Guidelines in the Endovascular Management of Carotid Artery Disease

Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. These guidelines should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by a responsible health care professional(s) in consultation with the patient and caregiver as appropriate. These guidelines have an impact on clinical practice and hence quality criteria have been established to make all decisions transparent to the user. The level of evidence and strength of recommendation of particular mangement options were weighed and graded according to pre-defined scales as outlined in tables 1 and 2 (1).

In cases of conflict in classes of recommendation or levels of evidence, the higher class of recommendation or level of evidence is accepted and presented without discussing the intricacies or minutae of the conflict. We have also not presented controversial/ in-adequate recommendations or recommendations that require more evidence before widespread acceptance that may or may not be published by individual societies or journals. These guidelines have been combined and amalgamated from a number of existing guidelines from different societies, journals and textbooks in a way so as to represent our combined position on the subject in a balanced and unbiased manner.

Table 1: Classes of recommendations

Classes of recommendations	**Definition**	**Suggested wording to use**
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence and/or general agreement that a given treatment or procedure is not useful/effective and in some cases may cases may be harmful.	Is not recommended

Table 2: Levels of evidence

Level of evidence A (LOE A)	Data is derived from multiple randomised clinical trials or meta-analyses.
Level of evidence B (LOE B)	Data is derived from a single randomised clinical trial or large non-randomised studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies,

(LOE C)	retrospective studies, registries.

Introduction

Stroke is the third leading cause of death and the most important cause of long term disability. The case fatality rate varies between 15%-35% with the first episode that rises to 65% with subsequent episodes. The majority of these episodes recur in the same anatomic region as the first stroke and occur within one year. Ischemic strokes comprise 85% of all strokes. A large majority of ischemic strokes upto 76% have angiographic evidence of complete occlusion of internal carotid artery, middle cerebral artery or its branches. Furthermore, a large number of these strokes are embolic in nature and cerebrovascular in origin (2).

Carotid artery stenosis is responsible for 10%-15% of all ischemic strokes. The unique hemodynamics in this location predisposes this region to atherosclerotic plaque formation (3, 4). The largest plaque accumulation is typically seen on the outer wall of proximal segment of carotid sinus. This region has the lowest wall shear stress (5). Plaque disruption and atheroembolism are the commonest mechanism of ischemic stroke (3, 4).

Pathophysiology

Atherosclerotic plaques are predisposed to develop at flow dividers and branch points where both turbulence and shifts in shear stress are frequent. Early plaques are initiated by intimal accumulation of lipoproteins. Subsequent, oxidative modification and cytokines facilitate their uptake and migration of monocytes into the arterial wall. The monocytes accumulate lipid and form “foam cells”, that further release cytokines, oxidants and matrix metalloprotineases. Subsequently, smooth muscle cells migrate from media to intima, proliferate and secrete extracellular matrix forming the central necrotic lipid core surrounded by connective tissue and fibrous plaque that gets calcified in an advanced stage.

Cerebrovascular events occur due to artery-to-artery embolism of plaque thrombus or atheromatous debris/cholesterol crystals, acute thrombotic occlusion secondary to plaque rupture, arterial wall damage due to dissection/ subintimal hematoma and reduced cerebral perfusion from critical stenosis/ occlusion due to progressive plaque growth. Insufficient intracranial collateral circulation is also responsible for a minority of patients who present with neurological symptoms due to arterial stenosis/occlusion (4).

Definition

Atherosclerotic plaque undergoes an initial phase of outward growth. This process is called “arterial remodelling”. With continued growth there is luminal compromise and stenosis. Plaque disruption and thrombus formation that cause progressive luminal compromise and increasing degree of stenosis. Also, plaque rupture, superficial plaque erosion and erosion of a calcific nodule cause plaque disruption and subsequent cerebral thromboembolism. Intraplaque hemorrhage from friable microvessels at plaque base contributes to plaque expansion (4).

Disease Burden

In Framingham Heart Study population, the prevalence of carotid stenosis (>50%) was 7% in women and 9% in men (4). The prevalence of moderate (>50%) asymptomatic carotid stenosis (ASCS) in men aged <50 years and men aged >80 years varies between 0.2% and 7.5% and in women it varies between 0% and 5%. The prevalence of severe (>70%) ASCS in men aged <50 years and men aged >80 years

varies between 0.1% and 3.1% and in women it varies between 0% and 0.9% (6). In India, a multicenter study conducted in individuals >40 years of age found the prevalence of moderate (>50%) ASCS and severe (>70%) ASCS to be 5.2% and 1.6% respectively (7). However, it is important to bear in mind that even subclinical carotid disease is associated with furture stroke as also is mild carotid stenosis associated with symptomatic cryptogenic strokes that are often recurrent (4).

Diagnosis

There are two different methods of measurement of degree of carotid stenosis. These measurements are derived from the techniques used in their eponymous trials namely the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST). The NASCET method is used as the measurement methodology throughout this document. The ECST method has an advantage in the rare condition of large bluky plaques within capacious carotid bulbs where the residual luminal diameter is only slightly less than that of distal normal carotid artery and is often underestimated as carotid stenosis <50% by NASCET method. In such a condition, revascularization should be considered in patients with an ESCT carotid stenosis >70% (8).

Duplex ultrasound (DUS) is usually the first line imaging modality due to its low cost and accessibility. DUS criteria used to define stenosis thresholds involve measurement of peak systolic velocity, end diastolic velocity and ratio of internal and common carotid artery velocities based on NASCET method. These criteria are described in further detail elsewhere (8). DUS has a sensitivity of 94% and a specificity of 92% in diagnosing 60-99% carotid stenoses. However, the accuracy of DUS varies considerably especially in inexperienced hands.

Magnetic resonance angiogram (MRA) and computed tomogram angiogram (CTA) have the advantage of simultaneous assessment of aortic arch, supra-aortic vessels, carotid arteries and intracranial circulation (8). Contrast-enhanced MRA has a greater accuracy compared to noncontrast MRA techniques. A Health Technology Assessment (HTA) meta-analysis has shown that DUS, MRA and CTA are equivalent in detecting significant stenosis. The HTA also advise that in centers relying solely on DUS to assess severity should undergo a second corraborative DUS scan, preferably by a second operator. Cerebral digitral subtraction angiogram (DSA) is required in patients with significant discrepancies on cross-sectional imaging (8).

Interventions in asymptomatic carotid artery stenosis (ASCS)

The Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST-1) were responsible for establishing practice guidelines advocating CEA when 30 day mortality/stroke rate was <3% and patient had a life expectancy of >5years. However, these trials recruited patients between 1983-2003, when the concept of BMT (Best Medical Therapy) did not include statins and a greater proportion of patients smoked (8).

Caveats related to Age, Gender and Stenosis severity in ASCS

The aforementioned studies showed that more than half the patients >75 years of age randomised to CEA(Carotid Endarterectomy) were dead within 5 years. However, once the perioperative risks were included (3.7%) there was no evidence that CEA conferred any benefit in patients aged >75 years. An early meta-analysis of pooled data from the above studies showed that at 5 years; CEA conferred no benefit in females. After a 10-year follow-up, ACST-1 reported that females now gained a similar benefit to men. This was attributed to lower background stroke risk in females, so benefit took longer to manifest. Both the aforementioned studies, reported that increasing stenosis severity was not associated with increased rates of late stroke, unlike that seen in symptomatic carotid stenosis (SCS). A further meta-analysis of 41 studies, showed no statistically significant difference in ipsilateral stroke risk due to ASCS between 50-70% stenosis and 70-99% stenosis (8).

Management

Medical Management or Best Medical Therapy (BMT)

Control of Risk factors:

A healthy diet, smoking cessation and physical activity is recommended for all patients with ASCS **(Class I, LOE B)** (8)**.**

Antiplatelet therapy

Montherapy with low dose aspirin has been shown to confer benefit by decreasing stroke severity at presentation and improved functional outcomes at discharge in patients with large artery atherosclerotic strokes and reducing the number of non-fatal myocardial infarctions.

Monotherapy with low-dose aspirin (75-325 mg) is recommended in ASCS patients for prevention of late myocardial infarction and other cardiovascular events **(Class I, LOE A).**

Clopidogrel 75mg daily is reserved for patients with aspirin intolerance **(Class IIa, LOE C)** (8).

Lipid lowering therapy

The mainstay of lipid lowering therapy in carotid artery stenosis patients is statins. The dosage and/or intensity of statin therapy is based on studies of patients with symptomatic and asymptomatic cardiovascular disease. These studies advise high-intensity statin with treatment goals like low-density lipoprotein (LDL) level <1.8mmol/L (70mg/dl) or 50% decrease in LDL levels by either 40-80mg atorvastatin or 20-40mg rosuvastatin. Statin therapy is also known to decrease peri-operative strokes and deaths following CAS (Carotid Artery Stenting) and CEA (8).

Statin therapy is recommended for long-term prevention of stroke, myocardial infarction and other cardiovascular events in ASCS patients **(Class I, LOE A).**

Management of systemic hypertension

Management of hypertension is associated with decreased progression and regression of CAS. A randomised, double-blind multi-center European trial showed greater reductions in carotid IMT progression, plaque regression, fewer atherosclerotic plaques despite smaller falls in blood pressure with a calcium channel blocker compared to a beta-blocker suggesting an independent, anti-atherosclerotic action of

calcium channel blocker in patients with systemic hypertension. Both calcium channel blockers (CCBs) and ACE inhibitors (ACEIs) are known to decrease carotid intima-media thickness (IMT) progression. However, CCBs reduce IMT progression more than diuretics, beta-blockers or ACEIs.

Antihypertensive treatment is recommended in hypertensive ASCS patients to maintain long term blood pressure <140/90mmHg **(Class I, LOE A).**

The target blood pressure in diabetic ASCS individuals should be <140/85mmHg **(Class I, LOE B)** (8).

Management of Diabetes Mellitus

Diabetes mellitus is associated with increased risk of ASCS and doubles the risk of stroke. However, meta-analyses do not show evidence of a statistically significant reduction of stroke risk with tight glycemic control, though it does reduce microvascular diabetic complications (8).

In diabetic ASCS patients strict glycaemic control is recommended **(Class I, LOE C).**

Screening for ASCS patients

Routine population screening for ASCS patients is not recommended **(Class III, LOE C).**

Controversy over modern BMT

There have been questions raised regarding the relevance of ACAS and ACST-1 trials in the era of modern BMT. Several studies have indicated that the current annual stroke risk may be less than when ACAS and ACST-1 were recruiting. In a meta-analysis; the rate of ipsilateral stroke was 2.3/100 person-years in studies that completed recruitment prior to 2000, compared to 1.0/100 person-years in studies with recruitment between 2000-2010. This nearly 40% decline was attributed to improvement in BMT and smoking cessation. A review in 2011, suggested there was a temporal trend of decreasing annual stroke rates across all grades of stenosis at baseline. This trend was also evident in the ACAS and ACST-1 trials. This awareness has given impetus to a number of ongoing trials that have included a BMT arm in ASCS patients. These trials include CREST-2, ECST-2, ACST-2 and ACTRIS.

The American Heart Association (AHA) has repeatedly advised that only "highly selected" asymptomatic patients should undergo CEA but without defining the "highly selected" group (8). Accordingly, some believe an uncritical recommendation to revascularize "highly-seleected" patients without defining the group as unjustifiable.

It has been suggested that while awaiting data from the aforementioned trials, it is imperative to identify a smaller but higher risk ASCS cohort who need carotid angioplasty and stenting/ CEA. The following clinical and imaging criteria have been used to segregate patients with higher risk of stroke in patients with 60%-99% carotid stenosis. The criteria are listed in Table 3 (1, 8).

Table 3: Features associated with increased risk of stroke in ASCS patients managed medically

Clinical	Contralateral stroke/TIA
Cerebral Imaging	Ipsilateral silent infarction
Ultrasound Imaging	Stenosis progression (>20%) Spontaneous embolization on transcranial Doppler (HITS) Impaired cerebrovascular reserve Large (>40mm^2) plaques Echolucent plaques

	Increased juxtablack (hypoechogenic) area
MRA	Intra-plaque hemorrhage Lipid-rich necrotic core

Interventions in symptomatic carotid artery stenosis (SCS)
The term "symptomatic" means a patient has suffered carotid territory symptoms within the preceeding 6 months. These symptoms are 1. Hemi-sensory (numbness, paraesthesia of face/arm/leg) 2. Hemi-motor (weakness of face/arm/leg or limb clumsiness) and 3. Higher cortical dysfunction (dysphasia/aphasia, visuospatial problems). Most symptoms involve loss of function but occasionally a "limb shaking" TIA can occur. This is characterised by involuntary limb movements caused by haemodynamic failure due to severe carotid stenosis or occlusion.

Management

Medical Management or Best Medical Therapy (BMT)

Control of Risk factors:
A healthy diet, smoking cessation and physical activity is recommended for all patients with SCS **(Class I, LOE B)** (8)**.**

Antiplatelet therapy
Antiplatelet therapy should be initiated as early as possible after an index event as a meta-analysis found that early initiation of anti-platelet therapy had a 60% reduction in 6 week recurrent stroke and a 70% reduction of disabling or fatal stroke (8). Clopidogrel is the anti-platelet drug of choice in SCS patients. Early initiation of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in patients with "high-risk TIA" defined as ABCD score ≥4 (Age, Blood pressure, Clinical features, Duration of TIA and presence or absence of diabetes mellitus); found a significant (32%) RRR of recurrent stroke compared to asprin alone with no excess riks of moderate/severe hemorrhage. Subgroup analysis found DAPT was particularly beneficial in patients with extracranial carotid or MCA stenoses. Early DAPT therapy prior to urgent CEA found significant decrease from 21% to 5%, p=0.0047 in spontaneous embolization with a significant reduction from 13% to 3%, p=0.01 in recurrent events prior to CEA (8).
SCS patients should receive clopidogrel 75mg daily as the first line anti-platelet agent. If patient is clopidogrel intolerant; aspirin 75mg daily and modified release dipyridamole 200mg twice daily should be used. If intolerant to dipyridamole or clopidogrel, aspirin 75-325mg daily monotherapy should be used. If patient is intolerant to aspirin and clopidogrel; modified release dipyridamole 200mg twice daily should be used **(Class I, LOE A).** This guideline is also recommended by NICE (National Institute for Health and Clare Excellence).
Early institution of DAPT after TIA/minor stroke may be considered in SCS patients with >50% stenosis to reduce early recurrent events while awaiting further intervention **(Class IIb, LOE C).**

Antiplatelet therapy during CEA – A large RCT has demonstrated that regular administration of 150mg daily aspirin with a single 75mg clopidogrel dose on the night before CEA significantly reduced embolization rates in the first 3 hours after CEA compared to aspirin with placebo (p=0.01). Low dose aspirin (75-325mg daily) is recommended rather than high dose aspirin (>625mg daily) in patients undergoing CEA (8).

Antiplatelet therapy during CAS – It is recommended that patients undergoing CAS receive DAPT with aspirin (75-325mg daily) and clopidogrel (75mg daily). Clopidogrel should be started atleast 3 days prior to stenting or as a single 300mg loading dose in urgent cases. Perioperative DAPT is recommended for atleast 4 weeks after CAS **(Class I, LOE B).**

This recommendation is based on coronary literature with no data from large RCTs in patients with carotid stenosis (8).

Long term DAPT is not recommended in patients undergoing CAS unless indicated for cardiac reasons **(Class III, LOE C).**

Gastric protection in patients on antiplatelet therapy – Though, there was a substantial reduction in gastric bleeding in patients taking clopidogrel with proton pump inhibitors (PPIs); studies suggest that PPIs may reduce the effectiveness of clopidogrel. Current advise is to prescribe clopidogrel without any gastric protection medications in patients without risk factors. In patients with one or more risk factors, empirical ranitidine should be considered. If a proton pump inhibitor is preferrred, pantaprazole should be considered as it does not appear to interact with clopidogrel (8).

Concurrent gastroprotection treatment or proton pump inhibition with pantoprazole should be considered in patients prescribed clopidogrel who have one or more risk factors that increase the patient's risk of gastrointestinal bleeding (prior history of gastrointestinal bleeding, older age, Helicobacter pylori infection and concomitant use of aspirin/ other non-steroidal anti-inflammatory agents (NSAIDs), anticoagulants, selective serotonin reuptake inhibitors (SSRIs) or steroids) **(Class IIa, LOE B).**

Lipid lowering therapy

In the SPARCL study, 80mg atorvastatin at 30 days conferred a 33% RRR in fatal/non-fatal stroke as well as a 42% RRR in cardiovascular events in patients with prior TIA/stroke with a median carotid stenosis of 51% (8).

Statin therapy is recommended for long-term prevention of stroke, myocardial infarction and other cardiovascular events in SCS patients **(Class I, LOE A).**

Statins during CEA – Several studies have reported significant reductions in 30 day death/stroke in patients undergoing CEA started on pre-operative statin therapy (8). Patients on pre-operative statin therapy also have a significant reduction in spontaneous embolization compared to patients not on statins. Patients on statin therapy should not have it withdrawn abruptly as this is associated with significant increase in pre-operative cardiovascular morbidity and mortality.

Statins during CAS – Statin therapy is associated with significant reduction in 30 day death/stroke in patients undergoing CAS and pre-treatment with statins is advocated (8).

It is recommended that patients start statin therapy prior to stenting and that statin should not be stopped during the perioperative period and should be continued long term **(Class I, LOE B).**

Management of systemic hypertension
A meta-analysis of 13 trials in stroke patients showed a significant (34%) RRR in stroke in patients on anti-hypertensive therapy. Hypertensive symptomatic stroke patients should have long-term anti-hypertensive therapy to maintain blood pressure <140/90mmHg. As a blood pressure >180 mmHg is an independent predictor of stroke, patients requiring urgent carotid intervention and having a pre-operative blood pressure >180mmHg, should received urgent anti-hypertensive therapy to control blood pressure before carotid intervention. Furthermore, persistent or worsening blood pressure after carotid intervention, should receive anti-hypertensive therapy as raised blood pressure is associated with increased risk of hyperperfusion syndrome, intra-cranial haemorrhage, bleeding complications and cardiac events in the early post-operative period. Additionally, symptomatic patients with bilateral severe carotid stenosis should not undergo aggressive pre-operative blood pressure control (8).
Antihypertensive treatment is recommended in hypertensive SCS patients to maintain long term blood pressure <140/90mmHg **(Class I, LOE A).**
Caution should be exercised in significantly reducing blood pressure immediately prior to stenting in the early period after symptom onset, but uncontrolled hypertension (>180/90mmHg) should be treated **(Class IIa, LOE C).**
The target blood pressure in diabetic SCS patients should be <140/85mmHg **(Class I, LOE B) .**

Management of Diabetes Mellitus
In diabetic SCS patients strict glycaemic control is recommended **(Class I, LOE C).**

Interventions in asymptomatic carotid artery stenosis (ASCS)
The Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST-1) were responsible for establishing practice guidelines advocating CEA when 30 day mortality/stroke rate was <3% and patient had a life expectancy of >5 years. However, these trials recruited patients between 1983-2003, when the concept of BMT did not include statins and a greater proportion of patients smoked (8).

CAS versus CEA

"Average risk" for CEA patients:
There have been five RCTs that have compared CAS with CEA in "average-risk for CEA" patients. A meta-analysis of data from these revealed a 30-day death/stroke rate of 1.6% (95% CI 1.02-2.45) after CEA versus 2.7% (95% CI 2.1-3.6) after CAS (OR1.71, 95%CI 0.99-2.94, p=.0553). However, of these five RCTs, only two studies (CREST-1 and ACT-1) had experienced and credentialed CAS interventionists. Accordingly, in CREST-1, the 4-year rate of ipsilateral stroke was 8% with CAS versus 6.7% with CEA. Restenosis (>70%) was 6.7% at 4 years with CAS versus 6.2% with CEA (8). Furthermore, in the CEA group; there was a excess of peri-operative heart attacks that was associated with a 3.5 fold increased risk of death (HR-0.5, p=0.03) at 4 years (9). In ACT-1, perioperative stroke/death/MI, the 1-year rate of ipsilateral stroke was 3.8% with CAS versus 3.4% with CEA. The 5-year rate of ipsilateral stroke (excluding peri-operative events) was 2.2% with CAS versus 2.7%

with CEA (p=.51). Similarly, the 5-year rate of any stroke (excluding peri-operative events) was 6.9% with CAS versus 5.3% with CEA. At 1 year, the freedom from "target-lesion" revascularization was 99.4% after CAS and 97.4% after CEA (8). In ASCS patients, the 4-year rate of primary end-point (30-day rate of stroke, death and myocardial infarction and 4-year ipsilateral stroke rate) was 5.6% for CAS versus 4.9% for CEA (HR 1.17). By comparison, in SCS patients, the rates were 8.6% with CAS versus 8.4% with CEA (HR 1.08). This was further confirmed by ICSS (International Carotid Stenting Study), a large multicenter, randomised international study of SCS patients where the cumulative 5-year risk of fatal or disabling strokes, did not differ between CAS and CEA (6.4% versus 6.5% HR=1.06) (10). Similarly in ASCS patients, ACT-1 has shown non-inferiority and shown clinical equipoise between CAS and CEA (11). Thus, currently equipoise between CAS and CEA is established in both SCS and ASCS patients (12).
However, in ACT-1 (largest completed RCT), the death/stroke rate was 2.9% after CAS barely less than the accepted threshold of <3% for carotid interventions, that many believe is too high, as there is significant apparent reduction in strokes after BMT alone. Also, concerns have been raised whether death/stroke rates in RCTs can be replicated in "real world" scenarios. An european systematic review of large registries found that 40% of registries reported stroke/death rates after CAS >3% and 14% reported stroke/death rates after CAS >5%. Similarly, multi-state audits have suggested that stroke/death rates after CEA often exceed the <3% established threshold (8).

"High risk" for CEA patients:

The SAPPHIRE study, Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy randomised "high risk for CEA" patients to either CAS or CEA arm. The high risk group was defined as patients with 70-99% stenosis with one or more of the following criteria: clinically significant cardiac disease (congestive cardiac failure, abnormal stress test or need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery, cervical radiation therapy, recurrent stenosis after CEA and age>80 years. There was no difference found in 1-year stroke, death and myocardial infarction in SCS patients. However, the majority of patients (70%) were asymptomatic, in whom the 30 day stroke/death rate was 5.8% with CAS and 6.1% with CEA. In ASCS patients, CAS had a better outcome than CEA (9.9% versus 21.5%; p=0.02). Furthermore, at 1-year significantly more patients required repeat revascularization (4.3% versus 0.6%; p=0.04) than CAS patients (13, 14). However, at these levels of risks, none would benefit from late stroke prevention, suggesting these patients should be treated with BMT alone (8).

Carotid Artery Stenting

CAS has emerged as a therapeutic alternative to CEA for the treatment of extracranial carotid artery disease. The potential advantages of CAS include: avoidance of general anaesthesia, avoidance of neck incision and subsequent cranial and cutaneous nerve damage, decrease in general surgery complications like myocardial infarction, treatment of surgically inaccessible lesions, decreased patient discomfort, reduced procedure and recuperation time (3, 15). The potential disadvantages include non-removal of atherosclerotic plaque and distal embolism during catheterization causing periprocedural stroke. The potential for atheromatous plaque disruption and dislodgement led to the introduction of cerebral protection devices. The chief purpose

of carotid stenting is prevention of long term stroke risk. CEA has been shown to be effective in preventing stroke over long term follow up periods of 10 years or longer. To be adjudged as an effective alternative to CEA, CAS needs to have similar long term effectiveness (15).
A Cochrane review of CAS compared to CEA and BMT in ASCS and SCS patients to assess its benefits and risks was conducted in 2012. The review included studies that did not require stenting as a compulsory part CAS procedures, studies that did not require compulsory use of protection devices and also studies where the operators had experience levels less than 10 CAS cases. Despite these obvious shortcomings, the review came to a number of useful conclusions. In SCS patients <70 years of age stenting may be offered as an alternative to CEA in centres with periprocedural stroke/death rates <6%. CAS must not be routinely offered to patients >70 years provided they are surgically fit and willing to undergo CEA that can be performed at standard risk. Stenting must also be considered in patients in whom surgery is contraindicated, associated with high risk of complications or when CEA is technically unfeasible. However, the review found inadequate data to justify stenting as an alternative to CEA in ASCS patients, but recommended continued inclusion of patients in randomised clinical trials offering both CAS and CEA i.e., SPACE-2/ECST-2 trials. The review recommended collection of more data to assess long term outcomes in patients treated with CAS to assess whether there is a high rate of re-stenosis after CAS in modern stenting procedures and to answer the question whether re-stenosis leads to higher rate of late recurrent stroke (3).
Furthermore, a cochrane review of randomised controlled trials in 2017, concluded that CEA has some benefit in patients with 50% to 69% SCS and is highly beneficial in 70% to 99% SCS without near-occlusion. There was no benefit seen in patients with near-occlusion in SCS (2). Near-occlusion is defined as 95%-99% stenosis with distal ICA collapse or a narrow calibre lumen with 'trickle flow' (8). However, this is applicable when surgery is done in surgically fit individuals. Furthermore, there was no evidence of benefit in women with 50% to 69% SCS with little evidence of benefit if CEA is delayed beyond 2 weeks of presenting symptoms (2).

The recommendations pertinent to CAS procedures in ASCS and SCS patients are as follows (1, 8, 16).

Diagnosis. *DUS (as first-line imaging), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses* **(Class I, LOE A).**
When CAS is being considered, it is recommended that the estimation of carotid stenosis by DUS be followed by MRA or CTA to evaluate the aortic arch as well as the extra and intracranial circulation **(Class I, LOE A).**
Vascular units that base management decisions on DUS stenosis measurement should state which measurement method is being used **(Class I, LOE C).**
Intra-arterial digital subtraction angiogram should not be performed in patients being considered for revascularization, unless there are significant discrepancies on non-invasive imaging **(Class III, LOE A).**

Embolic Protection Devices. *The use of embolic protection devices should be considered in patients undergoing CAS* **(Class IIa, LOE B).**
Proximal protection devices are not recommended in patients with advanced common carotid artery or external carotid artery disease or in patients with contralateral occlusion with insufficient collateralization **(Class III, LOE C).**

Stenting procedure. *It is recommended that atropine or glycopyrrolate be administered prior to balloon inflation during CAS to prevent hypotension, bradycardia or asystole* **(Class I, LOE B).**

Post Procedure. *First-line treatment of post carotid intervention hypotension should be adminstration of intravenous crystalloids together with volume expanders. If this fails to improve blood pressure, titrated intravenous vasopressors (dobutamine, dopamine, noradrenaline, phenylephrine) should be considered to maintain blood pressure >90mmHg* **(Class IIa, LOE C).**
It is recommended that invasive blood pressure monitoring be continued for 3 to 6 hours after CAS, followed by hourly noninvaive blood pressure monitoring for the first 24 hours **(Class I, LOE C).**
It is recommended that vascular units have written criteria for treating post procedural hypertension **(Class I, LOE C).**

Follow-up. *Patients suffering a late ipsilateral stroke/TIA in the presence of ipsilateral 50%-99% restenosis should undergo redo CEA/CAS* **(Class I, LOE A).**
It is recommended that patients suffering from a late ipsilateral stroke/TIA in the presence of ipsilateral <50% restenosis should be treated medically **(Class I, LOE A).**
It is recommended that CAS patients with asymptomatic restenosis >70% are treated medically **(Class I, LOE A).**
Serial surveillance and reintervention for asymptomatic restenosis >70% is recommended in patients who developed neurological symptoms during balloon inflation (or proximal flow reversal) during CAS **(Class I, LOE C).**
When a decision has been made to undertake revascularization in patients with a restenosis, it is recommended that the choice of redo CEA/CAS should be based on multi-disclipinary team review, local surgeon/interventionist preference and patient choice **(Class I, LOE C).**

In ASCS Patients:
In 'average surgical risk' patients with 60%-99% stenosis, in the presence of clinical/imaging characteristics that may be associated with an increased risk of late ipsilateral stroke (Table 3), CAS may be an alternative to CEA, provided documented peri-operative stroke/death rates are <3% and the patient's life expectancy is >5 years **(Class IIb, LOE B).**
In patients deemed 'high-risk for CEA', with 60%-99% stenosis, in the presence of clinical/imaging characteristics that may be associated with an increased risk of late ipsilateral stroke (Table 3), CAS should be considered, provided documented peri-operative stroke/death rates are <3% and the patients life expectancy is >5 years **(Class IIa, LOE B).**

In SCS Patients:

When revascularization is indicated in 'average surgical risk' patients, CAS may be considered an alternative to CEA, provided the documented procedural stroke/death rate is <6% **(Class I, LOE B).**

In recently symptomatic patients with 50%-99% stenosis, with adverse anatomical features (restenosis, high cervical [above C2 vertebral level], intrathoracic [below level of clavicles], post radiation therapy) or medical comorbidities that are considered to make them 'high risk for CEA' CAS should be considered, provided the documented procedural stroke/death rate is <6% **(Class IIa, LOE B).**

It is recommended to perform revascularization in patients with 50%-99% stenosis as soon as possible, preferably within 14 days of symptom onset **(Class I, LOE A).**

Revascularization is not recommended in patients with <50% stenosis **(Class III, LOE A).**

CAS is not recommended in SCS patients with a chronic internal carotid near-occlusion, unless associated with recurrent ipsilateral symptoms (despite optimal medical therapy) and following multidisciplinary team review **(Class III, LOE C).**

Carotid revascularization should be deferred in SCS patients with 50%-99% stenosis with disabling stroke (modified Rankin scale ≥3), area of infarction exceeds one-third ipsilateral MCA territory and in those with altered consciouness or drowsiness to reduce risks of post procedural parenchymal hemorrhage **(Class I, LOE C).**

SCS patients with 50%-99% stenosis presenting with crescendo TIAs/stroke-in-evolution should be considered for urgent revascularization preferably <24 hours **(Class IIa, LOE C).**

CEA or CAS may be considered in patients with <50% carotid stenosis if they suffer from recurrent symptoms despite best medical therapy and following multidisciplinary team review **(Class IIb, LOE C).**

In conclusion, there are some patients with better outcomes on CEA(for example, tortuous aorta and its branches) and some with better outcomes on CAS (for example, high surgical risk patients), but most patients can be treated with either procedure. Clinical equipoise has been reached between CAS and CEA and future trial designs on carotid stenosis acknowledge this equipoise.

References:

1. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). European heart journal. 2018 Mar 1;39(9):763-816. PubMed PMID: 28886620. Epub 2017/09/10. eng.

2. Orrapin S, Rerkasem K. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database of Systematic Reviews. 2017 (6). PubMed PMID: CD001081.

3. Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database of Systematic Reviews. 2012 (9). PubMed PMID: CD000515.

4. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. Stroke; a journal of cerebral circulation. 2011 Aug;42(8):e420-63. PubMed PMID: 21282494. Epub 2011/02/02.

5. Virmani R, Ladich ER, Burke AP, Kolodgie FD. Histopathology of carotid atherosclerotic disease. Neurosurgery. 2006 Nov;59(5 Suppl 3):S219-27; discussion S3-13. PubMed PMID: 17053606. Epub 2006/10/21. eng.

6. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke; a journal of cerebral circulation. 2010 Jun;41(6):1294-7. PubMed PMID: 20431077. Pubmed Central PMCID: PMC4254855. Epub 2010/05/01. eng.

7. Kaul S, Alladi S, Mridula KR, Bandaru VC, Umamashesh M, Anjanikumar D, et al. Prevalence and risk factors of asymptomatic carotid artery stenosis in Indian population: An 8-year follow-up study. Neurology India. 2017 Mar-Apr;65(2):279-85. PubMed PMID: 28290390. Epub 2017/03/16. eng.

8. Writing G, Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, et al. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2018 Jan;55(1):3-81. PubMed PMID: 28851594. Epub 2017/08/31. eng.

9. Blackshear JL, Cutlip DE, Roubin GS, Hill MD, Leimgruber PP, Begg RJ, et al. Myocardial infarction after carotid stenting and endarterectomy: results from the carotid revascularization endarterectomy versus stenting trial. Circulation. 2011 Jun 7;123(22):2571-8. PubMed PMID: 21606394. Pubmed Central PMCID: PMC3173718. Epub 2011/05/25. eng.

10. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet (London, England). 2015 Feb 7;385(9967):529-38. PubMed PMID: 25453443. Pubmed Central PMCID: PMC4322188. Epub 2014/12/03. eng.

11. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. The New England journal of medicine. 2016 Mar 17;374(11):1011-20. PubMed PMID: 26886419. Epub 2016/02/18. eng.

12. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke; a journal of cerebral circulation. 2011 Jan;42(1):227-76. PubMed PMID: 20966421. Epub 2010/10/23. eng.

13. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. The New England journal of medicine. 2004 Oct 7;351(15):1493-501. PubMed PMID: 15470212. Epub 2004/10/08. eng.

14. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. The New England journal of medicine. 2008 Apr 10;358(15):1572-9. PubMed PMID: 18403765. Epub 2008/04/12. eng.

15. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation. 2014 Jul;45(7):2160-236. PubMed PMID: 24788967. Epub 2014/05/03. eng.

16. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/ SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Vasc Med. 2011 Feb;16(1):35-77. PubMed PMID: 21471149. Epub 2011/04/08.