Stroke risk management in carotid atherosclerotic disease:

A Clinical Consensus Statement of the ESC Council on Stroke and the ESC Working Group on Aorta and Peripheral Vascular Diseases

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Abstract

Carotid atherosclerotic disease continues to be an important cause of stroke, often disabling or fatal. Such strokes could be largely prevented through optimal medical therapy and carotid revascularization. Advancements in discovery research and imaging along with evidence from recent pharmacology and interventional clinical trials and registries and the progress in acute stroke management have markedly expanded knowledge base for clinical decisions in carotid stenosis. Nevertheless, there is variability in carotid-related stroke prevention and management strategies across medical specialities. Optimal patient care can be achieved by (1) establishing a unified knowledge foundation and (2) fostering multi-specialty collaborative guidelines. The emergent Neuro-Vascular Team concept, mirroring the multi-disciplinary Heart Team, embraces diverse specializations, tailores personalized, stratified medicine approaches to individual patient needs, and integrates innovative imaging and risk-assessment biomarkers. Proposed approach integrates collaboration of multiple specialists central to carotid artery stenosis management such as neurology, stroke medicine, cardiology, angiology, ophthalmology, vascular surgery, endovascular interventions, neuroradiology and neurosurgery. Moreover, patient education regarding current treatment options, their risks and advantages, is pivotal, promting patient's active role in clinical care decisions. This enables optimization of interventions ranging from lifestyle modification, carotid revascularization by stenting or endarterectomy, as well as pharmacological management encompassing statins, novel lipid-lowering and antithrombotic strategies and targeting inflammation and vascular dysfunction.

This consensus document provides a harmonized multi-specialty approach to multimorbidity prevention in carotid stenosis patients, based on comprehensive knowledge review, pinpointing research gaps in an evidence-based medicine approach. It aims to be a foundational tool for interdisciplinary collaboration and prioritized patient-centric decision-making.

Keywords

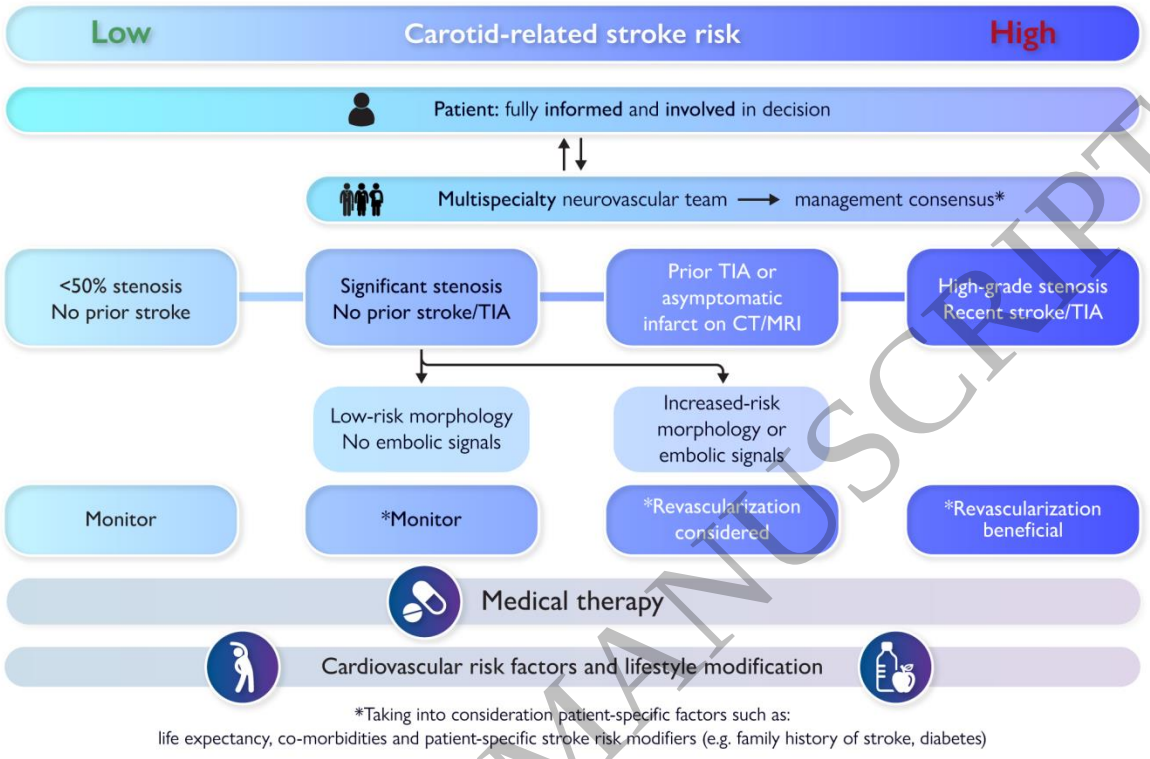
•Atherosclerotic carotid disease •Evidence base •State-of-the art review •Recent trials and registries •Stroke risk reduction •Imaging •Biomarkers •Antithrombotic management •Interventional management •Mutlispecialty team •Neuro-Vascular team

Frame 1. List of abbrevaitions

AsxCs – asymptomatic (absence of clinical symptoms) atherosclerotic carotid artery stenosis
CABG – coronary artery bypass graft
CAD – coronary artery (atherosclerotic) disease
CAS – carotid artery stenting
CarAD – carotid atherosclerotic disease
CEA – carotid endarterectomy
CI – confidence interval
CT – computed tomography
CTA – computed tomography angiography
DAPT – double antiplatelet therapy
DUS – duplex ultrasound
DWI – diffusion-weighted magnetic resonance imaging
FLAIR – fluid-attenuated inversion recovery (imaging)
^{18}F-FDG – ^{18}F-fluorodeoxyglucose
GA – general anaestheia
GITR – glucocorticoid induced tumour necrosis factor receptor family-related protein
HR – hazard ratio
ICA – internal carotid artery
IPH – intra-plaque haemorrhage
LA - local anaesthesia
mAHEI – modified alternative Healthy Eating Index,
MCA – middle cerebral artery
MRA – magnetic resonance angiography
mRS – modified Rankin score
MRI – magnetic resonance imaging
NASCET [method] – North American Symptomatic Carotid Endarterectomy Trial [method of evaluation carotid stenosis severity]
NICE – [UK] National Institute for Health and Clinical Excellence
NOAC – Non-vitamin K Antagonist Oral Anticoagulant
OMT – optimized medical therapy
OR – odds ratio
PAD – peripheral artery (atherosclerotic) disease
PCSK9 – protein called proprotein convertase subtilisin/kexin type 9

PET – positron emission tomography
RCT – ramdomized controlled trial
SAPT – single antiplatelet therapy
TIA – transient ischaemic attack
TCAR – trans-carotid artery revascularization
TF – trans-femoral
TR – trans-femoral

Central Illustration



Grpahical abstract: stroke risk stratification determines management of carotid stenosis.

The graphic illustrates, from left to right, the gradient of stroke risk. ”Significant” stenosis is typically defined as ≥50% reduction of the carotid artery luminal diameter. Patients with increased stroke risk should be evaluated for revascularization on top of cardiovascular risk factors and lifestyle modification and optimized medical therapy. The decision on performing vs. deferring revascularization should ideally be based on a multidisciplinary (Neuro-Vascular Team) consensus statement. To assist the patient in their decision, Neuro-Vascular Team may also advise a preferred revascularization mode (according to patient-specific factors and local expertise). The patient, holding a central position in the decision process regarding their care, requires full information about disease-related stroke risk and treatment options, including risks associated with the different treatments and their advantages.

INTRODUCTION

Carotid atherosclerotic disease (CarAD) continues to be an important cause of stroke,[1] and carotid-related strokes are often disabling or fatal.[2] Despite progress in stroke prevention and therapies, stroke incidence and overall stroke burden are projected to increase in Europe over the next decades.[3,4] Multiple modeling approaches show that in Europe, by 2047, there will be an additional 40 000 incident strokes (+3%) and the population of stroke-affected individuals wil increase by 2.58 (+27%).[5] Importantly, carotid-related strokes are potentially preventable with medical therapy and carotid revascularization by carotid endarterectomy (CEA) or carotid artery stenting (CAS). Optimal treatment strategies depend on patient factors and available local expertise, and patients with atherosclerotic carotid stenosis benefit from multi-speciality decision-making and treatment within a Neuro-Vascular Team, including specialists in the medical, surgical and endovascular treatment of carotid artery stenosis. This is analogous to the multi-disciplinary Heart Team decision-making concept in patients with coronary artery disease.[6]

The evidence base and innovation for CarAD treatments have evolved since it was last addressed in the 2017 ESC guidelines,[7] with new randomised trial data, observational studies, and improvements in the medical, surgical and endovascular treatments for CarAD. This clinical consensus statement provides a state-the-art review of the current knowledge base and an update on the contemporary clinical management of CarAD, complementing recent European and American guidelines[8-10] which vary in methodology and perspective.[11-13] To develop an effective consensus update on the contemporary management of carotid atherosclerotic disease, ESC Council on Stroke Scientific Documents Task Force and ESC Working Group on Aorta and Peripheral Arterial Disease set up in 2021 a multispecialty expert panel from Europe and USA. The panel involved different specialties that provide patient advice and care covering the spectrum and stages of carotid disease (neurology and stroke medicine, angiology,

ophthalmology, vascular surgery, endovascular interventions, cardiology, neuroradiology and neurosurgery), and it also included a representative of patient interests.

A diverse author group, including key opinion leaders of different specialities, both non-interventional and interventional, enabled – along with a representative of patients interests – a balanced approach. This clinical consensus statement not only considers data from the large number of high-quality randomised trials in CarAD, but also incorporates evidence from mechanistic studies and large observational studies and procedural registries which may more accurately describe contemporary procedural risks of carotid intervention.

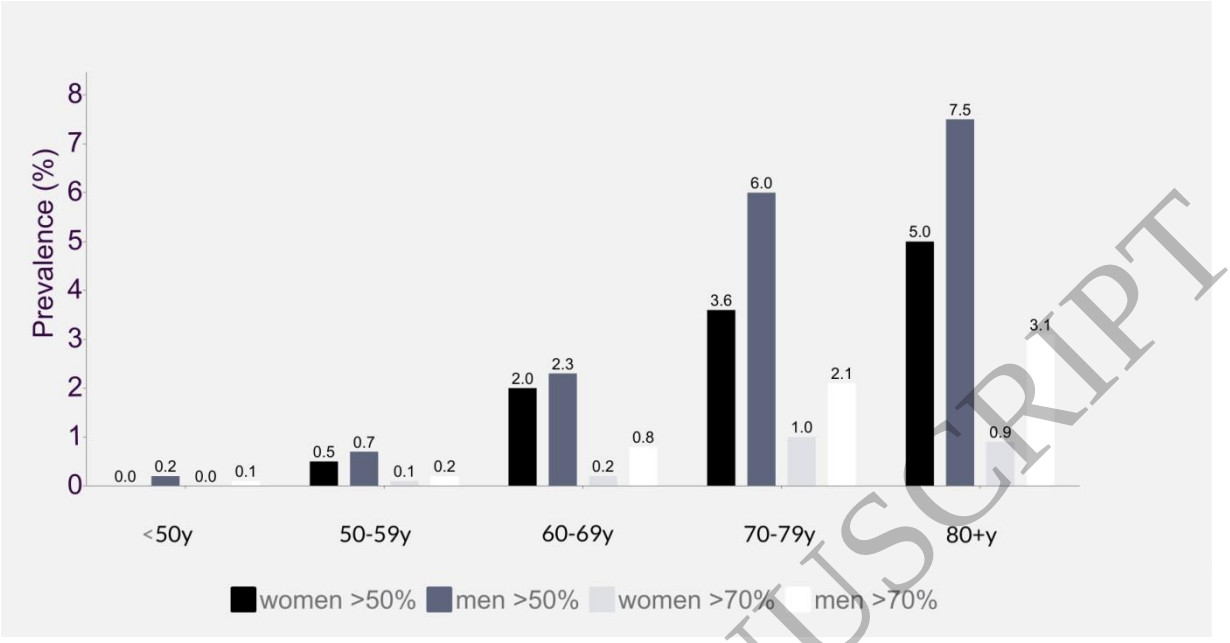
EPIDEMIOLOGY AND RISK FACTORS

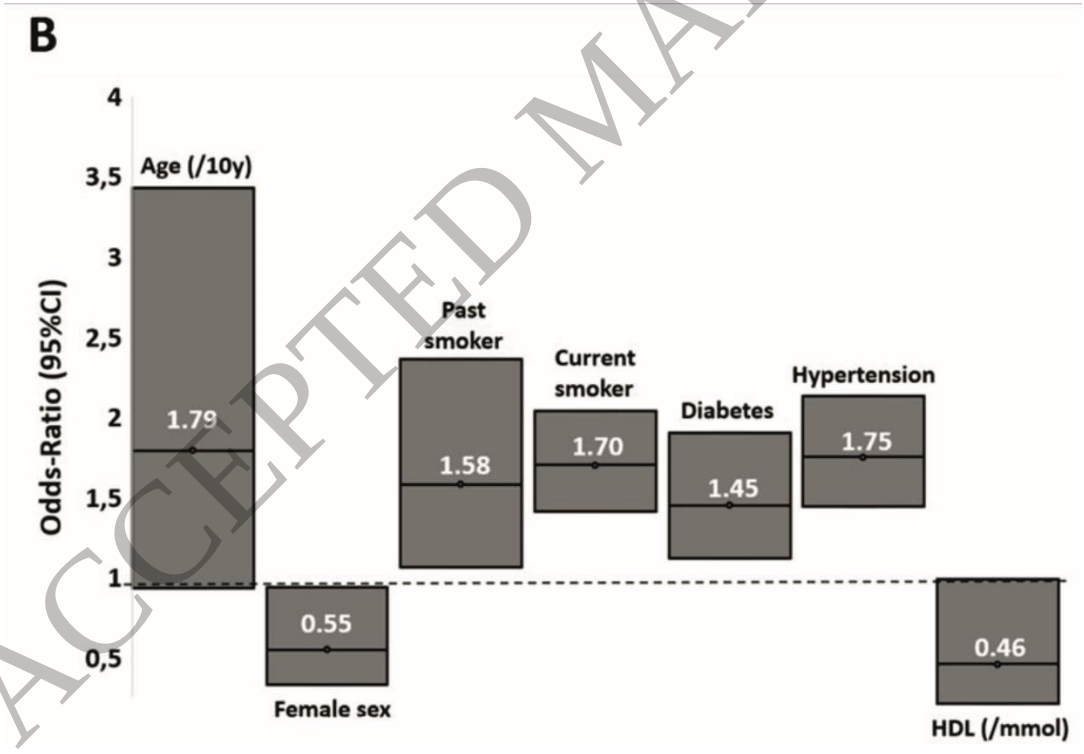
CarAD underlies 15% to 20% of ischaemic strokes.[14,15] In symptomatic patients the risk of stroke generally increases with an increase in stenosis severity.[16] Asymptomatic lesions above the threshold of ≈50-60% luminal diameter stenosis may show a less clear relationship between increasing stenosis severity and stroke risk,[17,18] consistent with the findings that lesional characteristics other than the luminal stenosis severity may play an important role in modulating the stroke risk.[19] Some observational data suggest that stroke risk with CarAD may have declined recently due to improved medical management, specifically an increase in the adoption of anti-thrombotic, anti-hypertensive and LDL cholesterol-lowering therapies (ie, 'triple medical therapy').[20] However, there is no randomized evidence for efficacy of pharmacologic therapy in reducing the risk of carotid-related strokes, and no evidence that medical therapy could be sufficient to control carotid-related stroke risk. Patients with "tandem" lesions (carotid artery occlusion/subocclusion plus intracranial large artery occlusion) constitute 20-30% of contemporary acute ischaemic stroke population.[1] CarAD not only remains an important cause of stroke, but it is also a marker of an increased risk of myocardial infarction and other ischaemic cardio-vascular events.[6]

CarAD is a broad diagnostic term, ranging from haemodynamically insignificant carotid plaques to tighter (>50%) stenoses. Observational data on CarAD prevalence and consequent stroke risk are prone to the population and inter-observer variability, and are also affected by imaging modality and the method to calculate stenosis severity.[21] The prevalence of tight carotid artery disease rises sharply with age and is higher in men. In an individual participant data meta-analysis of 4 population-based studies (23 706 participants), the prevalence of >50% stenosis increased from 0.2% in male participants <50 years to 7.5% in those >80 years, with corresponding rates of 0.1% to 3.1% in women. (Fig 1A) [22] The global burden of CarAD is high. In a recent systematic review the number of individuals of 30-79 years worldwide with any carotid plaque was estimated at 816 million people, including 137.6 million in Europe. The same study estimated that 58 million individuals worldwide had carotid stenosis (1.5%). [23] CarAD is driven by traditional cardiovascular risk factors (Fig 1B),[23] and patients with atherosclerotic disease in other vascular beds are at increased risk of CarAD. For example, the prevalence of carotid stenosis is 5% - 9% in patients with coronary artery disease (CAD) and 14% - 19% in patients with peripheral artery disease (PAD).[7]

Fig 1.

A





Epidemiology of carotid atherosclerotic disease (CarAD). A – prevalence of carotid stenosis >50% and >70% in 4 population-based epidemiological studies (adapted from de Weerd et al.[22]). B – Association of cardiovascular risk factors with carotid plaque (adapted from Song et al.[23]).

DISTINCT PATHOPHYSIOLOGIC FEATURES OF CAROTID ATHEROSCLEROSIS

Substantial part of the knowledge base regarding mechanisms of atherosclerosis in humans originates from carotid plaque studies.[24-31] Although mechanisms of atherosclerosis appear to be broadly similar between the different vascular beds, increasing evidence suggests that carotid atherosclerotic plaques have some distinct features that may translate into the need for specific therapeutic approaches.[32-34] Transcriptomic identification of carotid atherosclerotic plaque components using single cell RNA sequencing[35] demonstrated differences in gene expression in ruptured carotid plaques in relation to the location along flow direction. Ruptures were less common at distal locations and occurred predominantly proximally to, or in the maximally stenotic regions. The rupture sites were characterized by a marked endothelium damage and thrombosis. The proinflammatory profile in plaque's proximal areas involved immune cells such as macrophages, T, B, and natural killer cells, whereas distal regions had more smooth muscle cells.[36] Martix metalloproteinase 9, immunoglobulin kappa constant, and phospholamban were the 3 most differentially expressed genes between the high and low risk regions of carotid plaques.[36] Moreover, martix metalloproteinase expression has been linked to carotid stiffness.[37] Neovascularization, an important marker of plaque vulnerability that today can be evaluated non-invasively with contrast-enhanced ultrasound and dynamic contrast-enhanced magnetic resonance imaging,[38,39] is more prevalent in carotid lesions of diabetic (vs non-diabetic) patients.[39] Rearrangement of cellular components and extracellular matrix in diabetes results in adverse vessel wall remodeling that involves changes in elastin structure and extensibility[40] and remodeling of the capillaries.[41] Diabetic intra-plaque new vessel formation due to excessive/abnormal neovasculogenesis and angiogenesis[42,43] increased vascular permeability of the capillary vessels and tissue edema, result in frequent atherosclerotic plaque hemorrhage and plaque rupture.[43] In plaques from patients with diabetes/pre-

diabetes surface thrombi persist for longer after ischaemic symptoms compared to plaques from patients with normal glucose tolerance; this may contribute to the increased risk of recurrent carotid-related stroke that is associated with diabetes/ pre-diabetes. [44]

Recent comparison of carotid endarterectomy specimens obtained from patients with cerebrovascular events (n = 100) compared to asymptomatic patients (n = 93) demonstrated an elevated expression of glucocorticoid induced tumour necrosis factor receptor family-related protein (GITR) that correlated with parameters of plaque vulnerability, including plaque macrophage, lipid and glycophorin A content, and levels of interleukin (IL)-6, IL-12, and C-C-chemokine ligand 2.[31] GITR is a co-stimulatory immune checkpoint protein that drives atherosclerosis, thereby inducing plaque growth and vulnerability.[45] Depleting GITR reduced atherosclerotic plaque development in mice, suggesting that GITR may pose a novel therapeutic target in atherosclerosis to impede plaque progression and prevent plaque rupture, while leaving the adaptive immune system intact.[31]

With regard to the trigger of clinical ischaemic events, differences have been reported in relation to prevalence of atherosclerotic plaque erosion as the underlying mechanism in the coronary tree compared to carotid arteries. Coronary plaque erosion is found in 20–40% of young female smokers suffering from sudden death. In contrast, plaque erosion is far less frequent in the carotid arteries. [46] In coronary plaques, the thickness of rupture-prone fibrous cap is estimated at ≈65μm.[47] In contrast, in carotid vulnerable lesions, the risk of plaque rupture and thrombosis occurs at a much greater cap thickness (≈200μm).[30,32,44] This difference has not only important pathophysiologic consequences but it is also relevant in the context of resolution of the different non-invasive and invasive visualization techniques. [33,48]

Plaque content and prevalence of certain plaque phenotypes is different in carotid vs coronary arteries. For instance, carotid plaques generally express a higher proportion of the fibro-fatty component[34]

Nodular calcifications and the projecting calcific nodules (vulnerable) plaque phenotype, are more common in males and occur less frequently in the coronary than the carotid arteries where they may be related to plaque haemorrhage. [33] In a population-based Rotterdam Study, carotid plaque composition was examined with high-resolution magnetic resonance imaging in relation to stroke and coronary artery disease (CAD) in 1,349 participants (mean age of 72; half of whom female) with subclinical atherosclerosis and no prior history of stroke or CAD.[49] Intraplaque haemorrhage was identified as an independent risk factor for stroke, suggesting its potential as a marker for carotid plaque vulnerability in those with subclinical atherosclerosis. [49,50]

Meta-analysis of 42 articles reporting fundamental carotid plaque characteristics, including calcifications, lipid-rich necrotic core, intraplaque hemorrhage, thin or ruptured fibrous cap, plaque ulceration, degree of stenosis, plaque size, and plaque inflammation, revealed sex differences in carotid atherosclerosis. [51] Men had more frequently a larger plaque compared to women (in whom the lesions are generally smaller in volume) and, in addition, had more often plaques with calcifications (odds ratio=1.57 [95% CI, 1.23-2.02]), lipid-rich necrotic core (odds ratio=1.87 [95% CI, 1.36-2.57]), and intraplaque hemorrhage (odds ratio=2.52 [95% CI, 1.74-3.66]), or an ulcerated plaque (1.81 [95% CI, 1.30-2.51]). Furthermore, pronounced sex differences existed for lipid-rich necrotic core in symptomatic opposed to asymptomatic participants, highlighting that sex may be an important variable to include in both study design and clinical-decision making.[51]

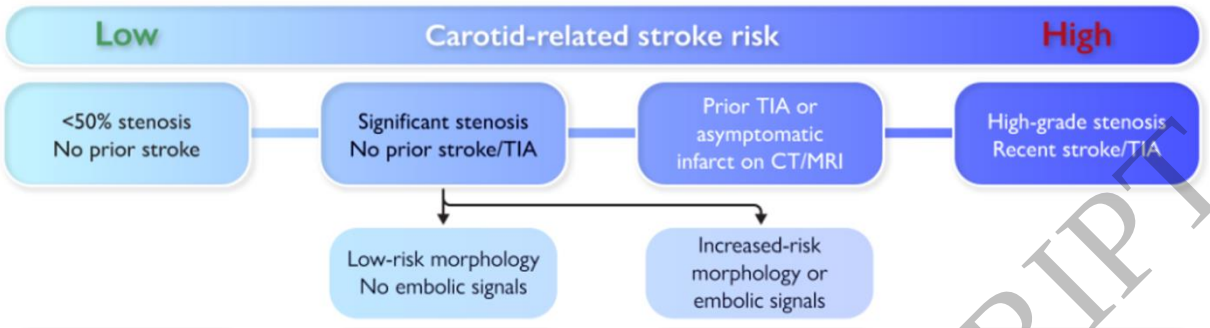
Finally, in coronary atherosclerosis, impaired plasma fibrin clot properties have been shown to increase the risk of myocardial infarction and cardiac death. [52-56] The role of fibrin clot properties as a modulator of carotid-related stroke risk is yet to be elucidated.

CLINICAL PRESENTATIONS OF CarAD

Asymptomatic carotid stenosis

An asymptomatic carotid stenosis (AsxCS) is a lesion that has never caused neurological symptoms. A more commonly used definition is stenosis without an associated and recent (typically, <6 months, though the "symptomatic" cutoffs may vary between 1-12 months or include even remote symptoms[57] of ipsilateral stroke, transient ischaemic attack (TIA) or episode of transient mono-ocular blindness. Patients with a history of contralateral or posterior circulation stroke or TIA, and also patients with evidence of silent brain infarction on cross-sectional brain imaging or retinal emboli (e.g., detected at diabetic retinopathy screening) with ipsilateral carotid stenosis are conventionally considered 'asymptomatic', despite clear evidence of prior brain infarction. Therefore, AsxCS population reflects a broad spectrum of patients, some of whom are at a higher risk of stroke. (Fig 2)

Fig 2. Spectrum of Stroke Risk in individuals with CarAD



This heterogeneity is reflected in clinical studies of ASxCS disease: those at higher stroke risk tend towards interventional management,[58,59] and are less likely to be included in either observational studies of medical therapy alone or randomized trials comparing medical therapy alone versus carotid surgery or stenting. Conversely, those at lower stroke risk are unlikely to be randomized to trials comparing two invasive treatment options, and much more likely to be included in observational 'natural history studies'. This important subtlety should be considered when interpreting trial results and deciding upon treatment strategies.

Symptoms of carotid stenosis

Most symptoms caused by CarAD arise from plaque inflammation and disruption with subsequent embolism of locally formed thrombus or plaque debris, leading to occlusion of retinal or cerebral arteries, most commonly in the anterior circulation (athero-thromboembolism).[60] With a high-grade stenosis or occlusion, carotid-related cerebral ischaemia may also arise from flow reduction (a haemodynamic mechanism). Focal neurological deficits caused by cerebral ischaemia lasting <24 hours (but more typically, <60 minutes) are called TIA, while the clinical definition of ischemic stroke usually involves symptoms lasting >24 hours.[61] Patients with TIA caused by carotid stenosis are at a markedly increased risk of stroke, up to 20% in the first three months in studies performed two decades ago,[62,63]

but ≈6% in the first year in a more recent registry.[64,65] Still, carotid stenosis >50% is been the strongest predictor of a new vascular event after TIA.[66] Focal neurological symptoms include, alone or in combination, motor (e.g. isolated paresis of the hand, arm, arm and face, or – more rarely – the leg) or sensory deficits, aphasia (in the left hemisphere), hemineglect (predominantly in the right hemisphere), and hemianopsia (in the case of optic tract involvement, or – more rarely – if the posterior cerebral artery originates from the carotid artery). Another recognized stroke mechanism includes thrombus propagation from an occluded carotid artery, manifested by symptom progression over hours to days ("stuttering stroke"/aggravating stroke), and haemodynamic impairment leading to a reduction in cerebral perfusion, which may be associated with positive motor phenomena, so-called "limb-shaking TIA".[67]

Depending on the efficacy of compensatory collateral supply via the circe of Willis and/or the external carotoid artery, internal carotid artery occlusion may present a whole spectrum of symptom gravity, from clinically silent to catastrophic.

Ocular presentations related to carotid artery stenosis

Carotid artery stenosis involving either the internal carotid artery or the ophthalmic artery can cause a variety of ocular manifestations. Retinal artery occlusion or embolism can be clinically silent or present as ocular symptoms. Transient mono-ocular visual loss (amaurosis fugax) and retinal stroke are common modes of presentation, but several other chronic ocular signs and symptoms (ocular ischaemic syndrome) should trigger a request for a carotid artery duplex scan or alternative carotid imaging. For details, see Suppl Table 1 in Appendix 1.

IMAGING OF CAROTID ARTERY DISEASE

Evaluating plaque morphology to assess stroke risk

In addition to the degree of stenosis, carotid plaque morphology and composition may affect stroke risk, and may thus it may play an important role in CarAD risk stratification and contemporary clinical decisions.[7,19,68]

Several non-invasive and invasive imaging modalities can be used,[69,70] including ultrasound (transcutaneous[71,72] and intravascular with the "virtual histology" modality[73,74]), computed tomography (CT)[75], Magnetic resonance imaging (MRI)[19,50,76,77] and positron emission tomography (PET).[78,79] The following features are suggestive of vulnerable carotid plaques: increased plaque volume/carotid wall thickness, DUS echolucency, increased inflammation, neovascularisation, intra-plaque haemorrhage (IPH), ulcerations and endothelial erosions, lipid-rich necrotic cores, ruptured fibrous cap, as well as microbubbles and discordant flow.[68,80-82]

Inflammation[83-87] and microcalcification[33,88,89] are interrelated processes importantly contributing to carotid atherosclerotic plaque vulnerability; both can be non-invasively tracked in vivo using dual-tracer PET (inflammation – ^{18}F-fluorodeoxyglucose, ^{18}F-FDG; microcalcification – ^{18}F-sodium fluoride).[90,91]

^{18}F-FDG-PET reveals inflammation in ≈30% carotid atherosclerotic lesions.[92] Recent systematic review and meta-analysis of 14 articles (539 patients) demonstrated that ^{18}F-FDG-PET – detected carotid plaque inflammation is a significant marker of symptomatic disease.[93] Apart from serving a marker of atherosclerotic disease activity, ^{18}F-FDG-PET can serve as a surrogate for effectiveness of inflammation-reducing drugs.[94] Three time point ^{18}F-FDG PET carotid plaque imaging demonstrated that statin's anti-inflammatory effect continues throughout its use up to 1 year, even though yielding stable below-target plasma LDL-C levels at 3 months.[95] Meta-analysis of eleven cohorts including a total of 290 subjects

scanned with ^{18}F-FDG PET demonstrated that carotid arteries ipsilateral to recent cerebral ischemic events had significantly higher ^{18}F-FDG uptake than asymptomatic arteries (Cohen's d =0.492; CI=0.130-0.855; P=0.008) regardless of degree of carotid stenosis, [96] suggesting a potential role for ^{18}F-FDG PET asa an aid in clinical decision-making.[97] Indeed, ^{18}F-FDG PET may also

With regard to clinical use feasibility, IPH on MRI currently apears the leading non-invasive risk factor of ipsilateral ischemic strokes (hazard ratio [HR] 10.2; 95% confidence interval [CI]: 4.6 to 22.5) for symptomatic and HR 7.9; 95% CI: 1.3 to 47.6 for asymptomatic individuals).[19,76,77,99] In addition, plaque progression is a feature of a biologically active plaque that may be associated with an increased stroke risk.[68,81,100-103]

Estimation of severity of carotid stenosis

Accurate assessment of stenosis severity is important because stenosis severity remains a fundamental parameter in decisions regarding patient care.[7-10] In asymptomatic patients, intervention is considered when the degree of stenosis exceeds 60-70%.[5-8] In symptomatic cases, the threshold for intervention is >50%, and the risk of recurrent stroke rises sharply with the degree of stenosis.[7,18]

The first line investigation is Duplex ultrasound (DUS) scanning, which is cheap, non-invasive and safe. DUS is effective in identifying carotid stenosis but its accuracy in any precise determination of moderate-to-high-grade stenosis severity is rather poor.[7,104-106] Recent analysis of >33,000 DUS recordings in 338 accredited DUS labs demonstrated that whether or not a person is said to have moderate carotid stenosis and enters surveillance, and whether or not they "have" severe stenosis and are candidates for revascularization, can depend on which center performs their ultrasound.[106] Cross-sectional angiography, by either CT (CTA) or MR (MRA), are alternative and can also image the cerebral circulation proximal and

distal to the carotid bifurcation. With DUS use for stenosis severity evaluation, 1 out of 6 arteries would be reclassified by CTA.[107]

The severity of stenosis is typically assessed using the "NASCET" method, which uses the "normal diameter" distal to the stenosis as a reference for the narrowest part of the stenosis (smallest diameter)[108] and is expressed as % diameter stenosis. Stenosis can also be measured from CTA and/or MRA, often expressed as % area (rather than diameter) stenosis.[109,110] The relationship between diameter stenosis and area stenosis is non-linear[111-112] as it is determined by the $\pi \times (d/2)^2$ formula. With a concentric lumen reduction, 50% area stenosis corresponds to 75% diameter stenosis, and 75% diameter stenosis is 94% area stenosis.[112] Some trials have used one specific imaging modality to determine the stenosis severity inclusion criterion;[113,114] others have applied different thresholds depending on the imaging modality used or developed detailed algorithms for stenosis severity verification.[115] As using different imaging modalities and measurement methods can impact management decisions,[61] when applying trial evidence to clinical decisions regarding their patients, clinicians should best consult the stenosis measurement method(s) in individual trials. Because of clinically important measurement outcomes, the "% stenosis" measurement methods using different guideline-approved imaging modalities may require rectification in future guidelines.

With increasing stenosis severity, there is an increase in blood flow velocities measured by DUS.[111] Validation of DUS velocities as a tool to determine stenosis severity was performed against the classic measurement of angiographic diameter stenosis.[116] Although ultrasound velocities predict ≥50% diameter stenosis (with a cutoff of ≈2.5 m/s for peak-systolic velocity and of ≈0.7 m/s for end-diastolic velocity),[117] DUS may fail in any precise determination of stenosis severity. In a recent validation of routine non-invasive techniques against the vascular imaging "gold" standard, intravascular ultrasound, CTA was found to be the sole independent non-invasive imaging modality.[117] While DUS remains the

first-line imaging modality in identifying carotid stenosis, 2017 ESC guidelines recommend CTA (or MRA) for evaluating stenois severity prior to any intervention.[7] Nevertheless, according to a recent study, CTA overestimation error of % diameter stenosis may result in wrong classification of ≈20% lesions (patients) compared to intra-arterial catheter evaluation that is routinely performed with the endovascular method of carotid revascularization.[118] A prospective study of early recurrent stroke prediction in patients within 30 days from carotid-related non-severe stroke (modified Rankin score ≤3) or TIA (derivation cohort of 109 patients, validation cohort of 87 patients) suggested that a combined stenosis (CTA, NASCET method)–inflammation (^{18}F-FDG uptake) strategy could improve selection for carotid revascularization where benefit is currently uncertain[119] but larger studies in lower-risk populations are needed. Algorithms combining evaluation of stenosis severity with that of plaque morphology are likely to play an increasing role in clinical decisions on carotid revascularization.[19,119] 3D Ultrasound is a new promising technique that must yet establish its clinical role in assessing the degree of stenosis, and plaque volume and morphology.[120,121]

Cerebral ischemic changes due to carotid stenosis

The most sensitive method of detecting recent cerebral ischaemia is diffusion-weighted magnetic resonance imaging (DWI), which shows potentially reversible cellular energy failure and early cytotoxic oedema (cell swelling) as areas of hyperintense signal within minutes of ischaemia onset.[122] DWI lesions do not indicate cell death, and they may be reversible, particularly if small and/or acted upon quickly.[123,124] Once ischemia causes cellular death, hyper-intense lesions become visible on fluid-attenuated inversion recovery (FLAIR) imaging. The typical finding in embolic stroke arising from carotid disease is multiple small cortical infarcts located in the territory of the middle cerebral artery and vascular border-zone areas between the middle, anterior and posterior cerebral arteries.[125]

Haemodynamic cerebral lesions typically occur in watershed zones. DWI/FLAIR may define tissue infarction even among patients with transient symptoms without a persisting deficit (ie, a TIA). In a recent study which included 633 patients with a TIA, a positive DWI was associated with an increased 10-year risk of recurrent ischemic stroke after an index TIA (hazard ratio [HR] 2.66, 95%confidence interval [CI] 1.28-5.54, p = 0.009).[125,126] While stroke is a cerebral *emergency*,[127,129] TIA is a cerebral *urgency* that should prompt rapid assessment, including brain and carotid imaging.[126,131,132] The UK National Institute for Health and Clinical Excellence (NICE) has recently recommended same-day MRI (including DWI and FLAIR sequences) and carotid artery imaging with Duplex Doppler ultrasound or computed tomography/magnetic resonance angiography (CTA/MRA) for all patients presenting with a suspected stroke or TIA.[126] A more recent definition of stroke is "[…] cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury".[61] According to this increasingly adopted definition, stroke is diagnosed in the presence of brain infarction on DWI/FLAIR, even if the associated symptoms are only transient.[133]

A clinically silent cerebral infarction is defined as imaging or neuropathological evidence of cerebral infarction without a history of acute neurological dysfunction attributable to the lesion.[61] Patients with asymptomatic CarAD have a higher prevalence of silent brain infarction upstream from their stenosis than in the contralateral cerebral hemisphere.[62] And, similar to a prior TIA, silent brain infarction on cerebral imaging is associated with a 2-fold increased risk of future stroke.[134-137] Consequently, revascularization (as per symptomatic lesion severity threshold) may be warranted in CarAD patients with clinically silent but radiologically evident brain infarctions.[7,8,135,137]

Along with the conventional (clinical) definition of stroke, contemporary clinical trials increasingly incorporate in their inclusion criteria and endpoint definitions the tissue (cerebral infarct) definition of stroke.[61,138]

Watershed distribution strokes (ie., affecting firstly cerebral tissue in the border-zone supply regions of the major cerebral arteries) account for approximately 10% of all ischemic stroke cases[139] and are typically associated with severe carotid stenosis or occlusion.[140] In embolic strokes, efforts are being made to identify the eatilogy by radiologic clot analysis[141-144] but today's imaging and image processing technology have not yet reached the level to be able to reliably distinguish between CarAD-related stroke and cardioembolic stroke.

Contemporary stroke risk associated with atherosclerotic carotid disease

Stroke remains a leading cause of premature death, major morbidity, and permanent disability worldwide. However, improvements in triple medical therapy over the last two decades (particularly the more widespread use of statins) have been associated with a reduction in the natural stroke risk attributable to carotid stenosis. There is direct randomized evidence that statins are particularly effective in stabilising a vulnerable carotid plaque. Allocation to 40mg simvastatin halved the rate of carotid endarterectomy in the Heart Protection Study (0.4% vs 0.8%; p=0.0003).[145] In patients with an ischaemic stroke or TIA of documented atherosclerotic origin, achieving LDL-cholesterol of <70mg/dL avoided one subsequent major vascular event in 4 (number needed to treat 30).[146,147]

Several observational studies, despite their limitations and biases, have nevertheless suggested that carotid-related stroke risks in subjects with a significant carotid stenosis may have declined over time to around 1% per year in the highly selected populations included.[148-150] But residual risk persist, and strokes secondary to CarAD continue to occur, even in well-treated patients adherent to pharmacologic therapy.[77,151,152] These strokes can be fatal or disabling; eg., in ASxCS patients with an ipsilateral TIA or stroke during follow-up, 28.6% have severe disability based on the Rankin score.[100]

There is a risk gradient - a continuum from very low risk in entirely asymptomatic individuals (stroke risk <1% per year), through an increased risk in patients without symptoms but vulnerable plaque features

(ie., thin and/or ruptured fibrous cap, large lipid-rich and/or necrotic core, intraplaque haemorrhage, ulceration, mural thrombus)[99,153,154] to a high risk in patients with a recent ipsilateral neurologic event (stroke risk >10% per year) (Fig 2).

In individuals with CarAS, family history of stroke is an important risk factor. In a study cohort of 864 patients (72±8 years; 68% men) with CarAS and 1698 controls (61±11 years; 55% men) referred for noninvasive vascular testing, family history of stroke was present significantly more often in patients with CarAS than in controls, with a resulting odds ratios (95% confidence interval) of 2.02 (1.61-2.53), and the association remained significant after adjustment for age, sex, body mass index, smoking, diabetes mellitus, hypertension, and dyslipidemia (odds ratios: 1.41 (1.06-1.90)) even that only strokes before age 65 were considered.[155]

The risks of carotid intervention in extremely low-risk patients are unjustified, and, in contrast, the benefits of carotid intervention in extremely high-risk patients are abundantly clear, even in those on modern medical treatment.[156] But large numbers of patients with "significant" CarAD sit between these extremes, and the challenge is to identify a subset of patients with a significant carotid stenosis who are at an increased risk of stroke despite triple medical therapy (anti-platelet agent, statin, anti-hypertensive medication), who may derive substantial benefit from carotid surgery or stenting.[19,77] Furthermore, the recent STRATIS registry demonstrated a significant association of nonstenotic carotid plaques with cryptogenic stroke, suggesting a potential mechanistic role of "non-significant" lesions in embolic stroke of undetermined source.[157,158] The risk of recurrent stroke/TIA in nonstenotic carotid plaques is particularly not negligible in the presence of high-risk plaque features that increase in the risk of recurrent stroke/TIA from 2.6/100 person-years to 4.9/100 person-years.[159]

Whilst the 'average' stroke risk in a general population with stenotic CarAD is around ~1% per year,[150,160] the risk is substantially higher in patients with clinically manifest cardiovascular disease or diabetes (up

to 2.5% per year),[102,103] and yet higher in patients with clinical or radiological evidence of prior brain infarction. The stroke risk is cumulative over time, and consequently the "average statistical" 10-year risk of a carotid-related stroke is between 10-25% which is not negligible. Most major strokes occur without clinical warning;[161] hence the importance of primary prevention with, in the first line, intensive medical therapies. However, today there is no randomized evidence to indicate that intensive medical therapy would be sufficient to control stroke risk in individuals with ASxCS.[162] Moreover, contemporary evidence shows that strict compliance to medical treatment may fail in large proportions of ASxCS patients in relation to a substantial risk of neurologic events.[152,163,164] Clinical and imaging features associated with increased stroke risk in AsxCS are described in detail in Appendix 2 (Suppl Tab. 2).

It is notable that although the prevalence of ASxCS is similar to that of paroxysmal atrial fibrillation (AF), and the annual stroke risk in vascular clinics AsxCS patients on optimized medical therapy (OMT) is similar to that seen in paroxysmal AF patients receiving aspirin (≈2.0-2.5% in ASxCS vs. ≈2.1% in AF),[101,102,163-165] in contrast to CHA_2DS_2-VASC (and other clinically applicable risk stratification schemes in AF),[166-170] no prospectively validated risk quantification tools exist today for ASxCS subjects.[171,172]

TREATMENT OF CAROTID STENOSIS TO REDUCE STROKE RISK

Lifestyle modification

As with other cardiovascular diseases, lifestyle modification can reduce the risk of a carotid-related stroke and, importantly, reduces overall cardiovascular risk. Lifestyle measures, including smoking cessation, weight loss, regular exercise, and a balanced diet are to be encouraged.[173,174] In 31,546 women and men aged ≥55 years from 40 countries with cardiovascular disease or diabetes mellitus with end-organ damage receiving proven medications, a higher-quality diet (as per modified Alternative Healthy Eating Index, mAHEI) was associated with a significant 14% reduction of stroke over 56 months that was maintained after potential mediators of dietary effects that included body mass index, waist-to-

hip ratio, blood pressure, hypertension, and others (HR 0.81; 95% CI, 0.67– 0.98, top versus lowest quintile of mAHEI; p for trend 0.001).[175] Analysis of dietary components found a modest but significantly reduced risk of primary outcome with increased consumption of vegetables, fruit, soy protein and an increased risk with greater intake of meat, poultry, and eggs.[175] The high-quality diet was associated with a consistent benefit regardless of proven secondary prevention measures including aspirin, beta-blockers, and statins.[175]

Long-term Medical Management

Prescribing triple medical therapy (ie., anti-thrombotic, anti-hypertensive and LDL cholesterol-lowering drugs) in patients with asymptomatic and symptomatic carotid stenosis reduces the risk of stroke, myocardial infarction death.[176-179] Medical therapy has evolved considerably over the last few years, but few large randomised trials included a significant number of patients with CarAD, and hence the evidence for medical therapy in this population is mostly indirect. Nevertheless, patients with a significant ASxCs and those who have recovered from a carotid intervention should receive standard goal-directed medical therapy as recommended for secondary cardiovascular disease prevention, as summarised in recent ESC[180] and ESVS[9] guidelines.

Briefly:

(1) Intensive statin therapy, with ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor as an alternative or adjunctive therapies, aiming to achieve an LDL-C <55mg/dLis advised for all patients with significant CarAD.[181,182] Intensive LDL-C lowering in patients with CarAD is associated with several beneficial effects, both at the clinical and molecular levels.[176,183] (Suppl Table 3 in Appendix 3). Meta-analysis of 11 randomized studies in 20 163 patients indicated that more intensive LDL-cholesterol lowering was associated with a reduced risk of recurrent stroke in trials in which all patients showed

evidence of atherosclerosis (RR 0.79; 95% CI 0.69-0.90).[182] In addition to LDL-cholesterol lowering, statins exert antithrombotic properties through their direct interference with the clotting system and platelet activation;[183] an effect that may become relevant clinically particularly with high statin doses.[182] Prespecified analysis of cerebrovascular events in recent FOURIER randomized trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) in 27 564 patients with established atherosclerosis and LDL cholesterol levels ≥1.8 (or non-HDL [high-density lipoprotein] ≥2.6 mmol/L) on statin therapy, evolocumab (vs placebo) reduced ischemic stroke (HR 0.75 [95% CI, 0.62-0.92]; P=0.005); an effect consistent across all major subgroups including subjects with prior ischemic stroke.[184]

(2) Single anti-platelet therapy is required for 'stable' CarAD (ie, asymptomatic stenosis and long-term secondary prevention post-intervention), which should be low-dose aspirin or clopidogrel. Patients with carotid stenosis suffering a TIA or a minor stroke are at high risk of recurrent neurologic events particularly in the first few days after the onset of symptoms. A single-centre prospective audit in 100 consecutive recently symptomatic patients demonstrated that initiation of dual antiplatelet treatment (DAPT; aspirin 75mg + clopidogrel 75 mg) after exclusion of intracerebral or parenchymal haemorrhage resulted in a five-fold reduction in recurrent events compared with single antiplatelet treatment while awaiting CEA (3% vs 13%, respectively; odds ratio, 4.9; 95% CI: 1.5-16.6; p = 0.01) without an increase in major perioperative bleeding complications. Thus, OMT has a crucial role in both asymptomatic and recently symptomatic patients, in whom medical management reduces spontaneous embolism from the plaque.[177]

Patients with recently symptomatic CarAD should receive DAPT to reduce their risk of stroke recurrence. In a randomized, double-blind study in subjects with recently symptomatic ≥50% carotid stenosis (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis, CARESS), combination

therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization.[185]

In CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial patients with documented prior MI, ischemic stroke, or symptomatic PAD (n= 9,478), the rate of stroke was significantly lower in the clopidogrel plus aspirin arm than in the placebo plus aspirin arm: 3.8% versus 3.0% (hazard ratio [HR] 0.802; 95%CI 0.644–0.998, p=0.048). There was no significant difference in the rate of severe bleeding (1.7% versus 1.5%; HR 1.12, 95% CI 0.81 to 1.53, p = 0.50), but moderate bleeding was significantly increased (2.0% versus 1.3%; HR 1.60, 95% CI 1.16 to 2.20, p = 0.004).[186] A meta-analysis of 14 randomised controlled studies in 9,012 patients, DAPT was more effective than monotherapy in reducing risks of early recurrent stroke (RR 0.69; 95% CI, 0.60-0.80; p<0.001) and nonsignificantly increased risk of major bleeding (RR 1.35; 95% CI, 0.70-2.59, p=0.37).[187] In recent SOCRATES (Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes) trial, ticagrelor (as anti-platelet monotherapy) was superior to aspirin (as anti-platelet monotherapy) in preventing stroke, myocardial infarction or death by 90 days from acute ischaemic stroke or TIA in patients with ipsilateral atherosclerotic stenosis (hazard ratio, HR 0.68 [95% CI 0·53-0·88]; p=0·003, a prespecified analysis of 3081 patients with ipsilateral atherosclerotic carotid artery stenosis – 23% of the total 13,199 cohort).[188] There were no significant differences in the proportion of life-threatening bleeding or major or minor bleeding events in patients with ipsilateral stenosis in the ticagrelor group compared with the aspirin group.[188]

In patients submitted to CEA, surgeons may prefer to continue DAPT peri-procedurally, reducing from day 1 post CEA[9] to a single antiplatelet agent (low-dose aspirin or copidogrel) that should be typically maintained for 1-3 months.[189,190] Patients undergoing CAS typically receive DAPT, with clopidogrel loading three days prior to stenting and continuation for 1-3 months post-stenting (typically for 4-6

weeks if a single-layer stent is used[9] and up to 3 months with "mesh" stents), after which single anti-platelet therapy is advised.[189,190]

In the COMPASS trial, 1919 patients with either history of carotid revascularization or asymptomatic ≥50% stenosis were enrolled along with other patients with CAD or PAD, and randomized to three arms: aspirin 100 mg + rivaroxaban 2.5 mg b.i.d., or rivaroxaban 5mg b.i.d. alone or aspirin 100 mg alone.[191] Similar to other subgroups, those with carotid disease appeared to benefit from the aspirin+rivaroxaban combination, as compared to aspirin alone, although the benefit in this subgroup did not reach statistical significance.

Some antihypertensive medications may significantly reduce stroke risk despite only a modest reduction in blood pressure. For instance, in 9297 patients with vascular disease or diabetes plus an additional risk factor, followed for 4.5 years as part of the HOPE (Heart Outcomes Prevention Evaluation) randomized trial, the relative risk of any stroke was reduced by 32% in the ramipril group compared with the placebo group, and the relative risk of fatal stroke was reduced by 61% despite only modest reduction in blood pressure (3.8 mm Hg systolic and 2.8 mm Hg diastolic). Benefits were consistent across baseline blood pressures, drugs used, and subgroups defined by the presence or absence of previous stroke, coronary artery disease, peripheral arterial disease, diabetes, or hypertension,[192] indicating a mechanistic vasculoprotecive effect.

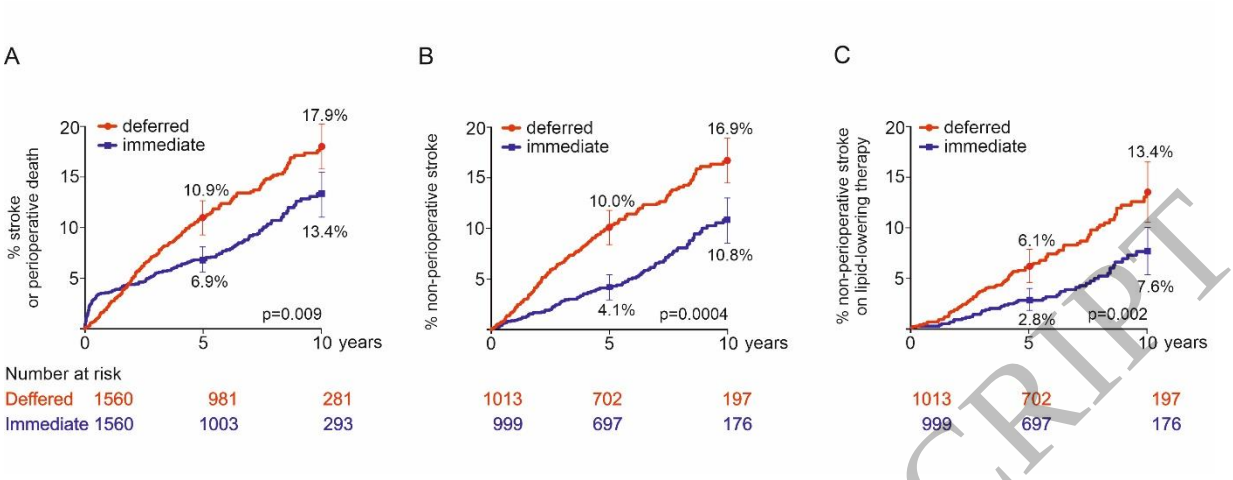
Carotid endarterectomy (CEA)

First performed in 1953, CEA is one of the most thoroughly evaluated surgical procedures ever, with two large trials randomising over 5000 patients with symptomatic carotid stenosis (ie., presenting with recent ipsilateral stroke or TIA) to carotid surgery versus medical therapy.[193,194] The results were highly significant with CEA halving the risk of recurrent stroke amongst those with carotid stenosis >50%

diameter stenosis. Tighter stenosis (ie., >70%) was associated with an increased risk of stroke without surgery, and hence greater absolute benefits with surgery. In contrast, patients with minor stenosis (ie., <50%), had a much lower background risk of stroke, and routine surgery was ineffective and potentially harmful.[194] The greatest absolute benefits of surgery were seen in patients operated soon after their presenting stroke. Pooled analysis of 5893 patients from he European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial, with 33000 patient-years of follow-up, demonstrated that benefit carotid revascularization was greatest for those randomised within 2 weeks after their last ischaemic event, and fell rapidly with increasing delay.[195,196] A more recent systematic review of ten studies with a total number of 2634 patients with carotid-related neurologid symptoms demonstrated that the risk of recurrence of cerebrovascular events within the first days after a neurologic index event was as high as 6.4% (1.5-23.8), 19.5% (12.7-28.7) and 26.1% (20.6-32.5) after 2-3, 7 and 14 days respectively.[197] Hence guidelines recommend to intervene promptly in symptomatic patients with a stenosis >50% considered suitable for intervention.

In the 1990s, over 6000 patients with ASxCs stenosis were randomized in three trials to either carotid surgery plus medical therapy versus medical therapy alone.[192-200] Successful carotid surgery halved the long-term risk of stroke, with clear benefits seen at five years after randomization and maintained at ten to fifteen years, even in patients on lipid-lowering therapy (Figure 3).[113] In contrast to the symptomatic lesions, for asymptomatic stenoses the evidence that stroke risk increases with an increase in stenoisis severity (beyond a critical threshold; such as ≈60-70%) is less consistent,[17,18] indicating a clinically-relevant role of other lesional features.[19,77,119] (cf., Suppl Table 2 in Appendix 2).

Fig 3.



10 year results from ACST-1, showing effects of carotid revascularization on major clinical outcomes: ***A*** *– perioperative stroke and death,* ***B*** *– non-perioperative stroke, and* ***C*** *–non-perioperative stroke in patients on lipid-lowering therapy* (Adapted from ref [113]). *In patients on triple therapy before any stroke, at 5-15 years there is no loss of early gain and the stroke risk curves continue to diverge, consistent with a lasting benefit of carotid revascularization.*

Carotid surgery (and CAS) expose patients to immediate risk, but this is offset by halving the long-term risk of stroke. Hence, two important factors must be considered before surgical intervention: first, whether the life expectancy is long enough (typically, at least 2 years) to benefit from the intervention, and secondly the procedural risks, ideally assessed by an independent neurologist 30 days post-procedure. As risks of carotid revascularization have decreased over the years (both for CEA and CAS)[201,202], traditional thresholds for "acceptable" major complication rates (≤6% in symptomatic patients and ≤3% in asymptomatic patients) may no longer be applicable today.[202,203]

New thresholds should be established based on complication rates in contemporary trials and registries, taking into account characteristics of the treated populations.

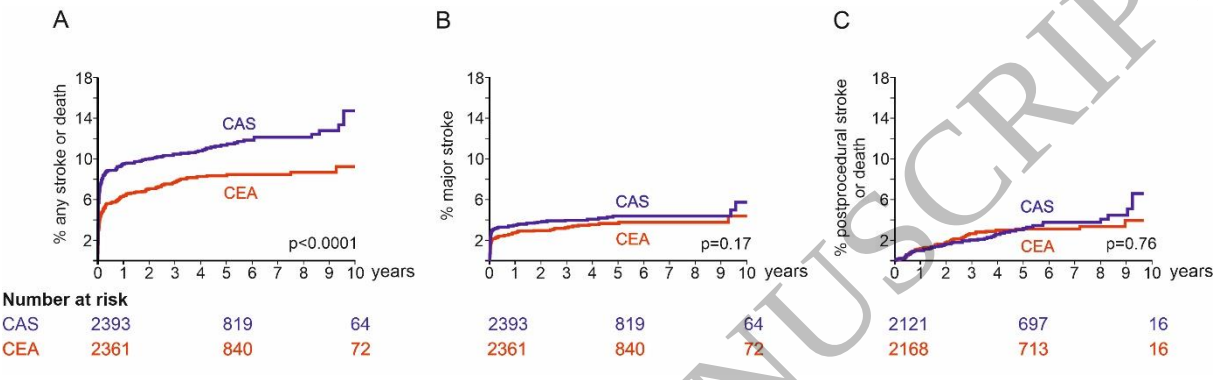
In the two large symptomatic trials comparing surgery with medical therapy, men and women benefited equally following successful CEA. Women appeared to have a higher procedural risk than men, but this finding is not replicated in much larger and more contemporary registries (which provide better evidence of procedural hazards than trials). In a meta-analysis of the three major trials comparing carotid surgery with medical therapy alone in asymptomatic patients, men and women benefit equally from carotid intervention.[204] Hence, gender is not relevant when considering whether or not to intervene in CarAD.

Carotid artery stenting (CAS)

CAS, a less invasive treatment for CarAD, has been evaluated in several large randomized trials, compared to CEA in symptomatic and then asymptomatic patients. The four major trials comparing CEA vs CAS in symptomatic patients, pooled in an individual patient data meta-analysis, show an increased absolute risk of peri-procedural stroke or death with 1st generation CAS (3.2% [95% CI 1.7%-4.7%]). This excess procedural risk seemed to be modified by age, with CEA safer than CAS in patients >70 years old.[205] Meta-analysis of 6,526 patients (with a mean follow-up of 5.3 years) from 5 trials that had exclusive use of embolic-protection devices found that composite outcome of periprocedural death, stroke, myocardial infarction (MI), or non-periprocedural ipsilateral stroke was not significantly different between therapies (OR: 1.22; 95% CI: 0.94 to 1.59).[206] However, the risk of any periprocedural stroke plus non-periprocedural ipsilateral stroke remained greater with CAS (OR: 1.50; 95% CI: 1.22 to 1.84).[206] The risk of higher stroke with CAS was mostly attributed to periprocedural minor stroke (OR: 2.43; 95% CI: 1.71 to 3.46).[206] However, CAS was associated with significantly lower risk of periprocedural MI (OR: 0.45; 95% CI: 0.27 to 0.75); cranial nerve palsy (OR: 0.07; 95% CI: 0.04 to 0.14); and the composite outcome of death, stroke, MI, or cranial nerve palsy during the periprocedural period (OR: 0.75; 95% CI: 0.60 to 0.93).[1206] Thus both meta-analyses[205,206] found that stenting was associated with lower risks of myocardial infarction and cranial nerve palsy than CEA. In the post-procedural period, CEA and CAS both

provided similarly durable long-term protection against stroke, with an annual ipsilateral stroke rate of 0.60% per year for CEA and 0.67% for CAS (Fig 4).[207]

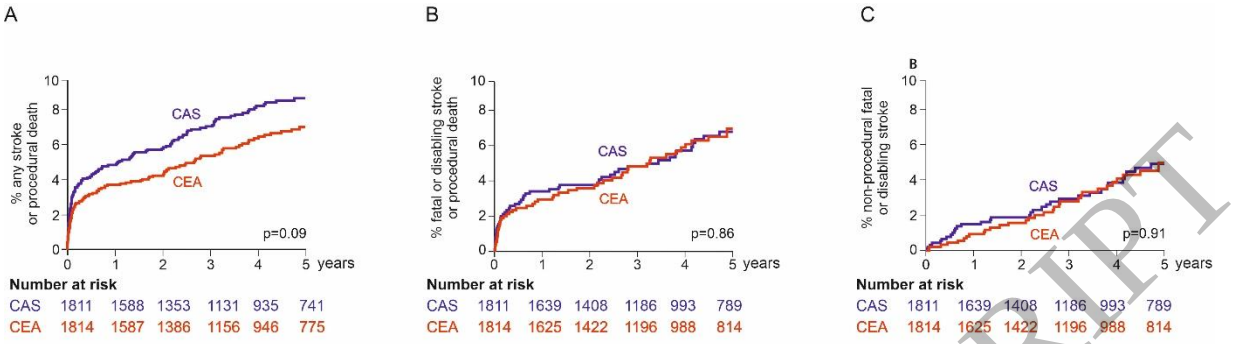
Fig 4.



Kaplan-Meier estimates of clinical event rates in EVA3S, SPACE, ICSS and CREST: ***A*** *– incidence of any stroke or death,* ***B*** *– incidence of major stroke,* ***C*** *– incidence of postprocedural stroke or death.* (Adapted from ref.[207])

Trials comparing CAS to CEA in asymptomatic patients have shown a slightly higher rate of procedure-related strokes and deaths; however, no significant differences in major procedural complications. A numerical excess of procedural strokes (mostly minor) with CAS is offset by an increased risk of peri-operative myocardial infarction with CEA. In ACST-2, there was no difference between CAS (that employed predominantly 1st generation stents)[208] vs. CEA in death, myocardial infarction, or any stroke (3.2% CEA vs. 3.9% CAS, p=0.22), but there was a 1% increase in the risk of a non-disabling stroke associated with stenting (1.6% CEA vs 2.7% CAS, p=0.03).[39] However, no difference between open surgery and endovascular treatment occurred in 30-day death or disabling stroke (1% CEA vs. 0.9% CAS, p=0.77).[114] Five-year data from ACST-2 are presented in Fig 5.

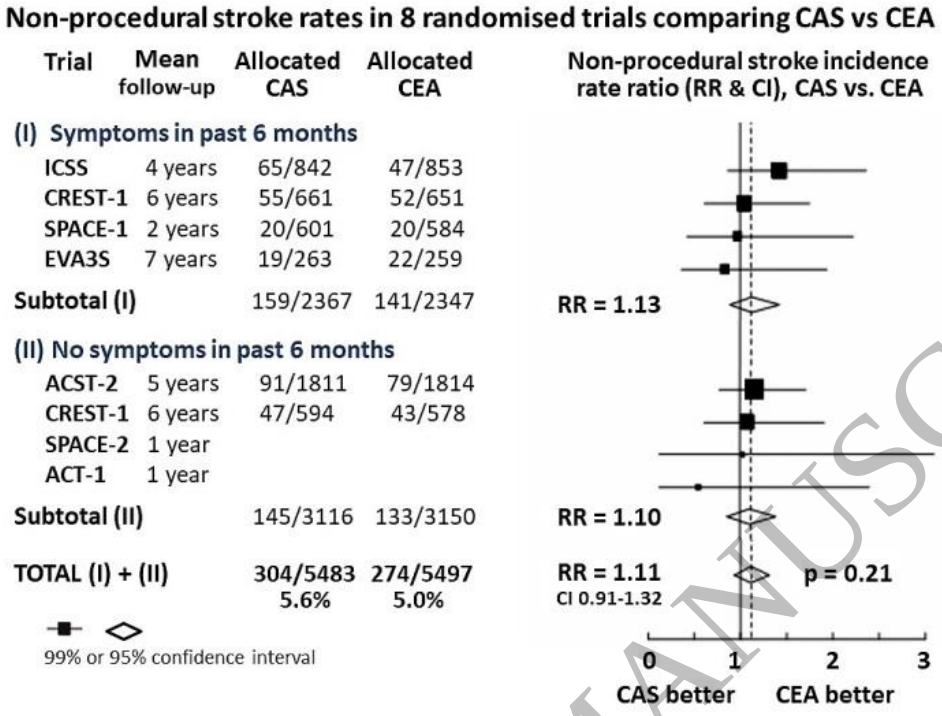
Fig 5.



*Fundamental outcomes in ACST-2 trial that compared CEA and (predominantly 1st-generation stent[208]) CAS: **A** – the proportion of any stroke or procedural death, **B** – the proportion of fatal or disabling stroke or procedural death, C – the proportion of non-procedural fatal or disabling stroke. (Adapted from ref [114]).*

Overall, the long-term outcomes of CEA and 1st generation CAS used to reduce stroke risk in symptomatic and asymptomatic carotid stenosis are similar (Fig. 4 – Fig 6).

Fig 6.



Tabular meta-analysis of post-procedural stroke onset rates in trials comparing CEA vs CAS (adapted from ref [114]).

RCTs vs Registries

Whilst randomised trials are essential for a reliable comparison of the long-term efficacy of CEA vs CAS, they present some drawbacks that are relevant to everyday clinical practice. One is that patients enrolled and randomized would be preselected, as others may not receive the offer to participate because of convictions the surgeon/interventionist may have with regard to the "better" option for a particular patient (selection bias). Also, surgeons/interventionists taking part in randomized trials may not represent the skills (and/or have access to equipment) of all others in real life. There is evidence that patients in routine clinical practice differ from RCT populations with respect to important characteristics, including age, comorbidities, and medications.[209] Although the RCT conclusions are valid only for a

specific subgroup, they are often used for application in a broad population.[210] Hence the procedural risks observed in randomized trials may not be generalizable. In contrast to randomized clinical trials, registries reflect real-life management and thus have greater relevance to clinical practice at large.[211] *Contemporary* procedural risks are best assessed in large registries in several centres that can also capture recent technical and experiential advances. When applying data from CarAD studies to everyday clinical practice, clinicians need to ba aware that both RCTs and registries give very valuable, albeit different, information.[211]

Rates of procedural complications from CEA have fallen over the past two decades due to a combination of improved adjuvant medical therapies, alteration in anaesthetic practice, better case selection and technical factors such as increased use of patching and centralisation of vascular services.[127] For CAS, technical developments combined with improved case selection and increased operator experience have led to a reduction in procedural stroke risks, as reported in several large high-quality registries.

Surveillance after CAS and after CEA

There is no srandomized or other strong evidence to support routine surveillance in all patients after CAS or CEA.[212] In general, the risk of restenosis is similar with carotd revascularization using the endovascular route or open surgery.[213-215] In most cases restenosis is clinically asymptomatic, though presentations as stroke or TIA may occur,[213-218] in particular with an "isolated" haemisphere and/or rapid progression of restenosis or thrombosis as a mechanism of lumen loss. Recent systematic review and a meta-analysis of 20 RCTs indicated no increase increase in late ipsilateral stroke with restenosis after CAS but an increase in late ipsilateral stroke (OR 3.87, 95% CI 1.96-7.67; $p < .001$) with a significant restenosis (70%-99%).[219] For both CAS and CEA, optimal technical quality of the procedure and its final luminal result (along with patient compliance with postprocedural antiplatelet regimen) minimize the risk of thrombosis and

restenosis. Principal clinical risk factors for restenosis include, for both CAS and CEA: diabetes, dyslipidemia, female gender, chronic kidney disease, and smoking.[216,220,221] Residual stenosis after the primary revascularization procedure is a principal angiographic risk factor for restenosis following CAS.[222] With concerns regarding increased risk of cerebral embolism with single-layer stent optimization through the "cheese-grater effect" (along with perceived risk of plaque preparation-related embolism risk – hence popularity of primary stenting with 1st generation carotid stents), trials used to accept <50% residual stenosis as a technical and procedural success with 1st generation stent CAS.[223] There is recent evidence that lesion preparation in single-layer stent CAS may reduce per-procedural cerebral embolism,[224] and optimal lesion preparation tended to reduce 30-day ipsilateral stroke in the SPACE trial (4.4% vs. 8.1%, p=0.14; note that cerebral protection was not mandatory in SPACE).[225] In CEA, completion imaging plays an important role in ensuring procedure quality and minimizing risk of thrombosis and restenosis (see below).

Post-CAS clinical and carotid duplex surveillance is typically performed at 1 month, 6 months, and then annually to assess for restenosis[226] and, in patients with contralateral disease, to monitor lesion progression as this is assocated with an incrased risk of symptomatic transformation. In-stent velocity thresholds for "significant" (ie., ≥70%) restenosis that may require angiographic verification in the context of interventional management include peak-systolic velocity of ≥3m/s and end-diastoloc velocity of ≥1.4m/s,[227] though the "normal" velocities may be affected by stent design relative to sits conformability (open-cell stents) vs. bending stiffness (closed-cell stents).[228] Use of velocity criteria for non-stented artery in stent monitoring post CAS is disadvised as it leads to a significant overestimation of in-stent restenosis. Recent evaluation of 2637 CAS procedures with follow-up for 24-193 (median 67) months with DUS performed every 12-months indicated a relationship between stent design and in-stent restenosis, with the braided design as an independent risk factor for first and recurrent in-stent restenosis (OR = 2.71, $p < 0.001$ and OR = 3.11, $p = 0.032$ respectively for the braided design vs. other

designs).[229] Although neointimal hyperplasia is considered the fundamental mechanism of in-stent restenosis after CAS, [230,231] intra-stent progression of atherosclerosis may manifest as (usually late) "in-stent restenosis"[217,232] as 1st generation (single-layer) carotid stents that may fail to effectively sequestrate the atherosclerotic lesion, [124,233,234] The prevalence of continued (intra-stent) plaque growth within single-layer stents requires further elucidation, similarly to the mechanism of increased (relative to CAS) risk of symptoms with post-CEA restenosis.[219] In CEA patients, DUS surveillance may be offered particularly to those at an increased clinical risk of restenosis, and it is also considered reasonable in those with contralateral stenosis >50%.[9]

Clinical follow-up with a formal neurologic examination plays an important part in assessment of peri-procedural complications and long-term efficacy of carotid revascularization in ipsilateral stroke prevention. [226,227] Study-specific definitions of neurologic outcomes should be respected when comparing trial results.[235]

Following CAS, DAPT is typically continued for 4-6 weeks if a single-layer stent is used[9] (and up to 3 months with "mesh" stents), after which single anti-platelet therapy is advised.[189,190] In patients receiving CEA, clopidogrel (or low-dose aspirin) is usually administered on day 1 post-CEA and it is continued for 1-3 months.[9,189,190] Patients after carotid irevascularization should receive guideline-indicated medical therapy along with advice on life style modification, as appropriate for primary/secondary prevention of cardiovascular disease.

Recent advances in CEA

A recent meta-analysis demonstrated that the 30-day stroke and death rates after CEA have fallen from 5.1% to 2.7% (symptomatic patients) and from 3.2% to 1.5% (asymptomatic patients) in studies completed before 2005 compared with those reporting up to 2016.[201] Growing overall experience in

CEA, improved perioperative medical therapy, alteration in anaesthetic practice, intraoperative morphological control, specialist training in vascular surgery and improved hospital-related structural factors could all have contributed to this decline in complication rates.

***Antiplatelet Therapy*:** It is widely accepted that perioperative continuation of single antithrombotic therapy (usually aspirin 75-325mg daily) has contributed to lower stroke rates after CEA (and perhaps also to lower rates of perioperative myocardial ischemia), but it took time to convince the vascular surgical community that aspirin did not increase procedural risk (especially neck haematoma).[236] In Germany, a decade ago, ≈10% of all CEAs were performed without antiplatelet therapy, and this rate has now halved to ≈5 %.[237] In a recent audit, early implementation of dual antiplatelet therapy (in the TIA clinic after CT/MR exclusion of parenchymal haemorrhage) was associated with a fivefold reduction in recurrent neurological events prior to expedited CEA and a fourfold reduction in spontaneous embolization min absence of any significant increase in major peri-operative bleeding complications.[238]

However, it is questionable whether the use of DAPT could further decrease post-operative stroke risk; a recent meta-analysis indicated that DAPT has no effect on the occurrence of ischaemic complications after CEA when compared to single antiplatelet regimens.[239] Importantly, DAPT may increase haemorrhagic complications of CEA.[240]

Statins: A systematic review from 2018 (six studies, 7053 patients) showed that statin users were at a significantly lower risk of periprocedural death after CEA when compared with statin-naïve patients (0.2% versus 1.3%).[241] Perioperative stroke risk was, however, not statistically different (1.4% versus 3%).[241] Additionally, a recent evaluation from the Vascular Quality Initiative (VQI, 97,835 CEAs) strongly indicated that statin users had a lower risk of in-hospital stroke or death (1.7% (no statin) vs statin 1.4% (statin); RR, 1.2; 95% CI 1.02-1.5).[242] At 5 years, no statin therapy at discharge was associated with higher 5-year mortality after CEA (15% vs 10%; HR, 1.8; 95% CI, 1.6-2).[242]

Blood pressure management: Strict hypertension management is important for CEA. Hyperperfusion syndrome and intracranial bleeding are in most cases preceded by an uncontrolled rise in blood pressure. In a single-centre study of consecutive patients, strict postoperative blood pressure control (up to 24 to 48 hours) decreased the risk of HS from 0.9% to 0.2%.[243] Vascular surgical units should therefore have written criteria for postoperative blood pressure control. European carotid guidelines recommend continuing antiplatelet and statins before and after CEA and strict control of perioperative blood pressure.[9,187]

CEA under Local anaesthesia (LA): A recent meta-analysis (31 studies, 152 376 patients) demonstrated that LA was associated with a 24% reduction in stroke risk (OR 0.76; 95%CI: 0.62-0.92), 41% reduction in cardiac complications (OR: 0.59; 95% CI: 0.47-0.73) and a 28% reduction in inpatient mortality (OR: 0.72; 95% CI: 0.59-0.90).[244] However, an updated Cochrane Review (16 RCTs, 4,839 patients) of patients undergoing CEA under LA or general anaesthesia (GA), did not show any clear difference in 30-day stroke and death rates (3.5% vs. 4.1%, OR: 0.85; 95% CI: 0.62-1.16; p=0.31).[245]

The type of cervical block can play a role; the current, safer standard of care is superficial/ intermediate block performed under ultrasound control.[246,247] The Carotid Stenosis Trialist Collaboration analysis found a 30% relative risk reduction of 30-day stroke/death rates in symptomatic patients operated under LA.[248] In CREST-1, CEA under LA was associated with a lower risk of myocardial ischemia, similar to CAS.[249] Finally, a recent RCT found that silent cerebral ischemia detected by MRI was more common after GA-CEA than LA-CEA (17.1% vs. 6.7 %).[250]

In summary, recent data indicate that LA with ultrasound-guided cervical blockage is probably safer than CEA under GA. Therefore, European guidelines now recommend that vascular units should offer both GA and LA anaesthetic options for CEA.[9,203]

Intraoperative quality control (completion studies): A recent systematic review has analysed the benefit of using intraoperative completion studies by angiography, DUS, angioscopy and/or flowmetry compared to no intraoperative completion. [251] Pooled analysis showed angiography to be significantly associated with a lower risk of stroke or death (RR 0.76; 95%CI, 0.70–0.83). Intra-operative DUS was also associated with lower stroke or death risk (RR 0.83; 95% CI, 0.74–0.93) and angioscopy with lower stroke risk only (RR 0.48; 95% CI, 0.033–0.68). Meta-analyses confirmed lower perioperative stroke or death rates for angiography and intra-operative DUS.[153] These data strongly indicate a significant beneficial effect of intraoperative completion studies on perioperative CEA outcomes. Consequently, this historical controversy is clarified by the most recent European CEA guideline recommendation to consider the use of intraoperative completion imaging in order to reduce the risk of peri-operative stroke.[9,203] In many centres, intra-operative DUS is now the preferred mode. [252]

Role of speciality in vascular surgery: A recent systematic review and meta-analysis (26 studies up to 2017) showed that for CEA performed by vascular surgeons compared with neurosurgeons, there was a lower unadjusted risk of stroke and death (RR, 0.63; 95%CI, 0.46-0.86).[253] There was a similar finding when vascular surgeons were compared with general surgeons (RR, 0.81; 95%CI, 0.66-0.99).[253] Canadian nationwide analysis found a higher 30-day stroke or death rate in CEA patients treated by neurosurgeons (4.1%; adj. OR, 1.27; 95%CI, 1.00-1.61) and cardiac surgeons (4.4%; adj. OR, 1.54; 95%CI, 1.04-2.30) when compared with vascular surgeons (2.9%).[254]

In Europe, vascular surgery guidelines recomend that CEA should be performed only by trained vascular surgeons.[9,203] In the USA, however, CEA remains a key component of neurosurgery residency training as an open extracranial cerebrovascular procedure required in the curriculum (the resident "must able to perform", considered essential for the area of practice).[255] Thus in the USA neurosurgeons, covering the whole spectrum of acute and elective cerebrovascular disease, continue to perform, using a "tailored"

approach, quailty CEAs in primary and secondary stroke prevention and (in the rare cases that may require surgical approach) in acute carotid-related stroke. [256]

Hospital-related structural factors: There is evidence that hospital-related structural factors can improve CEA outcomes: in a recent systematic review, larger hospitals were associated with lower mortality and stroke rates, as well as cardiac events, when compared with smaller hospitals (less than 130 beds). Adherence to established clinical pathways was also associated with reduced stroke and cardiac event rates. Large surgical intensive care units (≥7 beds) and dedicated intensivists were also associated with decreased mortality and stroke rates after CEA. The German-Austrian carotid guidelines give specific recommendations on appropriate hospital structure for undertaking CEA, including the availability of intraoperative angiography and/or duplex sonography, 24-h availability of a specialist in vascular surgery and of a neurologist/vascular specialist experienced in the treatment of cerebral ischemia, 24-h availability of DUS, CTA or MRI and 24-h availability of an endovascular service. Additionally, monitoring options (intermediate care, intensive care unit, stroke unit) should be available, including 24-h availability of treatment for intracranial oedema and bleed. [203]

Recent advances in CAS

The early randomized trial experience (CAVATAS, SPACE, EVA-3S, ICSS) comparing CAS and CEA has been burdened by (i) the limited experience of the interventionalists performing CAS, (ii) limited and/or inadequate use of devices protecting the brain against intra-procedural embolism and (iii) inability of the 1st generation (single-layer) carotid stents to sequestrate the carotid plaque, resulting in intraluminal prolapse of the atherothrombotic material after stent placement and translating into a relative excess of non-disabling strokes by 30 days. [257-266] Improved (ie., plaque-sequestrating) stents, better cerebral protection, and safer access (using trans-radial stenting or trans-carotid rather than trans-femoral route) may all contribute to a reduction in the procedural complications of CAS. [233]

Cerebral protection in trans-femoral (TF) CAS: Both surgical (CEA) and endovascular (CAS) management of carotid stenosis generate cerebral embolism.[267,268] With 1st generation carotid stents (single-layer stents) that may fail to seal the atherosclerotic plaque,[233,259-261] the risk of per- and post-procedural cerebral embolism is greater than with surgery that largely removes the embolic material.[267,268] Cerebral protection systems (distal – such as filters, and proximal – transient flow clamping and/or reversal) were developed to minimize procedural cerebral embolism in CAS.[269] Distal filters were used widely (though not necessarily in all patients) in most clinical trials of CAS vs CEA. In EVA-3S, the risk of stroke or death within 30 days after CAS was lower in those treated with cerebral protection devices (relative risk [RR] 0.38; 95%CI 0.17 to 0.85);[258,270] a finding confirmed in a systematic review focused on cerebral protection use in major randomized studies (45% reduction in 30-day risk of stroke or death (RR 0.55; 95%CI 0.41 to 0.73).[258] In the absence of large-scale randomized trials of protected versus unprotected CAS, large-scale registry data show reduced peri-procedural stroke rates when intra-procedural cerebral protection is used.[271]

Randomized evidence comparing different cerebral protection methods (distal filters, proximal protection with balloon-arrest or flow-reversal) suggests that proximal protection is superior to distal filters, reducing cerebral embolization of particles, monitored by trans-cranial Doppler or observed post-procedurally on DW-MRI.[272-275]

Distal filters may cause embolization of plaque material during lesion crossing whereas lesion crossing is *protected* when proximal systems are used. Hence, proximal balloon-occlusion (that may be enhanced with transient flow reversal) may be safer. The use of flow-reversal may reduce embolization during all stages of the procedure, and continuous removal of plaque debris might prevent embolization when antegrade flow is restored. Some patients may be intolerant to transient flow cessation/reversal but

intolerance should not lead to aborting cerebral protection, as transient intolerance does not increase the peri-procedural stroke risk.

Stent Design (2nd Generation Stents / dual-layer stents / "mesh" stents): After the embolic protection system has been removed, the stent is the main line of defence from embolic and thromboembolic complications arising from the newly remodelled plaque.[276] With single-layer carotid stents, plaque-related cerebral embolism continues to occur post-procedure[124,272] and accounts for up to two- thirds of the minor strokes observed in CAS trials.[264-267]

Atherosclerotic plaque prolapse through the stent struts is associated with asymptomatic and symptomatic cerebral embolism,[260] and is not eliminated with the conventional (single-layer) closed-cell stent design.[260,261] Effective plaque isolation has thus become a key focus for CAS innovation.[262,263,277]

Dual-layer "mesh" stents are designed to minimize and control plaque prolapse.[123,278,279] In a recent randomized study of a micronet-covered stent appropriately powered for reduction of DW-MRI cerebral embolism, embolic lesions were reduced by ≈50%, total embolic load to the brain was reduced by ≈80%, and permanent cerebral infarct numbers fell by ≈70% when compared to a conventional carotid stent (the CREST study device).[124] While the postprocedural cerebral embolism was totally eliminated with the micronet-covered stent, in contrast, it persisted with the CREST study device.[124] 12-month data from that study indicated a reduction in a combined adverse endpoint of death/stroke/myocardial infarction or restenosis/occlusion, suggesteing that a plaque-sequestrating stent might be associated with a clinical benefit.[280] A meta-analysis with *clinical* outcomes including 68 422 patients from 112 (mostly observational) studies supports this imaging-based RCT.[281] "Mesh stents" show fundamental design differences that translate into their mechanical properties[278,282-284] and may affetct outcomes such as the rate of in-stent restenosis.[284-286] Indeed, recent systematic reviews and meta-analyses support lack of a

clinical "class effect" of dual-layer carotid stents.[281,286] Raw clinical event rates in 2nd generation (dual-layer, "mesh") carotid stents are shown in Suppl Table 4 (Appendix 4).

Safer Access: Trans-radial (TR) CAS: Recently, TR access for CAS (being "less" invasive than TF) has been gaining popularity. It largely avoids the aortic arch (a common source of peri-procedural embolization)[287,288] and is particularly popular with cardiologists[287,288] and neuro-interventionalists.[289] TR CAS is safe[290], and TR access may be preferred by patients.[291]

Trans-carotid stent-assisted revascularization under dynamic flow reversal (TCAR):

Trans-carotid access for CAS (Suppl Fig 5 in Appendix 5) entirely bypasses the aortic arch and, thus, any cerebral embolism arising from arch cannulation.[292] Recently, the technique has gained popularity, particularly in the USA. However, a lack of prospective randomized evidence comparing TCAR with TFCAS with independent neurological or MRI-DWI assessments precludes, at present, any routine recommendation for TCAR (Suppl Table 5A and 5D in Appendix 5). Nevertheless, based on available data patients at high surgical risk and concomitant severe aortic or femoral artery pathology may be best treated using TCAR (Suppl Table 5C in Appendix 5). However, TCAR has specific anatomical considerations and requires a disease-free common carotid artery; thus, patients in TCAR studies may be somewhat different than those in CEA (or TFCAS) studies. With those limiations in mind, data from the Vascular Quality Initiative TCAR Surveillance Project registry suggest that TCAR hmay be associated with a lower risk of stroke or death in comparison to 1st-genaration stent TFCAS, and similar in-hospital stroke or death rate when compared to CEA. Thus TCAR has the potential to become the preferred treatment modality in higher-risk patients with (a)symptomatic carotid artery stenosis due to clinical and/or anatomic factors (Suppl Table 5B and 5C in Appendix 5). Patients with high lesions (extending cranially to the second cervical vertebra), cervical spine immobility, post-CEA restenosis, prior neck irradiation and hostile neck may have a lower risk of TIA or perioperative stroke period and at 30-days when treated with TCAR (Suppl Table 5C in Appendix 5). Nevertheless, specific anatomical requirments for TCAR

(including, though not limited to, the need for a ≥5cm clavicle-carotid bifurcation distance and minimal to no common carotid artery puncture-site atherosclerosis) need to be taken into consideration. Ideally, comparisions should be made in patients suitable for using the techniques being compared.

Randomized or large multicentre prospective trials with independent neurological and radiographic adjudication are needed to compare TCAR with TFCAS, CEA and/or best medical therapy strategies not only in high-surgical-risk patients but also in normal-risk patients. (see Suppl Table 5D in Appendix 5; also, for a more detailed list of TCAR references see Appendix 5).

Currently, TCAR is viewed in Europe as a promising technique, but its benefits still need appropriate demonstration through RCT prior to recommending TCAR as an alternative to CEA in patients with symptomatic carotid stenosis.[12] This is relevant as in a recent meta-analysis of TCAR using a 1st generation stent, symptomatic patients had a substantially higher risk of early stroke/TIA than asymptomatic patients (2.5% vs 1.2%; odds ratio [OR] 1.99; 95% CI 1.01 - 3.92).[293] Similarly, in a Vascular Quality Initiative analysis from 18,477 patients (62.0% asymptomatic) undergoing TCAR using a 1st generation stent, there was also a higher odds of stroke/death in patients with a recent stroke (odds ratio [OR], 2.8; 95% confidence interval [CI], 2.1-3.7; P < 0.01), a recent hemispheric TIA (OR, 2.0; 95% CI, 1.3-3.0; P < .01), and former symptoms (OR, 1.6; 95% CI, 1.1-2.5; p=0.02).[294] Multivariate analysis of 750 consecutive TCAR cases in two high-volume centres indentified symptomatic carotid lesion as an indpenedent predictor of stroke or death by 30 days (OR 14.49; 95% CI 1.80-116.94; p = 0.01),[295] suggesting room for improved containment of the atherosclerotic plaque in TCAR. [296]

Recent real-world analysis of 340 patients treated using TF vs TC access in CAS (both with 1st generation stents) in Europe failed to confirm the advantages of the transcervical approach[297] but larger prospective series are needed, including those combining the dynamic flow reversal in TCAR with anti-embolic stents to minimize post-proceural clinical events resulting from plaque/thrombus prolapse into the lumen

through single-layer stent struts.[260,262]

Percutaneous transcarotid (rather than surgical – as in TCAR) access, used as a bailout in emergent stroke treatment, is associated with a complication rate that may reach nearly 20% particularly in absence of use of a hemostatic closure device (OR 3.04, 95%CI 1.03 to 8.97; p=0043);[298] however, routine use of ultrasound to perform the transcutaneous puncture and device improvements may facilitate the direct carotid access for CAS (and cerebrovascular interventions) in the future.

Recent progress in peri-CAS DAPT: CAS with Ticagrelol (rather than Clopidogrel) as an add-on to ASA

PRECISE-MRI (Prevention of Cerebral Ischaemia in Stent Treatment for Carotid Artery Stenosis – A randomised multi-centre phase II trial comparing Ticagrelor versus Clopidogrel with outcome assessment on MRI) examined ticagrelor in relation to clopidogrel as an add-on to aspirin in preventing ischemic brain lesions during CAS using predominantly single-layer stents. The trial enrolled patients with ≥ 50% symptomatic or asymptomatic carotid stenosis undergoing CAS in line with local guidelines. After a baseline MRI scan and clinical examination, the patients were randomized to ticagrelor or clopidogrel plus aspirin 1 to 3 days before undergoing CAS. Ticagrelor was administered with a loading dose of 180 mg followed by a twice-daily 90-mg maintenance for 1 month. Clopidogrel was given with a 300-mg loading dose followed by a once-daily 75-mg maintenance dose. All patients also received daily aspirin (100 mg). A second MRI and clinical examination were performed at 1 to 3 days post-CAS, with a third set of examinations performed at 28 to 32 days after the procedure. [299] Efficacy analysis (n=172 patients, mean age 69.5 years, 71% male, 55% symptomatic stenosis) revealed no significant difference in the primary efficacy outcome of the presence of ≥ 1 new ischemic brain lesion on follow-up MRI at 1-32 days post procedure (74.7% for patients given ticagrelor vs 79.8% with clopidogrel, p=0.43). However, there was a significant 37% reduction in the number of new ischemic lesions, at a median of 2 (interquartile range [IQR] 0.5 - 5.5) with ticagrelor versus 3 with clopidogrel (IQR 1 - 8); an exponential beta value of

0.63 (95% CI, 0.42 - 0.95; p=0.027). Ticagrelor was also associated with a significant reduction in the total volume of lesions, at a median of 66 µl (IQR 2.5 - 2.19) versus 91 µl (IQR 25 - 394) for clopidogrel (p=0.030). Patients assigned to ticagrelor also had a lower rate of the primary clinical safety outcome – a composite of stroke, myocardial infarction, major bleeding, or cardiovascular death (2.9% versus 7.8%; a relative risk of 0.36 [95% CI, 0.08 - 1.20]), driven primarily by the reduction in rates of post-CAS stroke. Ticagrelol use was not associated with any increase in haemorrhagic lesions or microbleeds after CAS. Results from PRECISE-MRI suggest that ticagrelol may be be a safe alternative to clopidogrel as add-on to aspirin to cover CAS procedures, and that replacing clopidogrel with ticagrelol might reduce cerebral embolism in CAS.[299]

Volume-outcome relationship in CEA and CAS

For both CEA and CAS there is a inverse relationship between the volume of carotid interventions performed (both per operator and per centre) and the 30-day risk of stroke and death (Table 1).

For CEA, an observational study in the USA suggested a yearly threshold volume of 79 cases per centre was associated with improved procedural stroke and death rates,[300] whereas a similar analysis of the UK data suggested a threshold of 35 cases per centre.[300] This lower figure might be explained by the preponderance of symptomatic carotid cases in the UK compared to the US, and 35 cases per centre per year is the current national recommendation for centre volumes of CEA in the UK.[301]

A systematic review and meta-analysis of 87 articles showed a lower risk of death or stroke following CEA with high operator volume (adj. OR 0.50; 95%CI 0.28-0.87) and high hospital volume (adj. OR 0.62; 95%CI 0.42-0.90)[302] (Table 1).

Table 1. Relationship between annual volumes and the 30-day stroke/death rate after CEA and CAS (according to Ref. 302)

	High vs low volume operators	Threshold	High vs low volume hospitals	Threshold
Carotid Endarterectomy (CEA) 69 studies	OR 0.50; 95% CI 0.28–0.87	>12 - >40	RR 0.62; 95% CI 0.42–0.90	>40 - >123
Carotid Artery Stenting (CAS) 21 studies	OR 0.43; 95% CI 0.20–0.95	6 - >40	OR 0.46; 95% CI 0.26–0.80	27 - >122

Due to a variety of thresholds in individual studies, a recommended minimum number of CEA per hospital or per surgeon is difficult to establish. The Vascular Society of Great Britain and Ireland currently recommends a minimum hospital volume of 35 CEAs annualy[301] while the German-Austrian guidelines recommend that hospitals perform at least 20 CEAs annualy.[303]

TFCAS appears to have a steep learning curve, with a lifetime threshold of 72 cases necessary to achieve competence in one study, but, given the pace of evolution of CAS as a technology and shifts in clinical practice and case selection, centre or operator volume thresholds for better procedural outcomes are not clear.[304-309] A recent systematic review of 87 studies published up to 2017 demonstrated significantly lower perioperative stroke and death rates for surgeons, endovascular specialists and hospitals with high annual volumes. However, thresholds for better or worse outcomes differ widely (Table 1).[302,310-312]

The ESC, SVS, ESO, and ESVS carotid guidelines do not give specific recommendations on a preferred CEA technique or a minimum number of CEA or CAS procedures for individual operators or hospitals.[8,10,301] However, recent German-Austrian recommendation includes a minimum CEA centre volume of 20 cases/year and a minimum CAS centre volume of 10 cases/year.[303] These minimal thresholds, however, may not be sufficient to ensure competent procedures and optimal outcomes of CEA and CAS.

In summary, both CEA and CAS are best performed by high-volume physicians in high-volume hospitals.

Simulation training in CAS and CEA

The most typical learning curve for both CEA and CAS is estimated to be 50-80 cases.[314,315] Simulators are useful for both open and endovascular carotid training, and for both standard and complex interventions.[316-319] Simulator training on pulsatile vascular models significantly improves surgical skills and the quality of carotid patch plasty.[320] Despite reported limitations in research methods, there is consistent evidence from systematic reviews[321-323] and randomised studies[324-326] that simulator-based training, including formative feedback, may improve both technical and non-technical clinical skills, preventing avoidable mistakes and that the learning effect can then be transferred to the clinical environment. The few studies that evaluated the effects of simulation training on patient outcomes[327-332] showed either improved patient-related outcomes or no difference compared to patient-based training, indicating that simulator training is of value and without risks for patients. Patient-specific simulation and the feasibily to rehearse emergent procedures and management of complications may be of particular value.[325-328,333-336]

Delphi panels, grading metrics, and CE-marked/FDA-approved modules for case rehearsal aim to assure a quality standard for CAS rehearsal.[333,334] Recent guidelines incorporate simulation training as part of the credentialing in neurovascular procedures, including tandem lesions.[128,129]

DECISION-MAKING IN CAROTID ATHEROSCLEROTIC DISEASE

Role of the Multidisciplinary Team (Neuro-Vascular Team) and the Patient

The treatment of most vascular diseases (eg., coronary, valvular heart disease, peripheral arterial disease) is increasingly a multi-speciality task. Similarly, the management of acute stroke has become more multi-speciality, a trend accelerated by the move towards endovascular thrombectomy for large vessel stroke. Patients at risk need to be discussed by a multidisciplinary Neuro-Vascular Team. A neurologist/stroke specialist can evaluate the causal link between the carotid stenosis and presenting

stroke, a vascular surgeon (together with an anaesthetist) can assess suitability for surgery, and an interventionalist can assess suitability for stenting. Then, the multi-disciplinary team can weigh up the advantages and disadvantages of medical therapy alone, carotid stenting or carotid surgery. All treatment options should then be discussed with the patient, thereby allowing individualized, fully-informed, decision-making. Involving the patient (see **Central Illustration**) and, with consent, their carers or family, in the decision-making process may also help with long-term adherence to medical therapy that plays an important part in the long-term efficacy of the intervention.

Balancing the benefits and risks of intervention is particularly important when considering asymptomatic carotid intervention, and in contrast to the rapidity of decision-making required for acute stroke cases, where 'time is brain', all ASxCS cases being considered for intervention should be discussed by a multi-disciplinary team, ensuring that the risks of intervention are low, and justified when compared with the lifetime risk of stroke if the patient were managed with triple medical therapy alone.

CAROTID STENOSIS IN SPECIFIC CLINICAL SCENARIOS

Acute carotid-related stroke: isolated proximal internal carotid occlusion stroke and "tandem lesion" stroke

Tandem strokes, defined as acute ischemic events in a carotid territory presenting with an extra-cranial internal carotid artery stenosis or occlusion, and a co-incident ipsilateral large vessel occlusion, account for at least 25% of all stroke cases.[336-339] In fact, approximately 50% of all extracranial internal carotid artery (ICA) occlusions presenting as acute stroke will have a middle cerebral artery occlusion as well ("tandem" lesions); the other 50% are isolated occlusions of proximal ICA.[340-344]

The clinical presentations of carotid-related strokes, although very similar to strokes caused exclusively by intra-cranial occlusions, range from a transient ischemic event to a major stroke causing significant neurologic disability. With the large volume of affected cerebral tissue, carotid-related strokes are often

disabling or fatal. Indeed, a larger clot burden is seen in carotid-related strokes, and these strokes poorly respond to thrombolytic therapy (recanalization rates may not exceed 10%)[345-347] and tend to have a poorer prognosis in terms of permanent disability (ranging from 40-69%) and death (seen in 16-55% of cases), and a good recovery seen in only 2-12% of cases.[341,342] The large clot volume also impedes the delivery of tPA to the intracranial vasculature and reduces its efficacy.[341,342] In carotid atherothrombosis, the presence of an ipisilateral MCA occlusion usually is related to an artery-to-artery embolism, with platelet-rich lytic-resistant clot generated at the carotid plaque.[348] Carotid lesion-related strokes show poor recanalization rates with thrombolysiseven if the (atherosclerotic lesion-containing) carotid artery is patent.[349]

None of the pivotal clinical trials of mechanical thrombectomy for acute ischaemic stroke randomized patients with isolated extracranial carotid artery occlusions, and only a 2 studies allowed to enroll patients with "tandem" lesions.[350] Despite the HERMES meta-analysis which showed that the endovascular thrombectomy has an equivalent therapeutic effect in patients with isolated intracranial oclusions and tandem occlusions,[337] there is a lack of randomized data regarding management of acute extracranial stenosis or occlusion (particularly if "isolated"; ie., in absence of concomitant intracranial large vessel occlusion).[351] As the overall need for (and patient benefit from) emergency cerebral vessel recanalization in acute ischaemic stroke is evident, it is highly unlikely that any randomized trial evidence focused specifically on carotid-related stroke revascularization would be generated, particularly as randomizing patients with carotid-related stroke to intervention vs. no intervention would be considered unethical. With the overall progress of the field, it would be thus unreasonable today to expect level-1 evidence for revascularizing (vs not revascularizing) carotid-related stroke on an emergency basis, if the patient presents with viable cerebral tissue. Furthermore, the endovascular treatment horizons – now expanding to larger cores[352] – are anticipated to soon reach carotid-related stroke management.

2021 European Stroke Organization guideline on revascularization for carotid artery stenosis did not address carotid revascularization done as part of acute stroke therapy;[8] however, based on evidence suggesting that recanalization is key for improved outcomes, emergency carotid lesion treatment should be performed both in "isolated" carotid (sub)occlusions and in tandem lesions.[127,352] As in carotid-related stroke recanalization rates are low with intravenous thrombolysis,[345-349] mechanical reperfusion therapies are a powerful therapeutic option (Suppl Tab 6A and 6B in Appendix 6).[127,353] Endovascular extracranial carotid revascularization (with mechanical thrombectomy, MT, in case of coexisting intracranial large vessel occlusion) is associated with higher recanalization rates and markedly improved functional outcomes compared with thrombolysis.[354-357] Endovascular treatment strategies for tandem strokes include MT with or without CAS or balloon angioplasty for extracranial thrombotic/atherosclerotic burden. No consensus exists regarding the order of intervention, i.e., stenting first or thrombectomy first;[357,358] thus, in real life, this is driven by case-specific anatomic and lesional factors. For details see (Suppl Tab 6C in Appendix 6).

Scarce data suggest that emergency CEA may be a valid therapeutic option in selected patients with carotid-related acute stroke;[359-361] however, worse outcomes have been reported for CEA accompanied by cerebral endovascular intervention.[362]

Stroke in patients with both carotid disease and atrial fibrillation

High-grade carotid stenosis is present in around 10% patients with non-valvular AF[363] and aroud 10% of patients in all-comer CarAS revascularization registries have AF.[363-365] In stroke patients with carotid stenosis and AF, the cerebral infarct is more often on the side ipsilateral to the carotid lesion,[366] consistent with a mechanistic role of CarAS.

In the ROCKET-AF trial comparing rivaroxaban versus warfarin in patients with AF, co-existing carotid artery disease did not increase stroke risk.[367] Thus, there is no evidence to support the addition of aspirin to oral anticoagulation in patients with ASxCs stenosis and concomitant AF. In patients with a stroke or TIA who have an ipsilateral carotid stenosis and AF, it may be a challenge to identify the true underlying cause. Arguments for carotid aetiology include a severe degree of stenosis, clinical or imaging evidence for repetitive ipsilateral emboli, or imaging features of plaque instability. Reviewing patterns of cerebral ischaemia on DWI may be particularly useful if additional acute lesions are present in brain areas supplied by the contralateral carotid artery or in the vertebrobasilar territory, which is consistent with a proximal (i.e. aortic or cardiac) source of embolism.[368] Patients with symptomatic carotid stenosis and concomitant AF may benefit from temporarily adding antiplatelet therapy to prevent early recurrent stroke before carotid revascularisation or during the first few weeks and up to three months of conservative management, but a careful assessment of bleeding risks and anti-thrombotic benefits is essential. A recent retrospective analysis in 5708 patients with AF and CarAD after ischaemic stroke suggested that the use of a NOAC without an antiplatelet agent(s) was associated with a lower risk of major bleeding with no negative impact on recurrent stroke or mortality.[369] However, evidence from randomised trials is needed to confirm this finding.

Cardiac surgery in patients with significant carotid stenosis

The procedural stroke risk during or shortly after coronary artery bypass graft (CABG) is around 1-2%. But, for the ≈5% of patients undergoing CABG who also have a tight (ie., >80%) ICA stenosis, the risk of perioperative stroke is markedly elevated, at around 9%.[370-376] Significant predictive factors for post-CABG stroke include: (i) carotid bruit (OR 3.6, 95% CI 2.8-4.6), (ii) prior stroke/TIA (OR 3.6, 95% CI 2.7-4.9) and (iii) severe carotid stenosis (OR 4.3, 95% CI 3.2-5.7).[370,371] However, not all such strokes are directly related to carotid stenosis, and other mechanisms (e.g., clamping/de-clamping of the aorta) may

contribute to stroke risk.[370,371,377] In patients undergoing cardiac surgery, stroke risk is higher in bilateral CarAD (stroke risk increase from 3% in unilateral CarAD to 5% in bilateral CarAD),[370,371] and yet greater in patients with recent neurologic symptoms. There is no randomized evidence to guide practice when considering prophylactic carotid revascularization in patients undergoing CABG. Symptomatic carotid stenosis patients should have synchronous or staged carotid intervention.[378] For asymptomatic disease, bilateral high-grade stenosis or unilateral severe stenosis with contralateral occlusion may benefit from carotid intervention that is usually performed prior to cardiac surgery.[379,380] The timing and sequence of revascularization are influenced by the symptom status of the patient, the severity of disease, and the urgency of revascularization.[226] There is general agreement that patients with symptomatic carotid stenosis (peri-CABG stroke risk 8.5% in case of the carotid stenosis unaddressed) require carotid revascularization in the context of cardiac surgery.[370,381,382] Extreme-risk, unstable patients with symptomatic carotid stenosis may benefit from simultaneous single-stage cardiac surgery and endovascular carotid revascularization with carotid lesion sequestration (micronet-covered stent) under open-chest cardiopulmonary bypass[383] but larger-scale comparative studies are needed to determine optimal management in these patients.

Routine revascularisation is not recommended in unilateral ASxCS prior to or synchronous with CABG.[384,385] Patient-centered advice by a combined Heart Team and Neurovascular Team are encouraged, taking into consideration patient-specific factors (clinical presentation, cerebral and carotid imaging, lesion severity and characteristics) in the context of local feasibilities and expertise[257,386,387] (see **Central Illustration**). Some, but not all, cardiac surgery centres perform routine carotid DUS evaluaton prior to cardiac surgery to risk-startify the patients and tailor management.[387,388] Carotid bruit, age greater than 65 years, peripheral arterial disease, history of TIA or stroke, smoking, or left main coronary artery disease are associated with an increased risk of carotid stenosis that may require revascularization.[7,226]

EVIDENCE NEEDS, ON-GOING STUDIES, AND EMERGING RESEARCH AREAS

Screening for carotid stenosis: whether, whom, and how?

There is an ongoing debate on the role of screening for ASxCS in preventing ischaemic stroke.[389,390] There is no doubt that screening for AsxCS may expose health systems to additional costs.[389] But, identification of large numbers of patients with carotid stenosis may enable the use of evidence-based triple medical therapy to substantially reduce overall cardiovascular risk.[103,391-393] A proportion of patients may be at a particularly high risk for stroke, and intervention can then be discussed at a multi-disciplinary (Neuro-Vascular) team session, and intervention considered (taking into account preferences of the patient).[386] A selective screening for AsxCS[172], targeting a population at increased risk of prevalent disease (Suppl Tab. 8 in Appendix 8) includes determining the target population, determining the screening method, and establishing validated prognostic risk scores in AsxCS (such as CHA_2DS_2-VASC in AF)[171,172]. A recent survey of clinical practice of 223 respondents from 46 countries revealed that the first-line carotid imaging modality was an ultrasound, CTA and MRI, respectively, in 88.8%, 7% and 4.2% for asymptomatic disease[394] and some propose DUS[393] or MRI[395] as a first-line screening tool.

Twelve prediction models aiming to identify high-risk populations and detect ACS were developed in five studies (Suppl Tab. 8 in Appendix 8). The most reliable risk factors were diabetes, hypertension, history of cardiovascular disease and dyslipidaemia. Recent analysis of 400 000 individuals (aged 40-80 years) without cardiovascular disease indicated efficacy of selective (risk-based) screening for ASxCS, targeting populations at increased cardiovascular risk using the the Atherosclerosis Cardiovascular Disease Risk Equation.[396] Selective screening of participants with a predicted 10-year CVD risk of ≥20% identified 40% of ACAS cases (number needed to screen 27), whereas selective screening of those with a predicted 10-year CVD risk of ≥15% identified 54% of ACAS cases (number needed to screen 31).[397] However, no formalized screening recommendations exist at present.

Carotid revascularization and cognitive function

Carotid stenosis is associated with cognitive impairment in both asymptomatic and symptomatic patients, with cognitive decline present – even without visible pathological damage in the brain.[398-403] It is not clear whether this relationship is causal, and there is no reliable randomized evidence that treatment of CarAD with surgery or stenting prevents dementia or cognitive decline.[404] The results of non-randomized studies are inconsistent. Some report improved neurocognitive function after CAS[405-409], one study reports no change[410], whilst some describe a mixed effect.[411] However, cognitive decline has also been reported after CAS and CEA[412-414] whereas two papers reported benefits after CEA.[415,416] Studies evaluating the effect of CEA and CAS on cognitive function differed on a number of methodological issues such as sample size, type of patients (demographic, mood/depression, microemboli, TIA or stroke), control group, the severity and side of the carotid stenosis, intima-media thickness, the range of cognitive tests, type of analysis, and the time of assessment - which may explain differences in results.[398] Any RCT designed to assess the effect of carotid surgery or stenting on dementia needs to be both very large and have a very long follow-up due to the insidious nature of dementia. Alternatively, detailed and sophisticated cognitive testing at baseline and repeated at annual follow-up may allow detecting a more subtle effect on cognitive decline, which may be a pre-cursor to clinically evident dementia.

Ongoing research

Pharmacologic prevention studies are ongoing in patients with atherosclerosis, including investigation of new LDL-lowering molecules, new LP(a)-lowering molecules, and new anticoagulants such as FXIa inhibitors;[138] those studies usually include subjects with CarAD but are not specifically focused on this patient group.

While several fundamental questions regarding carotid revascularization to reduce stroke risk are being addressed in on-going clinical studies, others (such as level-1 evidence for cerebral protection in CAS, and large-scale trials comparing 2nd generation CAS with contemporary CEA) remain unanswered by RCTs. Large-scale RCTs are becoming more difficult to undertake, but are essential to compare the long-term efficacy of different treatments such as CAS vs CEA. Appropriately designed, large-scale trials are feasible[417] but the role of external data monitoring to ensure quality remains essential. In contrast, the contemporary procedural risks associated with different modes of carotid intervention are perhaps best captured in large registries, ideally with independent data monitoring and neurological assessment to reliably ascertain procedural stroke rates.

Whether (and to what extent) intervention in ASxCs still leads to worthwhile reductions in stroke in patients receiving intensive goal-directed medical therapy is being evaluated in three trials. ECST-2 has randomised over 400 patients to carotid intervention versus contemporary medical therapy and is in follow-up, with a primary imaging-based endpoint (cerebral MRI). CREST-2 is directly comparing CAS (and separately CEA) with intensive goal-directed medical therapy in ASxCS stenosis. CREST-2 has almost completed recruitment (n=2400 target) of asymptomatic patients to either CEA on top of intensive medical therapy vs intensive medical therapy alone (n=1200) or CAS on top of intensive medical therapy versus intensive medical therapy alone (n=1200), with results anticipated in the mid-2020s. Finally, a French study (ACTRIS) aims to randomize 700 asymptomatic patients with 'high-risk for stroke' features to intervention versus medical therapy. It needs to be understood that the ability of these studies to detect a difference between contemporary medical treatment alone vs intervention (CEA or CAS) performed on top of OMT to reduce stroke risk will critically depend on effective randomization (and retention in the medical-only arm) of clinically asymptomatic patients at increased stroke risk. This may be difficult as the 2017 ESC/ESVS Guidelines have introduced increased-risk features into clinical decision-making (a notion upheld in the 2021 ESO Guidelines); thus, increased-risk patients (Suppl Table

2) may tend to gravitate to intervention outside the study rather than randomization.[58] This problem is inseparably linked to the other research challenge – how to best apply in a cost-effective fashion[418] a personalised medicine approach to CarAS detection[419] and intervention[420] to identify high-risk patients that will benefit particularly from invasive treatments like surgery or stenting.

Summary and conclusions

The carotid atherosclerotic disease remains an important, modifiable risk factor for thromboembolic and haemodynamic stroke. Advances in medical therapies have been considerable, and all patients with CarAD should receive modern goal-directed triple medical therapy to reduce their overall cardio-vascular risk. However, effective lifestyle modification and uptake of OMT in CarAS patients remains a challenge even in well-developed healthcare systems[152,164,421] thus efforts are needed to enhance CarAD patient education about the stroke risk and overall cardiovascular risk to increase OMT uptake and to maximize patient adherence to OMT.

Furthermore, despite good medical therapy, the residual risk of stroke remains, and this can be reduced further in selected patients with competent carotid surgery or competent carotid stenting. Randomised trials and registries indicated that CEA, in the peri-procedural period, is safer than 1st generation CAS (with the difference driven mainly by minor strokes by 30-days); thus CEA is preferred in guidelines in most (not all) clinical scenarios. However, most recent registries and randomised evidence indicate that improved intra-procedural cerebral protection in CAS and 2nd generation (plaque-sequestrating) carotid stents may significantly reducie intraprocedural plaque-related embolism and eliminate post-procedural cerebral embolism. These technical improvements play an important role in contemporary, competent CAS.

Medical therapy, stenting and surgery will continue to evolve, as will the ability to identify patients at a particularly high risk of stroke on maximized medical therapy alone, in whom the intervention is appropriate to reduce stroke risk.

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