009;49:902-909.

271. Kakkos SK, Nicolaides AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. J Vasc Surg 2014;59:956-67.

272. Hirt LS. Progression Rate and Ipsilateral Neurological Events in Asymptomatic Carotid Stenosis. Stroke 2014;45:702-706

273. Nicolaides A, Kakkos SK, Kyriacou E, Griffin M, Thomas DJ, Geroulakos G et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. J Vasc Surg 2010;52:1486-1496

274. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D. et al. Carotid Plaque MRI and Stroke Risk: A Systematic Review and Meta-analysis. Stroke 2013;44:3071-77.

275. King A, Serena J, Bornstein NM, Markus HM on behalf of the ACES Investigators. Does Impaired Cerebrovascular Reactivity Predict Stroke Risk in Asymptomatic Carotid Stenosis: A Prospective Substudy of the Asymptomatic Carotid Emboli Study. Stroke 2011;42:1550-55

276. Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambrone AE et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: a systematic review and meta-analysis. Stroke. 2015;46:91-7.

277. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S. et al. Asymptomatic embolisation for prediction of stroke in the asymptomatic carotid emboli study: A prospective observational study. Lancet Neurology 2010;9:663-671.

278. Topakian R, King A, Kwon U, Schaafsma A, Shipley M, Markus H. Ultrasonic plaque echolucency and emboli signals predict stroke in asymptomatic carotid stenosis. Neurology 2011;77:751-8.

279. Karloff E, Buckler A, Liljeqvist M, Kronqvist M, Toonsi MA, Maegdefessel L et al. Carotid plaque phenotyping by correlating plaque morphology from computed tomography angiography with transcriptional profiling. Eur J Vasc Endovasc Surg 2021;62:716-726.

280. Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D et al. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2011;42:675-80.

281. Brooks W.H., McClure R.R., Jones M.R., Coleman T.L., Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: A randomised trial in a community hospital. Neurosurgery 2004;54:318-324.

282. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351:1493-1501.

283. Biller J, Feinberg WM, Castaldo JE, Whittemore AD, Harbaugh RE, Dempsey RJ et al. Guidelines for carotid endarterectomy: A statement for healthcare professionals from a special writing group of the Stroke Council, the American Heart Association. Stroke 1998;29:554-62.

284. Hill MD, Brooks W, Mackey A, Clark WM, Meschia JF, Morrish WF et al. Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Circulation 2012;126:3054-61.

285. Schneider PA, Naylor AR. Transatlantic debate. Asymptomatic carotid artery stenosis: Medical therapy alone versus medical therapy plus carotid endarterectomy or stenting. Eur J Vasc Endovasc Surg 2010;40:274-281.

Journal Pre-proof

286. Cambria RP, Conrad MF Asymptomatic carotid stenosis: Revisionist history is usually wrong. J Vasc Surg 2020;71:2-4

287. www.dementiastatistics.org (accessed 22nd December 2020).

288. Buratti L, Balucani C, Viticchi G, Falsetti L, Altamura C, Avitabile E, et al. Cognitive deterioration in bilateral asymptomatic severe carotid stenosis. Stroke 2014;45:2072–7.

289. Silvestrini M, Paolino I, Vernieri F, Pedone C, Baruffaldi R, Gobbi B, et al. Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis. Neurology 2009;72:1062–8.

290. Balucani C, Viticchi G, Falsetti L, Silvestrini M. Cerebral hemodynamics and cognitive performance in bilateral asymptomatic carotid stenosis. Neurology. 2012;79:1788–95.

291. Buratti L, Viticchi G, Falsetti L, Balucani C, Altamura C, Petrelli C, et al. Thresholds of impaired cerebral hemodynamics that predict short-term cognitive decline in asymptomatic carotid stenosis. J Cereb Bld Flow Metab 2016;36:1804–12.

292. Silvestrini M, Viticchi G, Falsetti L, Balucani C, Vernieri F, Cerqua R, et al. The role of carotid atherosclerosis in Alzheimer's disease progression. J Alzheimers Dis 2011;25:719–26.

293. Balestrini S, Perozzi C, Altamura C, Vernieri F, Luzzi S, Bartolini M, et al. Severe carotid stenosis and impaired cerebral hemodynamics can influence cognitive deterioration. Neurology 2013;80:2145–50.

294. Chen Y-H, Lin M-S, Lee J-K, Chao C-L, Tang S-C, Chao C-C et al. Carotid stenting improves cognitive function in asymptomatic cerebral ischaemia. Int J Cardiology 2012;157:104-107.

295. https://strokengine.ca/en/assessments/modified-rankin-scale-mrs/ (Accessed 21st August 2021)

296. Ortiz GA, Sacco RL. National Institutes of Health Stroke Scale (NIHSS). https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118445112.stat06823. (accessed 16th October 2021).

297. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19,435 patients with acute ischaemic stroke. Lancet 1997;349:1569 – 158.

298. Chinese Acute Stroke Trial Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 1997; 349: 1641-1649

299. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106

300. Sandercock P. Antiplatelet therapy with aspirin in acute ischaemic stroke. Thrombosis and Haemostasis 1997; 78: 180-182.

301. Diener HC, L. Cunha, C. Forbes, J. Sivenius, P. Smets, A. Lowenthal. European Stroke Prevention Study- 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1985:143:1-13.

302. ESPRIT Study Group Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. ESPRIT Study Group. Lancet. 2006;367:1665-73.

303. Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T et al. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. Lancet Neurol, 2010. 9:159-66.

Journal Pre-proof

304. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton AW et al for the PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. NEJM 2008;359:1238-1251.

305. King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke. 2009;40:3711-7.

306. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005;111:2233-40.

307. King A, Bath PM, Markus HS. Clopidogrel versus dipyridamole in addition to aspirin in reducing embolization detected with ambulatory transcranial Doppler: a randomized trial. Stroke 2011;42:650-5.

308. Batchelder AJ, Hunter J, Robertson V, Sandford R, Munshi A, Naylor AR. Dual antiplatelet therapy prior to expedited carotid surgery reduces recurrent events prior to surgery without increasing peri-operative bleeding complications. Eur J Vasc Endovasc Surg 2015;50:412-419.

309. Naylor AR, Sayers RD, McCarthy MJ, Bown MJ, Nasim A, Dennis M, London NJM, Bell PRF. Closing the Loop: A 21-year Audit of Strategies for Preventing Stroke and Death following Carotid Endarterectomy. Eur J Vasc Endovasc Surg 2013;46:161-70.

310. Payne DA, Jones CI, Hayes PD, Thompson MM, London NJM, Bell PRF, et al. Beneficial effects of Clopidogrel combined with Aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. Circulation 2004;109:1476-1481.

311. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): A randomised controlled pilot trial. Lancet Neurol 2007;6:961-9.

312. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C et al. Clopidogrel with aspirin in acute minor stroke or transient ischaemic attack. N Engl J Med. 2013;369:11-19.

313. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. J Am Coll Cardiol 2001;38:1589–95.

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

315. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: The International Carotid Stenting Study (ICSS) randomised trial. The Lancet. 2014. 385: 529-538.

316. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010;363:11-23.

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

318. https://cks.nice.org.uk/topics/stroke-tia/management/secondary-prevention-following-stroke-tia/ (accessed 5th September 2021)

Journal Pre-proof

319. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P. for the CHARISMA Investigators. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. N Engl J Med 2006; 354: 1706-1717.

320. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al., Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331-7.

321. Dawson J, Merwick A, Webb A, Dennis M, Ferrari J, Fonseca AC for the European Stroke Organisation. European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA. Eur Stroke J 2021;6: CLXXXVII-CXCI

322. Prasad K, Siemieniuk R, Hao Q, Guyatt G, O'Donnell M, Lytvyn L et al. Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: A clinical practice guideline. BMJ 2018;363:k5130.

323. Stroke Foundation (2019). Clinical Guidelines for Stroke Management. Melbourne Australia. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management. (accessed 5th September 2021)

324. Boulanger JM, Lindsay MP, Gubitz G, Smith EE, Stotts G, Foley N et al. Canadian Stroke Best Practice Recommendations for acute stroke management: Pre-hospital, Emergency Department and Acute Inpatient stroke care. 6th Edition, Update 2018. Int J Stroke 2018;13:949-984.

325. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. Stroke 1993;24:1125-8.

326. Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost 1999;25(Suppl 2);15-190.

327. Jackson AJ, Teenan RP, Orr DJ. The use of clopidogrel in carotid endarterectomy: An audit of current practice. Eur J Vasc Endovasc Surg 2007;34:312-313.

328. Shahidi S, Owen-Falkenberg A, Gottschalksen G, Ellerman K. Risk of early recurrent stroke in symptomatic carotid stenosis after best medical therapy and before endarterectomy. Int J Stroke 2016;11:41-51.

329. Stone DH, Goodney PP, Schanzer A, Nolan BW, Adams JE, Powell RJ et al. Clopidogrel is not associated with major bleeding complications during peripheral arterial surgery. J Vasc Surg 2011;54:779-84.

330. Illuminati G, Schneider F, Pizzardi G, Masci F, Calio FG, Ricco J-B. Dual antiplatelet therapy does not increase the risk of bleeding after carotid endarterectomy: Results of a prospective study. Ann Vasc Surg 2017;40:39-43.

331. Naylor AR, McCabe D. Cerebrovascular Disease: Decision Making Including Medical Therapy. In: Eds: Sidawy A, Perler B. Rutherford's Vascular and Endovascular Therapy (10th Edition). Elsevier (IN PRESS).

332. Gaglia MA, Torguson R, Hanna N, Gonzalez MA, Collins SD, Syed AI, et al. Relation of proton pump inhibitor use after percutaneous coronary intervention with drug-eluting stents to outcomes. Am J Cardiol 2010;105:833-8.

333. Collett J-P, Thiele H, Barbato E, Barthelemy O, Bauersauchs J, Bhatt DL et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without ST-segment elevation. Eur Heart J 2021;42:1289-1367.

Journal Pre-proof

Journal Pre-proof

334. Furuta T, Iwaki T, Umemura K. Influences of different proton pump inhibitors on the anti-platelet function of clopidogrel in relation to CYP2C19 genotypes. Br J Clin Pharmacol. 2010;70:383-392.

335. Chan FK, Kyaw M, Tanigawa T, Higuchi K, Fujimoto K, Cheong PK et al. Similar Efficacy of Proton-Pump Inhibitors vs H2-Receptor Antagonists in Reducing Risk of Upper Gastrointestinal Bleeding or Ulcers in High-Risk Users of Low-Dose Aspirin. Gastroenterology. 2017;152:105-110.

336. Kinsella JA, Oliver Tobin W, Tierney S, Feeley TM, Egan B, Coughlan T et al. Assessment of 'on-treatment platelet reactivity' and relationship with cerebral micro-embolic signals in asymptomatic and symptomatic carotid stenosis. J Neurol Sci 2017;376:133-139.

337. Murphy SJX, Lim ST, Kinsella JA, Tierney S, Egan B, McCabe DJH et al. Relationship between 'on-treatment platelet reactivity', shear stress, and micro-embolic signals in asymptomatic and symptomatic carotid stenosis. J Neurol 2020;267:168-184.

338. Dawson J, Quinn T, Lees KR, Walters MR. Microembolic signals and aspirin resistance in patients with carotid stenosis. Cardiovasc Ther 2012;30:234-239

339. Kakkos SK, Gohel M, Baekgaard N, Bauersachs R, Bellmunt-Montoya S et al. European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. Eur J Vasc Endovasc Surg 2021;61:9-82.

340. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ et al. 2017 American College of Cardiology expert consensus decision pathway for peri-procedural management of anticoagulation in patients with non-valvular atrial fibrillation J Am Coll Cardiol 2017;69:871-98.

341. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist CB et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498.

342. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest 2010;138:1093-1100.

343. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Destegne L et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330-93.

344. Patel IJ, Rahim S, Davidson JC, Hanks SE, Tam AL, Walker TG, et al. Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions-Part II: Recommendations: J Vasc Interv Radiol 2019;30:1168-1184.

345. Nii K, Takemura Y, Inoue R, Morinaga Y, Mitsutake T, Higashi T. Safety of direct oral anticoagulant- and antiplatelet therapy in patients with atrial fibrillation treated by carotid artery stenting. J Stroke Cerebrovasc Dis (IN PRESS) doi: 10.1016/j.jstrokecerebrovasdis.2020.104899.

346. Faggioli G, Pini R, Rapezzi C, Mauro R, Freyrie A Gargiulo M et al. Carotid revascularisation in patients with ongoing oral anticoagulant therapy: The advantages of stent placement. J Vasc Interv Radiol 2013;24:370-77.

347. Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J et al: Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis. A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke 2008;39:3297-302.

Journal Pre-proof

348. Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004; 363: 757–67.

349. Amarenco P, Bogousslavsky J, Callahan A, Goldstein LB, Hennerici M, Rudolph AE, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549-59.

350. Bond R, Narayan S, Rothwell PM, Warlow CP on behalf of the European Carotid Surgery Trialists' Collaborative Group. Clinical and radiological risk factors for operative stroke and death in the European Carotid Surgery Trial. Eur J Vasc Endovasc Surg 2002;23:108-116.

351. Rothwell PM, Howard SC, Spence JD. Carotid Endarterectomy Trialists' Collaboration. Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. Stroke 2003;34:2583-9

352. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NEF et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;:397-406.

353. Fuentes B, Ntaios G, Putaala J, Thomas B, Turc G, Díez-Tejedor E et al. European Stroke Organisation (ESO) guidelines on glycaemia management in acute stroke. Eur Stroke J. 2018; 3: 5-21.

354. Murphy SJ, Coughlan CA, Tobin O, Kinsella J, Lonergan R, Gutkin M, et al. Continuation and adherence rates on initially-prescribed intensive secondary prevention therapy after Rapid Access Stroke Prevention (RASP) service assessment. J Neurol Sci. 2016;361:13-8.

355. Chen DC, Armstrong EJ, Singh GD, Amsterdam EA, Laird JR. Adherence to guideline-recommended therapies among patients with diverse manifestations of vascular disease. Vasc Health Risk Manag. 2015;11:185-92.

356. Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. JAMA 1991;266:3289-94.

357. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003;361:107-16

358. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363:915-24

359. Rothwell PM, Gutnikov SA, Warlow CP; European Carotid Surgery Trialist's Collaboration. Sex differences in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischaemic attack and non disabling stroke. Stroke 2004;35:2855-61.

360. Alamowitch S., Eliasziw M., Algra A., Meldrum H., Barnett H.J.M. for the NASCET Group. Risk, causes and prevention of ischaemic stroke in elderly patients with symptomatic internal carotid artery stenosis. Lancet 2001;357;1154-60

361. Inzitari D, Eliasziw, Sharpe BL, Fox AJ, Barnett HJM for the NASCET Group. Risk factors and outcome of patients with carotid artery stenosis presenting with lacunar stroke. Neurology 2000;54:660-666

362. Kappelle LJ, Eliasziw M, Fox AJ, Sharpe BL, Barnett HJM for the NASCET Group. Importance of intracranial atherosclerotic disease in patients with symptomatic stenosis of the internal carotid artery. Stroke 1999;30:282-86

Journal Pre-proof

363. Henderson RD, Eliasziw M, Fox AJ, Rothwell PM, Barnett HJM for the NASCET Group. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. Stroke 2000;31:128-132

364. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet. 2010;375:985-997.

365. Cohen DJ, Stolker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, et al. CREST Investigators. Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). J Am Coll Cardiol 2011;58:1557-65.

366. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. Perioperative Myocardial Infarction. Circulation 2009;119:2936-2944.

367. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, de Hert S et al. ESC/ESA guidelines on non-cardiac surgery: Cardiovascular assessment and management. Eur Heart J 2014;35:2383-2431.

368. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41:407-477

369. Foucrier A, Rodseth R, Aissaoui M, Ibanes C, Goarin J-P, Landais P et al. The long term impact of early cardiovascular therapy intensification for post-operative Troponin elevation after major vascular surgery. Anesth Analg 2014;119:1053-1063

370. Rockman CB, Maldonado TS, Jacobowitz GR, Cayne NS, Gagne PJ, Riles TS. Early carotid endarterectomy in symptomatic patients is associated with poorer perioperative outcomes. J Vasc Surg 2006;44:480-487

371. Fairhead J.F., Mehta Z., Rothwell P.M. Population based study of delays in carotid imaging and surgery and the risk of recurrent stroke. Neurology 2005;65:371-375.

372. Purroy F, Montaner, J, Molina, CA, Delgado, P, Ribo, M, Alvarez-Sabin, J. Patterns and Predictors of Early Risk of Recurrence After Transient Ischemic Attack With Respect to aetiologic subtypes. Stroke 2007;38:3225-9.

373. Ois A, Cuadrado-Godia E, Rodriguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. Stroke 2009;40:2727-2731.

374. Bonifati DM, Lorenzi A, Ermani M, Refatti F, Gremes E, Boninsegna C. et al. Carotid stenosis as predictor of stroke after transient ischemic attacks. J Neurol Sci 2011;303:85-9

375. Johansson E P, Arnerlöv,C, Wester P. Risk of recurrent stroke before carotid endarterectomy: The ANSYSCAP study. Int J Stroke 2013;8:220-7.

376. Mono M-L, Steiger IL, Findling O, Jung S, Reinert M, Manis K et al. Risk of very early recurrent cerebrovascular events in symptomatic carotid artery stenosis. J Neurosurg 2013;119:1620-26.

377. Merwick A, Albers GW, Arsava EM, Ay H, Calvert D, Coutts SB et al. Reduction in early stroke risk in carotid stenosis with transient ischaemic attack associated with statin treatment. Stroke 2013:44:2814-20

378. Marnane M, Prendeville S, McDonnell C, Noone I, Barry M Crowe M et al. Plaque inflammation and unstable morphology are associated with early stroke recurrence in symptomatic carotid stenosis. Stroke 2014;45:801-6.

Journal Pre-proof

379. Johansson E, Nordanstig A. The issue of optimal timing of carotid revascularisation is both relevant and unresolved. Eur J Vasc Endovasc Surg (2022 in press). http://doi.org/10.1016/j.ejvs.2021.11.020).

380. Loftus IM, Paraskevas K, Johal A, Waton S, Heikkila K, Naylor AR et al. Delays to surgery and procedural risks following carotid endarterectomy in the UK National Vascular registry. Eur J Vasc Endovasc Surg 2016;52:438-443

381. Tsantilas P, Kuchnl A, Konig T, Breitkreuz T, Kallmayer M, Knappich C et al. Short Time Interval Between Neurologic Event and Carotid Surgery Is Not Associated With an Increased Procedural Risk. Stroke 2016;47:2783-90.

382. Stromberg S, Gelin J, Osterberg T, Bergstrom GM, Karlstrom L, Osterberg K. Very urgent carotid endarterectomy confers increased procedural risk. Stroke 2012;43:1331-1335.

383. Jonsson M, Gillgren P, Wanhainen A, Acosta S, Lindstrom D. Peri-procedural risk with urgent carotid artery stenting: A population-based study. Eur J Vasc Endovasc Surg 2015;49:506-12.

384. Rantner B, Goebel G, Bonati LH, Ringleb PA, Mas JL, Fraedrich G. The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms. J Vasc Surg 2013;57:619-26

385. Huibers A, Calvet D, Kennedy F, Czuriga-Kovács KR, Featherstone RL, Moll FL, et al. Mechanism of Procedural Stroke Following Carotid Endarterectomy or Carotid Artery Stenting Within the International Carotid Stenting Study (ICSS) Randomised Trial. Eur J Vasc Endovasc Surg. 2015;50:281-288.

386. Hill MD, Brooks W, Mackey A, Clark WM, Meschia JF, Morrish WF et al. Stroke After Carotid Stenting and Endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Circulation 2012;126:3054-61.

387. Naylor A.R. Time is brain! The Surgeon 2007;5:23-30.

388. Rantner B, Eckstein HH, Ringleb P, Woelfle KD, Bruijnen H, Schmidauer C, Fraedrich G. American Society of Anesthesiology and Rankin as Predictive Parameters for the Outcome of Carotid Endarterectomy Within 28 Days After an Ischemic Stroke. J Stroke Cerebrovasc Dis 2006;15:114-120.

389. Wolfle KD, Pfadenhauer K, Bruijnen H, Becker T, Engelhardt M, Wachenfeld-Wahl C, Schulze-Hamma E, Loeprecht H, Wohlgemuth WA. Early carotid endarterectomy in patients with a nondisabling ischemic stroke: results of a retrospective analysis. Vasa 2004;33:30-35.

390. Hause S, Schonefuss R, Assmann A, Neurmann J, Meyer F, Tautenhahn J et al. Relevance of infarct size, timing of surgery and peri-operative management of non-ischaemic cerebral complications after carotid endarterectomy. Eur J Vasc Endovasc Surg 2022 (in press). http://doi.org/10.1016/j.ejvs.2021.09.044).

391. Pini R, Faggioli G, Longhi M, Ferrante L, Vacirca A, Gallitto E et al. Impact of acute cerebral ischemic lesions and their volume on the revascularisation outcome of symptomatic carotid stenosis. J Vasc Surg 2017;65:390-7.

392. Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. Stroke 2009;40:e564-e572.

393. Capoccia L, Sbarigia E, Speziale F, Toni D, Biello A, Montelione N, Fiorani P. The need for emergency surgical treatment in carotid-related stroke in evolution and crescendo transient ischemic attack. J Vasc Surg 2012;55:1611-1617.

394. Gajin P, Radak D, Tanaskovic S, Babic S, Nenezic D. Urgent carotid endarterectomy in patients with acute neurological ischemic events within six hours after symptoms onset. Vascular 2014;22:167-173.

Journal Pre-proof

395. Goertler M, Blaser T, Krueger S, Hofmann K, Baeumer M, Wallesch C-W. Cessation of embolic signals after antithrombotic prevention is related to reduced risk of recurrent arterioembolic transient ischaemic attack and stroke. J Neurol Neurosurg Psych 2002;72:338-42

396. Hao Q, Chang HM, Wong MC, Wong KS, Chen C. Frequency of microemboli signal in stroke patients treated with low molecular weight heparin or aspirin. J Neuroimaging. 2010;20:118-21

397. Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC et al. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. Lancet Neurol. 2007;6:407-13.

398. Powers WJ, Raninstein AA, Ackerson T, Adeoye OM, Bambaakidis NC, Becker K et al. Guidelines for the early management of patients with acute ischaemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischaemic stroke. Stroke 2019;50:e344-e418.

399. Berge E, Whiteley W, Audebert H, Marchis GM, Fonseca AC, Padiglioni C, et al. European Stroke Organisation guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J 2021;6: I–LXII

400. Bartoli MA, Squarcioni C, Nicoli F, Magnan PE, Malikov S, Berger L et al. Early carotid endarterectomy after intravenous thrombolysis for acute ischaemic stroke. Eur J Vasc Endovasc Surg 2009;37:512-8.

401. Barroso B, Laurens B, Demasles S, Faik M, Ledoyer G. Early carotid artery endarterectomy after intravenous thrombolysis therapy. Int J Stroke 2013;8:E28.

402. Naylor AR. Thrombolysis and expedited carotid revascularization. J Cardiovasc Surg (Torino) 2015;56:159-64.

403. www.medicines.org (accessed 15th April 2021).

404. Vivien D, Gauberti M, Montagne A, Defer G, Touze E. Impact of tissue plasminogen activator on the neurovascular unit: from clinical data to experimental evidence. J Cereb Blood Flow Metab 2011; 31: 2119-34.

405. Trouillas P, Derex L, Philippeau F, Nighoghossian N, Honnorat J, Hanns M et al. Early fibrinogen degradation coagulopathy is predictive of parenchymal haematomas in cerebral rt-PA thrombolysis: a study of 157 cases. Stroke 2004; 35: 1323-8.

406. Ijas P, Aro E, Eriksson H, Vikatmaa P, Soinne L, Venermo M. Prior intravenous stroke thrombolysis does not increase complications of carotid endarterectomy. Stroke 2018;49:1843-49.

407. Bush CK, Kurimella D, Cross LJS, Conner KR, Martin-Schild S, He J, et al. Endovascular Treatment with Stent-Retriever Devices for Acute Ischemic Stroke: A Meta-Analysis of Randomized Controlled Trials. PLoS ONE 2016; 11(1): e0147287.

408. Papanagiotou P, Haussen DC, Turjman F, Labreuche J, Piotin M, Kastrup A et al. Carotid stenting with antithrombotic agents and intracranial thrombectomy leads to the highest recanalization rate in patients with acute stroke and tandem lesions. JACC Card Interv 2018;11:1290-99.

409. Jacquin G, Poppe AY, Labrie M, Daneault N, Deschaintre Y, Gioia LC et al. Lack of consensus among stroke experts on the optimal management of patients with acute tandem occlusion. Stroke 2019;50:1254-1256.

410. Park JS, Lee JM, Kwak HS, Chung GH. Endovascular treatment of acute carotid atherosclerotic tandem occlusions: Predictors of clinical outcomes as technical aspects and location of tandem occlusions. J Stroke Cerebrovasc Dis 2020;29:105090.

411. Poppe AY, Jacquin G, Roy D, Stapf C, Derex L. Tandem Carotid Lesions in Acute Ischemic Stroke: Mechanisms, Therapeutic Challenges, and Future Directions. AJNR 2020;41:1142-1148.

Journal Pre-proof

412. Gemmete JJ, Wilseck Z, Pandey AS, Chaudhary N. Treatment Strategies for Tandem Occlusions in Acute Ischemic Stroke. Sem Interv Radiol. 2020;37:207-213.

413. Goyal M, Yoshimura S, Milot G, Fiehler J, Jayaraman M, Dorn F. et al. Considerations for Antiplatelet Management of Carotid Stenting in the Setting of Mechanical Thrombectomy: Delphi Consensus Statement. AJNR 2020;41:2274-2279.

414. Da Ros V, Scaggiante J, Sallustio F, Lattanzi S, Bandettini M, Sgreccia A. et al. Carotid Stenting and Mechanical Thrombectomy in Patients with Acute Ischemic Stroke and Tandem Occlusions: Antithrombotic Treatment and Functional Outcome. AJNR 2020;41:2088-2093.

415. Karlsson L, Kangefjard E, Hermansson S, Stromberg S, Osterberg K, Nordanstig A et al. Risk of recurrent stroke in patients with symptomatic mild (20-49% NASCET) carotid artery stenosis. Eur J Vasc Endovasc Surg 2016;52:287-294.

416. Yoshida K, Fukumitsu R, Kurosaki Y, Nagata M, Tao Y, Suzuki M et al. Carotid endarterectomy for medical therapy-resistant symptomatic low-grade stenosis. World Neurosurg 2019;123:e543-8

417. Kashiwazaki D, Shiraishi K, Yamamoto S, Kamo T, Uchino H, Saito H, et al. Efficacy of carotid endarterectomy for mild (<50%) symptomatic carotid stenosis with unstable plaque. World Neurosurg 2019;121:e60-9.

418. Schermerhorn ML, Fokkema M, Goodney P, Dillavou ED, Jim J, Kenwood CT et al. The impact of Centers for Medicare and Medicaid Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry. J Vasc Surg 2013;57:1318-24.

419. Gates L, Botta R, Schlosser F, Goodney P, Fokkema M, Schermerhorn ML et al. Characteristics that define high risk for carotid endarterectomy from the Vascular Study Group of New England. J Vasc Surg 2015;62:929-36.

420. Droz NM, Lyden SP, Smolock CJ, Rowse J, Kirksey L, Caputo FJ. Carotid Endarterectomy Remains Safe in High-Risk Patients. J Vasc Surg. 2021;73:1675-1682.

421. van Lammeren GW, Reichmann BL, Moll FL, de Kleijn DP, de Vries JP, Pasterkamp G et al. Atherosclerotic plaque vulnerability as an explanation for the increased risk of stroke in elderly undergoing carotid artery stenting. Stroke 2011;49:2550-5.

422. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FLde Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis Stroke 2012;43:793–801

423. Meershoek AJA, Vonken EPA, Nederkoorn PJ, Kappelle LJ, de Borst GJ. Carotid endarterectomy in patients with recurrent symptoms associated with an ipsilateral carotid artery near occlusion with full collapse. J Neurol 2018; 265: 1900–1905.

424. Johansson E, Gu T, Castillo S, Brunstrom M, Holsti M, Wanhainen A. Intracerebral haemorrhage after revascularisation of carotid near occlusion with full collapse. Eur J Vasc Endovasc Surg 2022 (in press). https://doi.org/10.1016/j.ejvs.2021.10.057.

425. Carr K, Tew D, Becerra L, Siddall K, Dubensky L, Serulle Y. Endovascular aspiration of a symptomatic free-floating common carotid artery thrombus. Neuroradiology 2018;60:1103-1107.

426. Choi PM, Singh D, Trivedi A, Qazi E, George D, Wong J et al. Carotid webs and recurrent ischemic strokes in the era of CT angiography. Am J Neuroradiol. 2015;36:2134-2139.

427. Labeyrie M-A, Serrano F, Civelli V, Jourdaine C, Reiner P, Saint-Maurice J-P et al. Carotid artery webs in embolic stroke of undetermined source with large intracranial vessel occlusion. Int J Stroke 2021;16:392-395.

Journal Pre-proof

428. Kim YH, Sung MS, Park SW. Clinical features of ocular ischaemic syndrome and risk factors for neovascular glaucoma. Kor J Ophth 2017;31:343-50

429. Mendrinos E, Machinis TG, Pournaras CJ. Ocular ischaemic syndrome. Surv Ophth 2010;55:2-34.

430. Oller M, Esteban C, Perez P, Parera MA, Lerma R, Llagostera S. Rubeosis iridis as a sign of underlying carotid stenosis. J Vasc Surg 2012;56:1724-1726.

431. Kawaguchi S, Lida J, Uchiyama Y, Ocular circulation and chronic ocular ischemic syndrome before and after carotid artery revascularization surgery. J Ophthalmol 2012;2012:350475.

432. Katsi V, Georgiopoulos G, Skafida A, Oikonomou D, Klettas D, Vemmos K et al. Non-cardioembolic stroke in patients with atrial fibrillation. Angiology 2019;70:299-304.

433. Salem MK, Butt HZ, Watts APW, Sayers RD, Bown MJ, Naylor AR. Spontaneous Embolisation in Asymptomatic and Acutely Symptomatic Patients with TIA/Minor stroke. Eur J Vasc Endovasc Surg 2011;41:720-5

434. Kumar ID, Singh S, Williams G, Train J. Bilateral one-stage carotid endarterectomy: Is there an indication? Eur J Vasc Endovasc Surg 2001;21:575-6.

435. Xu RW, Liu P, Fan XQ, Wang Q, Zhang JB, Ye ZD, et al. Feasibility and Safety of Simultaneous Carotid Endarterectomy and Carotid Stenting for Bilateral Carotid Stenosis: A Single-Center Experience using a Hybrid Procedure. Ann Vasc Surg 2016;33:138-43

436. GALA Trial Collaborative. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial Lancet 2008;372:2132–42

437. Orlický M, Hrbáč T,Sameš M, Vachata P, Hejčl A, Otáhal D, et al. Anesthesia type determines risk of cerebral infarction after carotid endarterectomy. J Vasc Surg 2019;70:138-147

438. Mracek J, Kletecka J, Holeckova I, Dostal J, Mrackova J, Mork J et al. Patient Satisfaction with General versus Local Anesthesia during Carotid Endarterectomy. J Neurol Surg A Cent Eur Neurosurg 2019;80:341-344.

439. Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: a systematic review of complications. Brit J Anaesth 2007;99:159-69

440. Working Party: Association of Anaesthetists of Great Britain & Ireland.; Obstetric Anaesthetists' Association.; Regional Anaesthesia UK. Regional Anaesthesia and patients with abnormalities of coagulation. Anaesthesia. 2013;68:966-72

441. Stoneham MD, Stamou D, Mason J. Regional anaesthesia for carotid endarterectomy. Brit J Anaesth 2015;114:372-383.

442. Holt, P. J. E., Poloniecki, J. D., Loftus, I. M., & Thompson, M. M. (2007a). Meta-analysis and systematic review of the relationship between hospital volume and outcome following carotid endarterectomy. Eur J Vasc Endovasc Surg 2007;33:645-651.

443. Holt PJE, Poloniecki JD, Loftus IM, Thompson MM. Relationship between Hospital Case Volume and Outcome from Carotid Endarterectomy in England from 2000 to 2005. Eur J Vasc Endovasc Surg 2007;34:646-54

444. AbuRahma AF, Stone PA, Srivastava M, Hass SM, Mousa AY, Dean LS, Campbell JE, Chong BY. The effect of surgeon's specialty and volume on the perioperative outcome of carotid endarterectomy. J Vasc Surg 2013;58:666-672.

Journal Pre-proof

445. Killeen, S. D., Andrews, E. J., Redmond, H. P., & Fulton, G. J. Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures. J Vasc Surg 2007;45:615-626.

446. Bastounis E, Bakoyiannis C, Cagiannos C, Klonaris C, Filis C, Bastouni EE, Georgopoulos S. A short incision for carotid endarterectomy results in decreased morbidity Eur J Vasc Endovasc Surg. 2007;33:652-6

447. Marcucci G, Antonelli R, Gabrielli R, Accrocca F, Giordano AG, Siani A. Short longitudinal versus transverse skin incision for carotid endarterectomy: impact on cranial and cervical nerve injuries and esthetic outcome. J Cardiovasc Surg. 2011;52:145-52

448. Ascher E, Hingorani A, Marks N, Schutzer RW, Mutyala M, Nahata S, Yorkovich W, Jacob T. Mini skin incision for carotid endarterectomy: a new and safe alternative to the standard approach. J Vasc Surg 2005;42:1089-93.

449. Menon NJ, Krijgsman B, Sciacca L, Arena G, Hamilton G. The retrojugular approach to carotid endarterectomy: A safer technique? Eur J Vasc Endovasc Surg 2005;29:608-10.

450. Antoniou GA, Murray D, Antoniou SA, Kuhan G, Serracino-Inglott F. Meta-analysis of retrojugular versus antejugular approach for carotid endarterectomy. Ann R Coll Surg Engl. 2014;96:184-9.

451. Tang TY, Walsh SR, Gillard JH, Varty K, Boyle JR, Gaunt ME. Carotid sinus nerve blockade to reduce blood pressure instability following carotid endarterectomy: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2007;34:304-11

452. Ajduk M, Tudoric I, Sarliia M, Pavic P, Oremus Z, Held R. et al. Effect of carotid sinus nerve blockade on hemodynamic stability during carotid endarterectomy under local anesthesia. J Vasc Surg 2011;54:386-93

453. Kakisis JD, Antonopoulos CN, Moulakakis KG, Schneider F, Geroulakos G, Ricco JB. Protamine reduces bleeding complications without increasing the risk of stroke after carotid endarterectomy: A meta-analysis. Eur J Vasc Endovasc Surg 2016;52:296-307.

454. Patel RB, Beaulieu P, Homa K, Goodney PP, Stanley AC, Cronenwett JL, et al. Shared quality data are associated with increased protamine use and reduced bleeding complications after carotid endarterectomy in the Vascular Study Group of New England. J Vasc Surg 2013;58:1518-1524.

455. Chongruksut W, Vaniyapong T, Rerkasem K. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database Syst Rev 2014; CD000190.

456. Rerkasem K, Rothwell PM. Systematic review of randomized controlled trials of patch angioplasty versus primary closure and different types of patch materials during carotid endarterectomy. Asian J Surg 2011;34:32-40.

457. Ren S, Li X, Wen J, Zhang W, Liu P. Systematic review of randomized controlled trials of different types of patch materials during carotid endarterectomy PLoS One. 8 (2013) e55050

458. Demirel S, Goosen K, Bruijnen H, Probst P, Bockler D. Systematic review and meta-analysis of post-carotid endarterectomy hypertension after eversion versus conventional carotid endarterectomy. J Vasc Surg 2017;65:868-82.

459. Martins HFG, Mayer A, Batista P, Soares F, Almeida V, Pedro AJ, et al. Morphological changes of the internal carotid artery: A clinical and ultrasonographic study in a series of 19,804 patients over 25 years old. Eur J Neurol 2018;25:171-177.

460. Ballotta, E., Thiene, G., Baracchini, C., Ermani, M., Militello, C., Da Giau, G et al. Surgical vs medical treatment for isolated internal carotid artery elongation with coiling or kinking in symptomatic patients: a prospective randomized clinical study. J Vasc Surg, 2005;42:838-846.

Journal Pre-proof

461. Zhang L, Liu X, Gong B, Luo T, Lv F, Zheng Y et al. Increased internal carotid artery tortuosity is a risk factor for spontaneous cervicocerebral artery dissection. Eur J Vasc Endovasc Surg 2021;61:542-49.

462. Naylor AR, Moir A. An aid to accessing the distal internal carotid artery. J Vasc Surg 2009;49:1345-7.

463. Yousseff F, Jenkins MP, Dawson KJ, Berger L, Myint F, Hamilton G. The value of suction wound drain after carotid and femoral artery surgery: A randomised trial using duplex assessment of the volume of post-operative haematoma. Eur J Vasc Endovasc Surg 2005;29:162-6

464. Newman JE, Bown MJ, Sayers RD, Thompson JP, Robinson TG, Williams B, et al. Post-Carotid Endarterectomy Hypertension. Part 1: Association with Pre-operative Clinical, Imaging, and Physiological Parameters. Eur J Vasc Endovasc Surg 2017;54:551-63

465. Ricco JB, Marchand C, Neau JP, Marchand E, Cau J, Fe'brer G. Prosthetic Carotid Bypass Grafts for Atherosclerotic Lesions: A Prospective Study of 198 Consecutive Cases. Eur J Vasc Endovasc Surg 2009;37:272-8.

466. Dorafshar AH, Reil TD, Ahn SS, Quinones-Baldrich WJ, Moore WS. Interposition grafts for difficult carotid artery reconstruction: A 17 year experience. Ann Vasc Surg 2008;22:63-9

467. Lauder C, Kelly A, Thompson MM, London NJM, Bell PRF, Naylor AR. Early and late outcome after carotid artery bypass grafting with saphenous vein. J Vasc Surg 2003;38:1025-30

468. Roddy SP, Darling RC, Ozsvath KJ, Mehta M, Chang BB, Paty PSK et al. Choice of material for internal carotid artery bypass grafting: vein or prosthetic? Analysis of 44 procedures. Cardiovasc Surg 2002;10:540-44

469. Veldenz HC, Kinser R, Yates GN. Carotid graft replacement: A durable option' J Vasc Surg 2005;42:220-226

470. Branchereau A, Pietri P, Magnen PE, Rosset E. Saphenous vein bypass: An alternative to internal carotid reconstruction. Eur J Vasc Endovasc Surg 1996;12:26-30

471. Koncar I, Ribac JZ, Ilic NS, Dragas M, Mutavdzic P, Tomic IZ et al. Carotid replacement with Dacron graft. Vascular 2016;24:58-9.

472. Illuminati G, Belmonte R, Schneider F, Pizzardi G, Caliò FG, Ricco JB. Prosthetic bypass for restenosis after endarterectomy or stenting of the carotid artery. J Vasc Surg 2017;65:1664-72.

473. Ricco JB, Illuminati G, Belmonte R. Resection des cancers recidivants du cou avec remplacement de l'artere carotid. JMV – Journal de Medicine Vasculaire 2017;42,282-289.

474. Stilo F, Sirignano P, Montelione N, Mansur W, Capoccia L, Catanese V, Spinelli F, Speziale F. Bypass for symptomatic in-stent carotid restenosis. Int J Cardiol 2017;249:392-395.

475. Fluri F, Engelter S, Lyrer P. Extracranial to intracranial artery bypass surgery for occlusive carotid artery disease. Cochrane Database Syst Rev 2010; :CD005953

476. Powers WJ, Clarke WR, Grubb RL, Videen TO, Adams HP, Derdeyn CP. for the COSS Investigators. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study Randomized Trial. JAMA 2011;306:1983-92

477. Gupta R, Horowitz M, Jovin TG. Hemodynamic instability after carotid artery angioplasty and stent placement: a review of the literature. Neurosurg Focus 2005 ;18:e6

Journal Pre-proof

478. Trocciola SM, Chaer RA, Lin SC, Ryer EJ, De RB, Morrissey NJ, et al. Analysis of parameters associated with hypotension requiring vasopressor support after carotid angioplasty and stenting. J Vasc Surg 2006;43:714-20

479. Kwolek CJ, Jaff MR, Leal JI, Hopkins LN, Shah RM, Hanover TM, et al. Results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal. J Vasc Surg. 2015;62:1227-34.

480. Leal I, Orgaz A, Flores Á, Gil J, Rodríguez R, Peinado J. et al. A diffusion-weighted magnetic resonance imaging-based study of transcervical carotid stenting with flow reversal versus transfemoral filter protection. J Vasc Surg. 2012;56:1585-90.

481. Kashyap VS, Schneider PA, Foteh M, Motaganahalli R, Shah R, Eckstein HH, et al. Early Outcomes in the ROADSTER 2 Study of Transcarotid Artery Revascularization in Patients With Significant Carotid Artery Disease. Stroke. 2020;51:2620-2629.

482. Mendiz OA, Fava C, Lev G, Caponi G, Valdivieso L. Transradial Versus Transfemoral Carotid Artery Stenting: A 16-Year Single-Center Experience. J Interv Cardiol. 2016;29:588-593.

483. Montorsi P, Galli S, Ravagnani PM, Tresoldi S, Teruzzi G, Caputi L, et al. Carotid Artery Stenting with Proximal Embolic Protection via a Transradial or Transbrachial Approach: Pushing the Boundaries of the Technique While Maintaining Safety and Efficacy. J Endovasc Ther. 2016;23:549-60.

484. Timaran CH, Rosero EB, Higuera A, Ilarraza A, Modrall JG, Clagett GP. Randomized clinical trial of open-cell vs closed-cell stents for carotid stenting and effects of stent design on cerebral embolization. J Vasc Surg 2011;54:1310-1316.

485. Park KY, Kim DI, Kim BM, Nam HS, Kim YD, Heo JH. et al. Incidence of embolism associated with carotid artery stenting: open-cell versus closed-cell stents. J Neurosurg 2013;119:642-7.

486. Imamura H, Sakai N, Matsumoto Y, Yamagami H, Terada T, Fujinaka T, et al. Clinical trial of carotid artery stenting using dual-layer CASPER stent for carotid endarterectomy in patients at high and normal risk in the Japanese population. J Neurointerv Surg. 2021; 13:524-529.

487. Yilmaz U, Körner H, Mühl-Benninghaus R, Simgen A, Kraus C, Walter S, et al. Acute Occlusions of Dual-Layer Carotid Stents After Endovascular Emergency Treatment of Tandem Lesions. Stroke. 2017;48:2171-2175.

488. Baldi S, Zander T, Rabellino M, González G, Maynar M. Carotid artery stenting without angioplasty and cerebral protection: a single-center experience with up to 7-years' follow-up. AJNR 2011;32:759-63.

489. Giannakopoulos TG, Moulakakis K, Sfyroeras GS, Avgerinos ED, Antonopoulos CN, Kakisis JD, et al. Association between plaque echogenicity and embolic material captured in filter during protected carotid angioplasty and stenting. Eur J Vasc Endovasc Surg 2012;43:627–631

490. Touze E, Trinquart L, Chatellier G, Mas JL. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. Stroke 2009;40:e683-693.

491. Cremonesi A, Castriota F, Secco GG, Macdonald S, Roffi M. Carotid artery stenting: an update. Eur Heart J 2015;36:13-21.

492. Badheka AO, Chothani A, Panaich SS, Mehta K, Patel NJ, Deshmukh A et al. Impact of Symptoms, Gender, Co-Morbidities, and Operator Volume on Outcome of Carotid Artery Stenting (from the Nationwide Inpatient Sample [2006 to 2010]). Am J Cardiol 2014;114:933-941

493. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M et al. The CAPTURE Registry: Predictors of Outcomes in Carotid Artery Stenting with Embolic Protection for High Surgical Risk Patients in the Early Post-Approval Setting. Cath Cardiovasc Interv 2007;70:1025-1033.

494. Nallamothu BK, Gurm HS, Ting HH, Goodney PP, Rogers MAM, Curtis JP et al. Operator experience and carotid stenting outcomes in

Journal Pre-proof

Medicare beneficiaries. JAMA 2011;306:1338–1343.

495. Setacci C, Chisci E, Setacci F, Iacoponi F, de Donato G, Rossi A. Siena carotid artery stenting score: a risk modelling study for individual patients. Stroke 2010;41:1259-65

496. Calvet D, Mas J-L, Algra A, Becquemin J-P, Bonati LH, Dobson J, Fraedrich G et al Carotid Stenting Is There an Operator Effect? A Pooled Analysis from the Carotid Stenting Trialists' Collaboration. Stroke 2014;45:527-532

497. Aronow HD, Collins TJ, Gray WA, Jaff MR, Kluck BW, Patel RA et al. SCAI/SVM Expert Consensus Statement on Carotid Stenting: Training and Credentialing for Carotid Stenting. Cath Cardiovasc Interv 2016;87:188-199.

498. Shishehbor MH, Venkatachalam S, Gray WA, et al. Experience and outcomes with carotid artery stenting: an analysis of the CHOICE study (Carotid Stenting for High Surgical-Risk Patients; Evaluating Outcomes Through the Collection of Clinical Evidence). JACC Cardiovasc Interv 2014;7:1307–1317.

499. Krul JMJ, van Gijn J, Ackerstaff RGA, Eikelboom BC, Theodorides T, Vermeulen FEE. Site and pathogenesis of infarcts associated with carotid endarterectomy. Stroke 1989;20:324-328

500. Pennekamp CW, Moll FL, de Borst GJ. The potential benefits and the role of cerebral monitoring in carotid endarterectomy. Curr Opin Anaesthesiol. 2011;24:693-697

501. Naylor A.R., Sandercock P.A.G., Sellar R.J., Warlow C.P. Patterns of vascular pathology in acute, first-ever cerebral infarction. Scot Med J 1993;38:41-44.

502. Meershoek AJA, de Waard DD, Trappenburg J, Zeebregts C, Bulbulia R, Kappelle LJ, et al. On behalf of the Delphi consensus experts panel* Clinical Response to procedural stroke following carotid endarterectomy: A Delphi consensus study. Eur J Vasc Endovasc Surg 2021;62:350-7.

503. Huibers A, de Borst GJ, Thomas DJ, Moll FL, Bulbulia R, Halliday A. The mechanism of procedural stroke following carotid endarterectomy within the Asymptomatic Carotid Surgery Trial 1. Cerebrovasc Dis 2016;42:178-185.

504. Perler BA, Murphy K, Sternbach Y, Gailloud P, Shake JG. Immediate post-operative thrombolytic therapy: An aggressive strategy for neurologic salvage when cerebral thromboembolism complicates carotid endarterectomy. J Vasc Surg 2000;31:1033-1037

505. De Borst GJ, Moll FL, van de Pavoordt HDWM, Mauser HW, Kelder JC, et al. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate. Eur J Vasc Endovasc Surg 2001;21:484-489.

506. Ferguson GG, Eliasziw M, Barr HWK et al for the NASCET Trial. The North American Symptomatic Carotid Endarterectomy Trial: Surgical results in 1415 patients. Stroke 1999;30:1751-1758.

507. Doig D, Turner EL, Dobson J, Featherstone RL, de Borst GJ, Stansby G, et al. Risk Factors For Stroke, Myocardial Infarction, or Death Following Carotid Endarterectomy: Results From the International Carotid Stenting Study. Eur J Vasc Endovasc Surg. 2015;50:688-94.

508. van den Berg JC. Neuro-rescue during carotid stenting. Eur J Vasc Endovasc Surg 2008;36:627-36.

509. MacDonald S, Lee R, Williams R, Stansby G. Towards Safer Carotid Artery Stenting. A Scoring System for Anatomic Suitability. Stroke. 2009;40:1698-1703.

Journal Pre-proof

510. Doig D, Hobson BM, Müller M, Jäger HR, Featherstone RL, Brown MM, et al. Carotid Anatomy Does Not Predict the Risk of New Ischaemic Brain Lesions on Diffusion-Weighted Imaging after Carotid Artery Stenting in the ICSS-MRI Substudy. Eur J Vasc Endovasc Surg. 2016;51:14-20.

511. De Carlo M, Liga R, Migaleddu G, Scatturin M, Spaccarotella C, Fiorina C, et al. Evolution, Predictors, and Neurocognitive Effects of Silent Cerebral Embolism During Transcatheter Aortic Valve Replacement. JACC Cardiovasc Interv. 2020;13:1291-1300.

512. Wong JH, Findlay JM, Suarez-Almazor ME. Hemodynamic instability after carotid endarterectomy: risk factors and associations with operative complications. Neurosurgery 1997;41:35-43.

513. Tan TW, Eslami MH, Kalish JA, Eberhardt RT, Doros G, Goodney PP, Cronenwett JL, Farber A; Vascular Study Group of New England. The need for treatment of hemodynamic instability following carotid endarterectomy is associated with increased perioperative and 1-year morbidity and mortality. J Vasc Surg 2014;59:16-24.

514. Mylonas SN, Moulakakis KG, Antonopoulos CN, Kakisis JD, Liapis CD. Carotid artery stenting-induced hemodynamic instability. J Endovasc Ther 2013;20:48-60.

515. Csobay-Novák C, Bárány T, Zima E, Nemes B, Sótonyi P, Merkely B, et al. Role of stent selection in the incidence of persisting hemodynamic depression after carotid artery stenting. J Endovasc Ther. 2015;22:122-9.

516. Liu J, Xu ZQ, Yi X, Wang YJ, Zhou HD. A study on related factors of hemodynamic depression in carotid artery stenting. Eur Rev Med Pharmacol Sci. 2018;22:5255-5263

517. Chung C, Cayne NS, Adelman MA, Riles TS, Lamparello P, Han D, Marin ML, Faries PL. Improved hemodynamic outcomes with glycopyrrolate over atropine in carotid angioplasty and stenting. Perspect Vasc Surg Endovasc Ther 2010;22:164-70.

518. Sharma S, Lardizabal JA, Bhambi B. Oral Midodrine is effective for the treatment of hypotension associated with carotid artery stenting. J Cardiovasc Pharmacol Ther. 2008;13:94-7.

519. Sigaudo-Roussel D, Evans DH, Naylor AR, Panerai RB, London NL, Bell P et al. Deterioration in carotid baroreflex during carotid endarterectomy. J Vasc Surg 2002;36:793-8.

520. Smith BL. Hypertension following carotid endarterectomy: the role of cerebral renin production. J Vasc Surg 1984;1:623-7.

521. Ahn SS, Marcus DR, Moore WS. Post-carotid endarterectomy hypertension: association with elevated cranial norepinephrine. J Vasc Surg 1989;9:351-60.

522. Asiddao CB, Donegan JH, Whitesell RC, Kalbfleisch JH. Factors associated with perioperative complications during carotid endarterectomy. Anesth Analg 1982;61:631-7.

523. Rerkasem K, Bond R, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2004;;CD000126.

524. Mehta M, Rahmani O, Dietzek AM, Mecenas J, Scher LA, Friedman SG et al. Eversion technique increases the risk for post-carotid endarterectomy hypertension. J Vasc Surg 2001;34:839-45.

525. Newman JN, Bown MJ, Sayers RD, Thompson J, Robinson TG, Williams B et al. Post carotid endarterectomy hypertension: Part 2: Association with peri-operative clinical, anaesthetic and transcranial Doppler derived parameters. Eur J Vasc Endovasc Surg 2017;54:564-572

Journal Pre-proof

526. Towne JB, Bernhard VM. The relationship of postoperative hypertension to complications following carotid endarterectomy. Surgery 1980;88:575-80.

527. Payne DA, Twigg MW, Hayes PD, Naylor AR. Antiplatelet agents and risk factors for bleeding post-carotid endarterectomy. Ann Vasc Surg 2010;24:900-7

528. Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. Brit J Anaes 2009;102:442-52

529. Naylor A.R., Evans J., Thompson M.M., London N.J.M., Abbott R.J., Cherryman G., Bell P.R.F. Seizures after carotid endarterectomy: Hyperperfusion, dysautoregulation or hypertensive encephalopathy? Eur J Vasc Endovasc Surg. 2003;26:39-44

530. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. Catheter Cardiovasc Interv 2007;69:690-6.

531. Kirchoff-Torres KF, Bakradze E. Cerebral hyperperfusion syndrome after carotid revascularization and acute ischemic stroke. Curr Pain Headache Rep. 2018;22:24.

532. Baptista MV, Maeder P, Dewarrat A, Bogousslavsky J. Conflicting images. Lancet 1998; 351: 414.

533. Fassaert LMM, Immink RV, vn Vriesland DJ, de Vries JPPM, Toprop RJ, Kappelle LJ et al. Transcranial Doppler 24-hours after carotid endarterectomy accurately identifies patients not at risk of cerebral hyperperfusion syndrome. Eur J Vasc Endovasc Surg 2019;58:320-327

534. Doig D, Turner EL, Dobson J, Featherstone RL, de Borst GJ, Brown MM et al. Incidence, impact and predictors for cranial nerve palsy and haematoma following carotid endarterectomy in the International Carotid Stenting Study. Eur J Vasc Endovasc Surg 2014;48:498-504.

535. Hye RJ, Mackey A, Hill MD, Vocks JH, Cohen DJ, Wang K et al. Incidence, outcomes, and effect on quality of life of cranial nerve injury in the Carotid Revascularization Endarterectomy versus Stenting Trial. J Vasc Surg 2015;61:1208-15

536. Kakisis JD, Antonopoulos CN, Mantas G, Moulakakis KG, Sfyroeras GS, Geroulakos G. Cranial nerve injury after carotid endarterectomy: Incidence, risk factors and time trends. Eur J Vasc Endovasc Surg 2017;53:320-335

537. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al. ICSS-MRI study group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol 2010;9:353-62.

538. Gargiulo G, Sannino A, Stabile E, Perrino C, Trimarco B, Esposito G. New Cerebral Lesions at Magnetic Resonance Imaging after Carotid Artery Stenting Versus Endarterectomy: An Updated Meta-Analysis. PLoS ONE 2015;10:e0129209.

539. Haddad F, Wehbe MR, Hmedeh C, Homsi M, Nasreddine R, Hoballah JJ. Bilateral Carotid Patch Infection Occurring 12 years Following Endarterectomy. Ann Vasc Surg 2020;65:285.e11-15.

540. Terzian WTH, Schadt S, Sheth SU. Right carotid-cutaneous fistula and right carotid pseudoaneurysm formation secondary to a chronically infected polyethylene terephthalate patch. Int J Crit Illn Inj Sci 2018;8:48-51

541. Bannazadeh M, Sattari AR, Skripochnik E, Tzavellas G, Tassiopoulos A. Endovascular repair of infected carotid pseudoaneurysm: A case report. Int J Surg Case Rep 2020;72:163-165

542. Naylor AR. Management of prosthetic patch infection after carotid endarterectomy. J Cardiovasc Surg 2016;57:137-44

Journal Pre-proof

543. Lazaris A., Sayers R.D., Thompson M.M., Bell P.R.F., Naylor A.R. Patch corrugation on Duplex ultrasonography may be an early warning of prosthetic patch infection. Eur J Vasc Endovasc Surg. 2005;29:91-2

544. Chakfé N, Diener H, Lejay A, Assadian O, Berard X, Caillon J, et al. European Society for Vascular Surgery (ESVS) 2020 clinical practice guidelines on the management of vascular graft and endograft infections. Eur J Vasc Endovasc Surg 2020;59:339-84.

545. Thorbjørnsen K, Djavani Gidlund K, Björck M, Kragsterman B, Wanhainen A. Long-term Outcome After EndoVAC Hybrid Repair of Infected Vascular Reconstructions. Eur J Vasc Endovasc Surg 2016;51:724-32.

546. Matano F, Suzuki M, Mizunari T, Yamada T, Murai Y, Morita A. Radial artery graft for giant common carotid artery pseudoaneurysm after carotid artery stenting. World Neurosurg 2020;139:401-4

547. AbuRahma AF, Stone P, Deem S, Dean LS, Keiffer T, Deem E. Proposed duplex velocity criteria for carotid restenosis following carotid endarterectomy with patch closure. J Vasc Surg 2009;50:286-291

548. de Borst GJ, Meijer R, Lo RH, Vosmeer HW, Ackerstaff RG, Moll FL. Effect of carotid angioplasty and stenting on duplex velocity measurements in a porcine model. J Endovasc Ther. 2008;15:672-9.

549. Lal BK, Hobson RW, Tofighi B, Kapadia I, Cuadra S, Jamil Z. Duplex ultrasound velocity criteria for the stented carotid artery. J Vasc Surg 2008;47:63-73.

550. Stanziale SF, Wholey MH, Boules TN, Selzer F, Makaroun MS. Determining in-stent stenosis of carotid arteries by duplex ultrasound criteria. J Endovasc Ther 2005;12:346-353.

551. Bosch FTM, Hendrickse J, Davagnanam I, Bonati L, van der Lugt A, van der Worp HB et al. Optimal cutoff for duplex ultrasound compared with computed tomography for the diagnosis of restenosis in stented carotid arteries in the International Carotid Stenting Study. Eur Heart J 2016;2:37-45

552. Halsey J.H., McDowell H.A., Gelmon S., Morawetz R.B. Blood flow velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. Stroke 1989;20:53-58.

553. Ballotta E, Da Giau G, Meneghetti G, Barbon B, Militello C, Baracchini C. Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: a 10-year prospective study. J Vasc Surg. 2007;45:516-22.

554. Naylor A.R., John T., Howlett J., Gillespie I., Allan P., Ruckley C.V. Fate of the non-operated carotid artery after contralateral endarterectomy. Brit J Surg 1995;82:44-48

555. Kumar R, Batchelder A, Saratzis A, Naylor AR. A systematic review and meta-analysis of restenosis rates and late ipsilateral stroke in randomised trials of carotid interventions. Eur J Vasc Endovasc Surg 2017;53:766-75.

556. Fokkema M, Vrijenhoek JEP, Den Ruijter HM, Groenwold RHH, Schermerhorn ML, Bots ML, et al. Stenting Versus Endarterectomy for Restenosis Following Prior Ipsilateral Carotid Endarterectomy. An Individual Patient Data Meta-analysis. Ann Surg 2015;261:598-604

557. Naylor AR, Mehta Z, Rothwell PM, Bell PRF. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. Eur J Vasc Endovasc Surg 2002;23:283-294.

558. Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: an updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2011;41:607-624.

Journal Pre-proof

559. D'Agostino RS, Svensson LG, Neurmann DJ, Bakkhy HH, Warren A, Williamson WA. Screening carotid ultrasonography and risk factors for stroke in coronary artery surgery patients. Ann Thorac Surg 1996;62:1714-23.

560. Stamou SC, Hill PC, Dangas G, Pfister AJ, Boyce SW, Dullum MKC et al. Stroke After Coronary Artery Bypass: Incidence, Predictors, and Clinical Outcome Editorial Comment: Incidence, Predictors, and Clinical Outcome Stroke 2001;32;1508-1513

561. Schoof J, Lubahn W, Baemer M, Kross R, Wallesch C-W, Kozian A, et al. Impaired cerebral autoregulation distal to carotid stenosis/occlusion is associated with an increased risk of stroke with cardiopulmonary bypass. J Thorac Cardiovasc Surg 2007;134:690-6.

562. Li Y, Walicki D, Mathiesen C, Jenny D, Li Q, Isayev Y, et al. Strokes after cardiac surgery and relationship to carotid stenosis. Arch Neurol 2009;66:1091-1096

563. Katz E, Tunick PA, Rusinek H, Spencer FC, Kronzon I. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: Experience with intra-operative transesophageal echocardiography. JACC 1992;20:70-77

564. Sen S, Wu K, McNamara R, Lima J, Piantadosi S, Oppenheimer SM. Distribution, severity and risk factors for aortic atherosclerosis in cerebral ischemia. Cerebrovasc Dis. 2000;10:102-9.

565. Wareing TH, Davila-Roman VG, Daily BB, Murphy SF, Schechtman KB, Barzilai B et al. Strategy for the reduction of stroke incidence in cardiac surgical patients. Ann Thorac Surg. 1993;55:1400-7

566. Aboyans V, Lacroix P. Indications for carotid screening in patients with coronary artery disease. Presse Med 2009;38:977-986.

567. Klarin D, Patel V, Zhang S, Xian Y, Kosinski A, Yeokun B et al. Concomitant carotid endarterectomy and cardiac surgery does not decrease postoperative stroke rates. J Vasc Surg 2020;72:589-96.

568. Ashrafi M, Ball S, Ali A, Zeynali I , Perricone V. Carotid endarterectomy for critical stenosis prior to cardiac surgery: Should it be done? A retrospective cohort study Int J Surg 2016;26:53-7

569. Illuminati G, Ricco JB, Calio F, Pacile MA, Miraldi F, Frati G. et al. Short-term results of a randomized trial examining timing of carotid endarterectomy in patients with severe asymptomatic unilateral carotid stenosis undergoing coronary artery bypass grafting. J Vasc Surg 2011;54:993-9

570. Timaran CH, Rosero EB, Smith ST, Valentine RJ, Modrall JG, Clagett GP. Trends and outcomes of concurrent carotid revascularization and coronary bypass. J Vasc Surg 2008;48:355-360.

571. Fareed KR1, Rothwell PM, Mehta Z, Naylor AR Synchronous carotid endarterectomy and off-pump coronary bypass: an updated, systematic review of early outcomes. Eur J Vasc Endovasc Surg. 2009;37:375-8

572. Brener BJ, Hermans H, Eisenbud D, Creighton D, Mahoney CB, Brief DK, et al. The management of patients requiring coronary bypass and carotid endarterectomy. In: Moore WS, ed. Surgery for Cerebrovascular Disease (2nd Ed). Pennsylvania: W.B Saunders, 1996; 278-287.

573. Borger MA, Fremes SE, Weisel RD, Cohen G, Rao V, Lindsay TF, Naylor CD. Coronary bypass and carotid endarterectomy: Does a combined approach increase risk? A meta- analysis. Ann Thorac Surg 1999;68:14-21.

574. Naylor AR, Cuffe RL, Rothwell PM, Bell PRF. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. Eur J Vasc Endovasc Surg 2003;25:380-389.

Journal Pre-proof

575. Sharma V, Deo SV, Park SJ, Joyce LD. Meta-analysis of staged versus combined carotid endarterectomy and coronary artery bypass grafting. Ann Thorac Surg 2014;97:102-110.

576. Naylor R, Cuffe RL, Rothwell PM, Loftus IM, Bell PR. A systematic review of outcome following synchronous carotid endarterectomy and coronary artery bypass: influence of surgical and patient variables. Eur J Vasc Endovasc Surg 2003;26:230-241.

577. Paraskevas K, Batchelder A, Bown M, Naylor AR. Carotid stenting prior to coronary bypass surgery: An updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2017;53:309-319

578. Guzman LA, Costa MA, Angiolillo DJ, Zenni M, Wludyka P, Silliman S et al. A systematic review of outcomes in patients with staged carotid artery stenting and coronary bypass graft surgery. Stroke 2008;39:361-5.

579. Naylor AR, Mehta Z, Rothwell PM. A Systematic Review and Meta-analysis of 30-Day Outcomes Following Staged Carotid Artery Stenting and Coronary Bypass. Eur J Vasc Endovasc Surg 2009;37:379-387

580. Gopaldas RR, Chu D, Dao TK, Huh J, LeMaire SA, Lin P, et al. Staged versus synchronous carotid endarterectomy and coronary artery bypass grafting: analysis of 10-year nationwide outcomes. Ann Thorac Surg 2011;91:1323-1329

581. Dubinsky RM, Lai SM. Mortality from combined carotid endarterectomy and coronary artery bypass surgery in the US. Neurology 2007;68:195-197

582. Don CW, House J, White C, Kiernan T, Weideman M, Ruggiero N, et al. Carotid revascularization immediately before urgent cardiac surgery practice patterns associated with the choice of carotid artery stenting or endarterectomy: a report from the CARE (Carotid Artery Revascularization and Endarterectomy) registry. JACC Cardiovasc Interv 2011;4:1200-1208.

583. Axelrod DA, Stanley JC, Upchurch GR, Khuri S, Daley J, Henderson W, et al. Risk for stroke after elective noncarotid vascular surgery. J Vasc Surg 2004;39:67-72

584. Sharifpour M, Moore L, Shanks AM, Didier TJ, Kheterpal S, Mashour GA. Incidence, Predictors, and Outcomes of Perioperative Stroke in Noncarotid Major Vascular Surgery. Anesth Analg 2013;116:424–34

585. Jørgensen ME, Torp-Pedersen C, Gislason GH, Jensen PF, Berger SM, Christiansen CB, et al. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. JAMA. 2014 ;312:269-77

586. Sonny A, Gornik HL, Yang D, Mascha EJ, Sessler DI. Lack of association between carotid artery stenosis and stroke or myocardial injury after noncardiac surgery in high-risk patients. Anesthesiology. 2014 ;121:922-9.

587. Kikura M, Oikawa F, Yamamoto K, Iwamoto T, Tanaka KA, Sato S, et al. Myocardial infarction and cerebrovascular accident following non-cardiac surgery: differences in postoperative temporal distribution and risk factors. J Thromb Haemost. 2008;6:742-8.

588. Parvizi J, Mui A, Purtill JJ, Sharkey PF, Hozack WJ, Rothman RH. Total joint arthroplasty: When do fatal or near-fatal complications occur? J Bone Joint Surg Am. 2007;89:27-32.

589. Bateman BT, Schumacher HC, Wang S, Shaefi S, Berman MF. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. Anesthesiology. 2009;110:231-8.

590. Huang CJ, Fan YC, Tsai PS. Differential impacts of modes of anaesthesia on the risk of stroke among preeclamptic women who undergo Caesarean delivery: a population-based study. Br J Anaesth. 2010;105:818-26.

Journal Pre-proof

591. Mashour GA, Shanks AM, Kheterpal S. Perioperative Stroke and Associated Mortality after Noncardiac, Non-neurologic Surgery. Anesthesiology 2011;114:1289–96.

592. Biteker M, Kayatas K, Türkmen FM, Mısırlı CH. Impact of perioperative acute ischemic stroke on the outcomes of noncardiac and nonvascular surgery: a single centre prospective study. Can J Surg. 2014;57:E55-61.

593. Mashour GA, Moore LE, Lele AV, Robicsek SA, Gelb AW. Perioperative care of patients at high risk for stroke during or after non-cardiac, non-neurologic surgery: Consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care. J Neurosurg Anesth 2014;26:273-85.

594. Ballotta E, Renon L, Da Giau G, Barbon B, De Rossi A, Baracchini C. Prospective Randomized Study on Asymptomatic Severe Carotid Stenosis and Perioperative Stroke Risk in Patients Undergoing Major Vascular Surgery: Prophylactic or Deferred Carotid Endarterectomy? Ann Vasc Surg 2005;19:876-881

595. Vlisides PE, Moore LE, Whalin MK, Robicsek SA, Gelb AW, Lale AV et al. Peri-operative care of patients at high-risk for stroke during or after non-cardiac, non-neurological surgery: 2020 Guidelines from the Society of Neuroscience in Anesthesiology and Critical Care. J Neurosurg Anesthesiol 2020;32:210-16

596. Van de Weijer MAJ, Vonken EP, de Vries JP, Moll FL, Vos JA, de Borst GJ. Durability of endovascular therapy for proximal stenosis of the supra-aortic arteries. Eur J Vasc Endovasc Surg 2015;50;13-20.

597. Klonaris C, Kouvelos GN, Kafezza M, Koutsoumpelis A, Katsargyris A, Tsigris C. Common carotid artery occlusion treatment: Revealing a gap in the current guidelines. Eur J Vasc Endovasc Surg 2013;46:291-298.

598. Fry WR, Marin JD, Clagett GP, Fry WJ. Extrathoracic carotid reconstruction: the subclavian-carotid artery bypass. J Vasc Surg 1992;15:83-8.

599. Takach TJ, Reul GJ, Cooley DA, Duncan JM, Livesay JJ, Takach G et al. Brachiocephalic reconstruction I: Operative and long-term results for complex disease. J Vasc Surg 2005;42:47-54.

600. Compter A, van der Worp HB, Algra A, Kappelle LJ, for the Second Manifestations of ARTerial disease (SMART) Study Group. Prevalence and prognosis of asymptomatic vertebral artery origin stenosis in patients with clinically manifest arterial disease. Stroke 2011; 42:2795–800.

601. Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. Lancet Neurol. 2013;12:989-98.

602. Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med 2005;352:2618–26.

603. Searls DE, Pazdera L, Korbel E, Vysata O, Caplan LR. Symptoms and signs of posterior circulation ischemia in the New England medical center posterior circulation registry. Arch Neurol 2012;69:346–51.

604. Khan S, Cloud GC, Kerry S, Markus HS. Imaging of vertebral artery stenosis: a systematic review. J Neurol Neurosurg Psychiatry 2007;78:1218-25.

605. Khan S, Rich P, Clifton A, Markus HS. Non-invasive detection of vertebral artery stenosis: a comparison of contrast-enhanced MR angiography, CT angiography, and ultrasound. Stroke 2009;40:3499-3503.

Journal Pre-proof

606. Davis PC, Nilsen B, Braun IF, Hoffman JC, Jr. A prospective comparison of duplex sonography vs angiography of the vertebral arteries. Am J Neuroradiol 1986;7:1059-64.

607. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchurch AM et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369:293–98.

608. Mitchell J. Doppler insonation of vertebral artery blood flow changes associated with cervical spine rotation: Implications for manual therapists. Physiother Theory Practice 2007;23:303-313

609. Sultan MJ, Hartshorne T, Naylor AR. Extracranial and Transcranial ultrasound assessment of patients with suspected positional vertebrobasilar ischaemia. Eur J Vasc Endovasc Surg 2009;38:10-13

610. Chandratheva A, Werring D, Kaski D. Vertebrobasilar insufficiency: An insufficient term that should be retired. Pract Neurol 2021;21:2-3.

611. Gulli G, Marquardt L, Rothwell PM, Markus HS. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: pooled data analysis from prospective studies. Stroke 2013;44:598–604.

612. Eberhardt O, Naegele T, Raygrotzki S, Weller M, Ernemann U. Stenting of vertebrobasilar arteries in symptomatic atherosclerotic disease and acute occlusion: case series and review of the literature. J Vasc Surg 2006;43:1145–54.

613. Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, Uyttenboogaart M, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: A randomised open-label phase 2 trial. Lancet Neurol. 2015;14:606-14.

614. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011;365:993–1003.

615. Antoniou GA, Murray D, Georgiadis GS, Antoniou SA, Schiro A, Serracino-Inglott F, et al. Percutaneous transluminal angioplasty and stenting in patients with proximal vertebral artery stenosis. J Vasc Surg. 2012;55:1167-77.

616. Tank VH, Ghosh R, Gupta V, Sheth N, Gordon S, He W et al. Drug eluting stents versus bare metal stents for the treatment of extracranial vertebral artery disease: A meta-analysis. J Neurointerv Surg 2016;8:770-4.

617. Kieffer E, Praquin B, Chiche L, Koskas F, Bahnini A. Distal vertebral artery reconstruction: long-term outcome. J Vasc Surg 2002;36:549-554.

618. Habozit B. Vertebral artery reconstruction: Results in 106 patients Ann Vasc Surg 1991;5:61-65

619. Berguer R, Flynn LM, Kline RA, Caplan L. Surgical reconstruction of the extracranial vertebral artery: management and outcome. J Vasc Surg 2000;31:9-18.

620. Hanel RA, Brasiliense LB, Spetzler RF. Microsurgical revascularization of proximal vertebral artery: a single-center, single-operator analysis. Neurosurgery 2009;64:1043-50.

621. Ramirez CA, Febrer G, Gaudric J, Abou-Taam S, Beloucif K, Chiche L, Koskas F. Open repair of vertebral artery: a 7-year single-center report. Ann Vasc Surg 2012;26:79-85

622. Coleman DM, Obi A, Criado E, Arya S, Berguer R. Contemporary outcomes after distal vertebral reconstruction. J Vasc Surg 2013;58:152-7

Journal Pre-proof

623. Mert B, Boyacioglu K, Celik D, Polat A. Surgical treatment of vertebral artery stenosis: An overlooked surgery with low morbidity Ann Vasc Surg 2020;68:141-150.

624. Jenkins JS, Stewart M. Endovascular treatment of vertebral artery stenosis. Prog Cardiovasc Dis 2017;59:619-625.

625. Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. Stroke 2011;42:2212–16.

626. Langwieser N, Buyer D, Schuster T, Haller B, Laugwitz KL, Ibrahim T. Bare metal vs. drug-eluting stents for extracranial vertebral artery disease: a meta-analysis of nonrandomized comparative studies. J Endovasc Ther. 2014;21:683-92.

627. Li MKA, Tsang ACO, Tsang FCP, Ho WS, Lee R, Leung GKK, et al. Long-Term Risk of In-Stent Restenosis and Stent Fracture for Extracranial Vertebral Artery Stenting. Clin Neuroradiol. 2019;29:701-706.

628. Li L, Wang X, Yang B, Wang Y, Gao P, Chen Y, et al. Validation and comparison of drug eluting stent to bare metal stent for restenosis rates following vertebral artery ostium stenting: A single-center real-world study. Interv Neuroradiol. 2020;26:629-36.

629. Kakino S, Ogasawara K, Kubo Y, Kashimura H, Konno H, Sugawara A, Kobayashi M, Sasaki M, Ogawa A. Clinical and angiographic long-term outcomes of vertebral artery–subclavian artery transposition to treat symptomatic stenosis of vertebral artery origin. J Neurosurg 2009;110:943–947.

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Section 14. Information for the patient.

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

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.

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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 1**). 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.

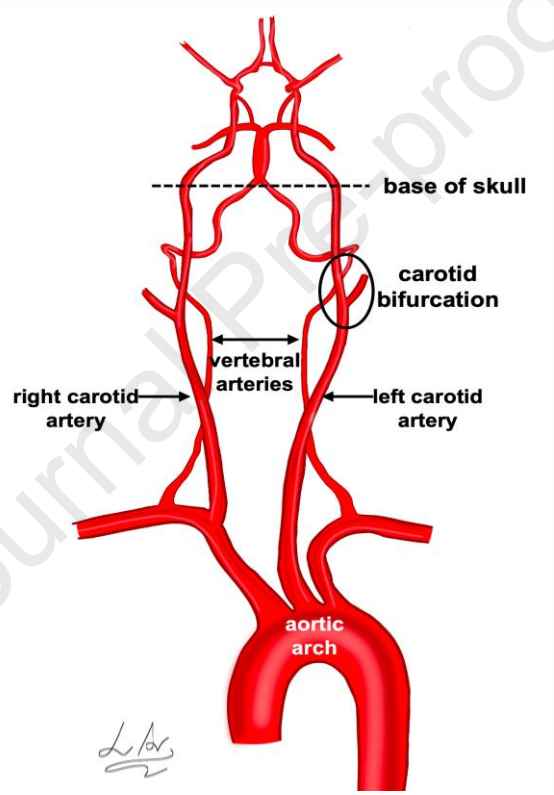


Figure 1: main blood supply to the brain comes from the carotid and vertebral arteries.

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 1**).

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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 amongst experts that the treatment is beneficial, useful, or effective) to III (agreement that the treatment is not effective or may be harmful).

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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.

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 (eg. 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 2**). 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 3**).

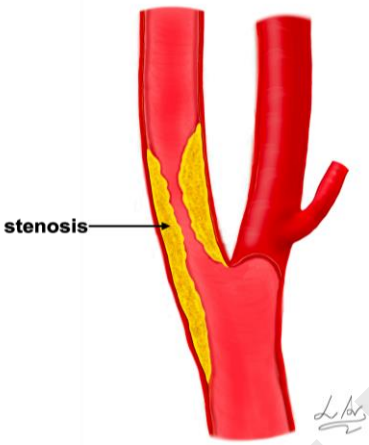


Figure 2
stenosis in the carotid artery

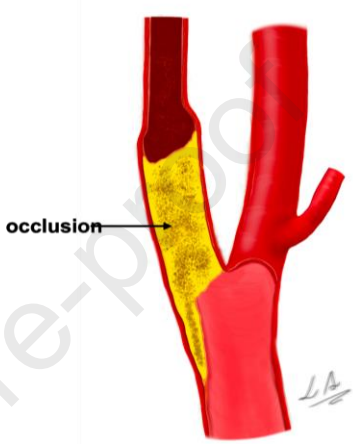


Figure 3
occlusion of the carotid artery

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

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factors for vascular disease (eg. 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.

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 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 4**).

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Figure 4: Emboli (made up of plaque debris and small blood clots) break off the narrowing and go up into the brain.

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 but 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 (eg. 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

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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.

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, in order 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.

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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.

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

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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.

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).

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 (eg. 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	
Non-diabetic patients	Under 65 years = <130/80mmHg 65 years and over = systolic 130-139mmHg and diastolic <80mmHg
Diabetic patients	Under 65 years = systolic 120-129mmHg)

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	= diastolic 70-79mmHg) 65 years and over = systolic 120-139mmHg = diastolic 70-79mmHg)
Cholesterol	
Total cholesterol LDL 'bad' cholesterol LDL 'bad' cholesterol in higher risk patients	<3.5mmol/L (<135mg/dL) <1.8mmol/L (<70mg/dL) <1.4mmol/L (<54mg/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.

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 in order to place a stent (a metallic meshlike cylinder) inside the carotid artery to open up the narrowing.

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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.

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 5**), and a medicine called heparin is given to prevent blood clots forming during the procedure. The carotid artery is then clamped and opened (**Figure 6**).



Figure 5
site of incision in the carotid artery (dotted line)



Figure 6
carotid artery is opened to reveal the narrowing

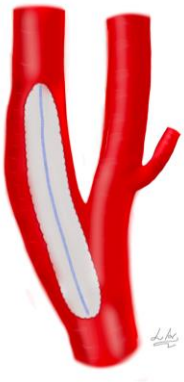


Figure 7
the narrowing is removed and the artery closed with a patch

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 7**) in order to make it a little wider and so reduce the chance of further narrowings developing in the future. The operation takes about 1 - 2 hours. When it is finished, you will be kept in the 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 commonest 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.

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 8**). As with carotid endarterectomy, you will be given heparin to reduce the chance of blood clots forming on the surface of the stent.



Figure 8
a catheter containing the stent is positioned within the stenosis and is then slowly opened out



Figure 9
once the stent has opened, the wires and catheters are removed

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.

The stent is then carefully positioned within the narrowed artery and released, which causes it to open within the artery (**Figure 9**). The operator will take lots of Xray 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.

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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.

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.

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

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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.

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.

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