Carotid artery interventions

Editor: Martin Veller

The most appropriate scientific foundation for a guideline or clinical recommendations is level 1 evidence derived from multiple prospective randomised trials and meta-analyses. Very often this is not available, and as a consequence recommendations have to be based upon large retrospective series, non-randomized studies or the experience of experts. In an effort to establish guidelines for South Africa, a meeting of eighteen South African vascular surgeons (listed at the end of this document) all of them members of the Vascular Society of Southern Africa (VASSA) was held in March 2011 – generously supported by the Crossroads Institute of South Africa and Baroque Medical. During this "Carotid and Thoracic Aortic Consensus Meeting all aspects concerning the management of these conditions was intensively discussed with additional input of two Belgium experts in this field (Patrick Peeters and Koen Keirse, Imelda hospital). These guidelines are therefore based upon the extensive discussions and lectures during this Consensus Meeting, as well as the latest publications and recommendations that were and have become available in the literature. Participants were also encouraged to evaluate and use guidelines developed by other societies and bodies and to if appropriate adapt these to South African circumstances. The intention is to cover the subject fully and as a result some recommendations will per force need to be repeated in some of the sections in order to ensure that each section comes to an appropriate conclusion.

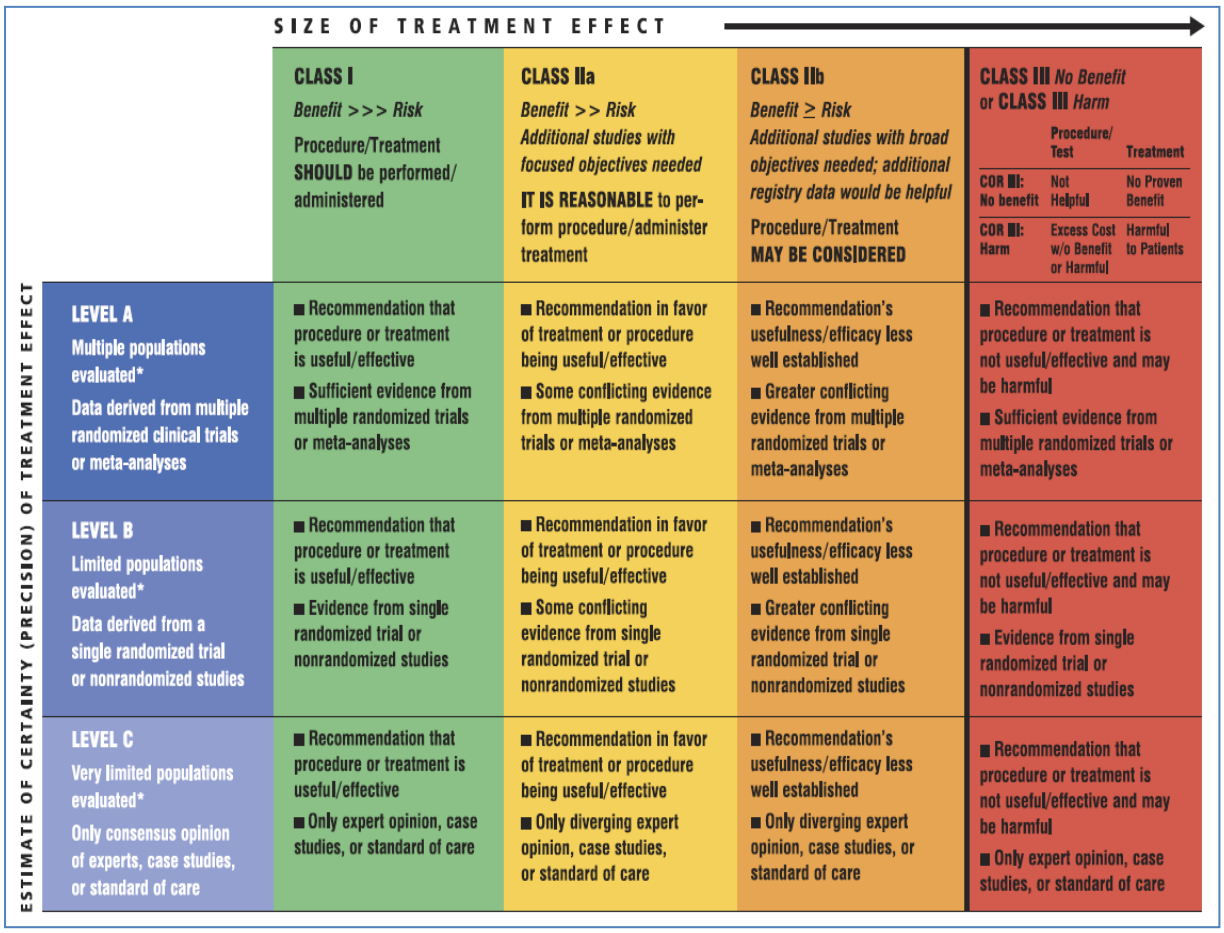
It is essential to note that these guidelines are not intended to be absolute dictates, but should provide a framework within which the reasonable physician can and should practice, and which will require exceptional circumstances to practice outside thereof. These guidelines when published will be the official guidelines of VASSA.

Presently, many new prospective trials exist or are being planned whose results may eventually change current practice. Undoubtedly future technological, pharmaceutical and other therapeutic developments and progress in the understanding of the diseases will become available. These guidelines will therefore have to be revised on a regular basis and it is envisaged that similar meetings will be held on a regular basis for this purpose.

Index:

Levels of Evidence and Class of Recommendations

It was agreed by the participants that many methods of evaluating the quality of data and making guideline recommendations on the basis of this information exist. A consistent easily applicable system is essential and as a consequence the method currently being used in most American cardiovascular guidelines would be adopted by VASSA[1]. This is reflected below:



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

From: TG Brott, JL Halperin, S Abbara, et al. Guideline on the management of patients with extracranial carotid and vertebral artery disease. J Am Coll Cardiol. 2011; 57: e16-94.

References:

1) TG Brott, JL Halperin, S Abbara, et al. Guideline on the management of patients with extracranial carotid and vertebral artery disease. J Am Coll Cardiol. 2011;57:e16-94

A. Defining symptoms in extracranial carotid disease

Dirk le Roux

Although there are new definitions for the symptoms of extracranial carotid disease – we still use the classical definition of TIA and stroke when we treat our patients as most of the major studies on this disease are based on these definitions.

Often, health professionals and the public consider TIAs as benign but regard strokes as serious. This assumption however is incorrect. Stroke and TIA are a spectrum of serious conditions involving brain ischaemia. Both are markers of reduced cerebral blood flow and an increased risk of disability and death. However, TIAs offer an opportunity to initiate treatment that can forestall the onset of permanently disabling injury.

Definitions

A transient ischaemic attack (TIA) is a brief episode of neurologic dysfunction resulting from focal temporary cerebral ischaemia not associated with cerebral infarction.[1]

TIA was originally defined as a sudden onset of a focal neurologic symptom and/or sign lasting less than 24 hours, brought on by a transient decrease in blood supply, which rendered the brain ischemic in the area producing the symptom.

However, this classic definition of TIA was inadequate for several reasons. Most notably, there is risk of permanent tissue injury (i.e. infarction) even when focal transient neurologic symptoms last less than one hour.

Thus, the benign connotation of "TIA" has been replaced by an understanding that even relatively brief ischemia can cause permanent brain injury.

The advantages of modern tissue-based definitions of TIA and stroke include the following:

- The defined end point is biologic (tissue injury, as confirmed or excluded by neuroimaging) rather than arbitrary (24 hours).
- The definition encourages use of neurodiagnostic tests to identify brain injury and its cause.
- The presence or absence of ischemic brain is more accurately reflected. [1,2]

The use of new definitions in epidemiologic studies is likely to modestly alter the incidence and prevalence rates of TIA and stroke, but these changes are encouraged because they should reflect more accurate diagnosis.

It is estimated that switching from the classic to tissue-based definition of TIA could reduce the annual incidence of TIA in the USA by 33% (19-44 %) and increase the annual incidence of stroke by 7 % (4-10%).[3]

Other definitions like acute neurovascular syndrome (ANS), transient symptoms with infarction (TSI) ("cerebral infarction with transient signs") have been proposed to supplement TIA in the description of transient symptoms related to ischemia. This terminology have been proposed but not been formally endorsed by the AHA.[4]

Patients with TSI have a higher short-term risk of recurrent ischemic stroke than patients who have transient symptoms without infarction[5]

Clinical presentation and differential diagnosis[6]

TIAs are negative symptoms (loss of function); positive symptoms refer to stimulated or increased function.

Hemiparesis, hemisensory loss, hemifacial weakness of upper motor neuron distribution, amaurosis fugax, and aphasia are some of the typical presenting symptoms of transient ischemic attack.

Positive findings, such as flashing lights or zigzag lines in the field of vision, twitching muscles, and tingling that slowly marches from the leg to arm to face are much less likely to indicate a transient ischemic attack.

Non-TIA syndromes

The following are not TIAs and these patient need to be actively investigated to exclude cerebral infarction.

- Syncope
- Dizziness - Cerebellar strokes or TIA's can present as dizziness but will be associated with ataxia.
- "Drop attack: Typically, the patient is elderly and experiences a forward fall, with bruising of the knees and nose. The cause is not well defined. About 25% of such cases are associated with either a cerebrovascular or a cardiac cause.
- Migraine and migraine aura
- Transient global cerebral hypoperfusion
- Transient global amnesia

TIA's are different in that they represent focal cerebral or retinal hypoperfusion.

Other causes — Less frequent causes of transient neurologic events include the following:

- Metabolic condition, e.g. hypoglycemia, may cause focal neurologic deficits.
- Multiple sclerosis – ataxia and dysarthria[7]
- Brain tumours - pressure on structures adjacent to the tumor[8]
- Subdural haematomas
- Intracerebral haemorrhage.
- Hepatic, renal, and pulmonary encephalopathies.
- Compressive myelopathy may rarely cause sudden transient sensory changes and motor deficits[9].
- Pressure- or position-related peripheral nerve or nerve root compression...
- Peripheral vestibulopathies.
- Hysteria and other psychiatric disorders.

Key concepts

- Most TIA's last less than 1 hour.
- Almost half of TIA's result in cerebral infarction on diffusion-weighted imaging; the chance of infarction increases with increasing duration of symptoms.
- According to new proposed criteria in 2009, the presence of a new infarction on CT or MRI in association with a referable symptom, regardless of symptom duration is defined as a stroke.
- Isolated dizziness (including vertigo) and syncope are rarely TIA's.
- Weakness in the face on the side opposite to weakness in the arm and leg suggests brainstem ischemia.
- Gaze deviation toward the side of weakness suggests brainstem ischemia, whereas gaze deviation away from the weakness suggests hemispheric ischemia.

Summary and conclusions

- TIA now defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.
    - This tissue-based definition of TIA relies on the absence of end-organ injury as assessed by imaging or other techniques.
    - The proposed advantages of the tissue-based definition are that the defined end point is biological (tissue injury) rather than arbitrary (24 hours). In

addition, a tissue based definition encourages the use of neurodiagnostic tests to identify brain injury and its cause.

- The "classic" definition of TIA is inadequate because even relatively brief ischaemia can cause permanent brain injury.

- A substantial proportion of patients with classically defined TIA (<24 hours in duration) have corresponding relevant ischemic lesions on diffusion-weighted or perfusion- weighted MRI. The associated infarctions associated are often very small.
- TIAs are associated with significant proximate risks for stroke, cardiovascular events, and death.
- Correct diagnosis depends on an accurate medical history and physical examination, combined with the appropriate neuroimaging.
- With the careful evaluation of symptoms based on this definition of transient ischaemic attack, a clinician can determine whether a transient ischaemic attack has occurred and thus propose treatment that may decrease the likelihood of a subsequent stroke.

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B. Extra-cranial arterial disease: Diagnostics

Martin Veller

Multiple diagnostic modalities are available to detect the presence and determine the severity of extra-cranial arterial occlusive disease. Those used most frequently for this purpose are duplex Doppler ultrasound (DD), magnetic resonance imaging angiography (MRA) and computer tomographic angiography (CTA). Standard angiography, while used rarely because of the risk of stoke being caused by this investigation – albeit low, is still considered the standard by which the accuracy of the other modalities is evaluated. In standard practice, angiography is only used when the information obtained from the less invasive modalities is unclear and if such information will make a significant difference to the recommended therapy.

In determining the degree of stenosis of the internal carotid artery origin the NASCET method of calculating the percentage stenosis is favoured (i.e. the diameter of the lumen at level of maximum degree of luminal narrowing compared to the luminal diameter within a normal portion of the internal carotid artery above the carotid bulb).

Carotid artery duplex Doppler ultrasound

DD when performed by experienced individuals using a well defined protocol compares well to angiography in detecting and evaluating occlusive disease of the extra-cranial cerebrovascular arteries. As a consequence many surgeons make management decisions without additional imaging. DD is most accurate when plaque has some level of echogenicity and when it is used for the purpose of determining the presence or absence of a 50% stenosis in the origin of the internal carotid artery. In order to differentiate between a 50 to 69% stenosis, a 70 to 99% stenosis and occlusion various B-mode and Doppler determined flow characteristics need to be used. These are described by CP Oates et al. in the guidelines for the reporting of carotid ultrasound in the United Kingdom – table 1.

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA)

Both modalities are accurate in detecting and evaluating the extent of extra-cranial arterial occlusive disease. Both are also valuable in evaluating the presence and extent of intracranial pathologies and therefore are being used more frequently in the early evaluation of patients with symptoms suggestive of ischaemic disease. Both modalities however require specific sequences to evaluate the arterial vasculature and also require use of contrast media (MRA can however be performed without gadolinium in patients with renal dysfunction when this is required). The main

concern regarding these modalities is their cost and their tendency to overestimate the degree of stenosis. On the other hand, unlike DD they are not limited to only evaluating the vessels within the neck.

Table 1: Haemodynamic criteria used in DD to determine the severity if an internal carotid artery origin stenosis (adapted from CP Oates et al.)

Degree of stenosis	**ICA peak systolic velocity (PSV) (cm/sec)**	**ICA end diastolic velocity (EDV) (cm/sec)**	**St. Mary's ratio ICA_{PSV}/CCA_{EDV}**
<50%	<120-125		<8
50-69%	>120-125		8-13
70-99%	>230	>120-125	>13
>90%	>400		>30
Near occlusion	Variable		Variable
Occlusion	No flow	N/A	N/A

<u>These haemodynamic criteria should be interpreted with caution:</u>

- If flow in the CCA cannot be detected or if the EDV is reversed – possible aortic valve disease.
- If the EDV in the ICA is low or the PSV is low in the CCA – possible aortic arch occlusive disease.
- When significant disease is present in both ICA origins – possibility of overestimating severity of disease.

ICA: Internal Carotid Artery, CCA: Common Carotid Artery

Table 2: Accuracy of non-invasive methods of detecting carotid artery stenosis (adapted from PJ Nederkoorn et al. and TG Brott et al.)

	50-69% vs. 70-99%	**Detecting occlusion**
DD	Sensitivity: 85-90% Specificity: 85-90%	Sensitivity: 94-98% Specificity: 99-100%
MRA	Sensitivity: 92-97% Specificity: 86-93%	Sensitivity: 94-100% Specificity: 99-100%
CTA	Sensitivity: 85-100% Specificity: 92-100%	Sensitivity: 92-100% Specificity: 97-100%

Recommendations for evaluating asymptomatic disease:

- DD is the recommended initial diagnostic modality in patients with suspected asymptomatic carotid artery stenosis (Class 1, Level of Evidence C).

- In the presence of known extra cranial arterial occlusive disease it is reasonable to repeat DD annually to assess the progression of disease and the response to therapy (Class 2a, Level of Evidence C).
- In asymptomatic patients without substantial risk factors for atherosclerosis or a neck bruit routine imaging of the extra-cranial arteries is not recommended (Class 3, Level of Evidence C).

Recommendations for evaluating symptomatic disease (transient or permanent retinal or focal hemispheric neurological symptoms):

- When available, DD should be the initial diagnostic modality used to detect extra-cranial arterial disease in symptomatic disease. MRA or CTA should be used if DD is not available, when the DD findings are equivocal or inconclusive or when common carotid artery origin disease is suspected (usually based on low common carotid artery systolic velocities or a significant discrepancy – 15 mmHG or more) between the left and right upper limb systolic blood pressures) and may be useful when occlusion of the internal carotid artery is found on DD (Class 1, Level of Evidence C).
- A cardiac source for emboli should be sought using echocardiography (ideally using a trans-oesophageal approach) if no source of embolisation (including modest carotid artery occlusive disease) is found in the extra-cranial carotid arteries (Class 1, Level of Evidence C).
- If no extracranial carotid artery or cardiac source of embolisation is found to account for well defined symptomatic disease or where cerebral imaging has clearly demonstrated a focal ischaemic lesion, MRA or CTA can be useful to search for intracranial or aortic arch disease (Class 2a, Level of Evidence C).
- In some patients multiple modalities of diagnosis are useful when intervention for extra-cranial arterial occlusive disease is planned (Class 2a, Level of Evidence C).
- MRA without contrast is useful in evaluating extra-cranial arterial occlusive disease in patients with curtailed renal function (Class 1, Level of Evidence C).

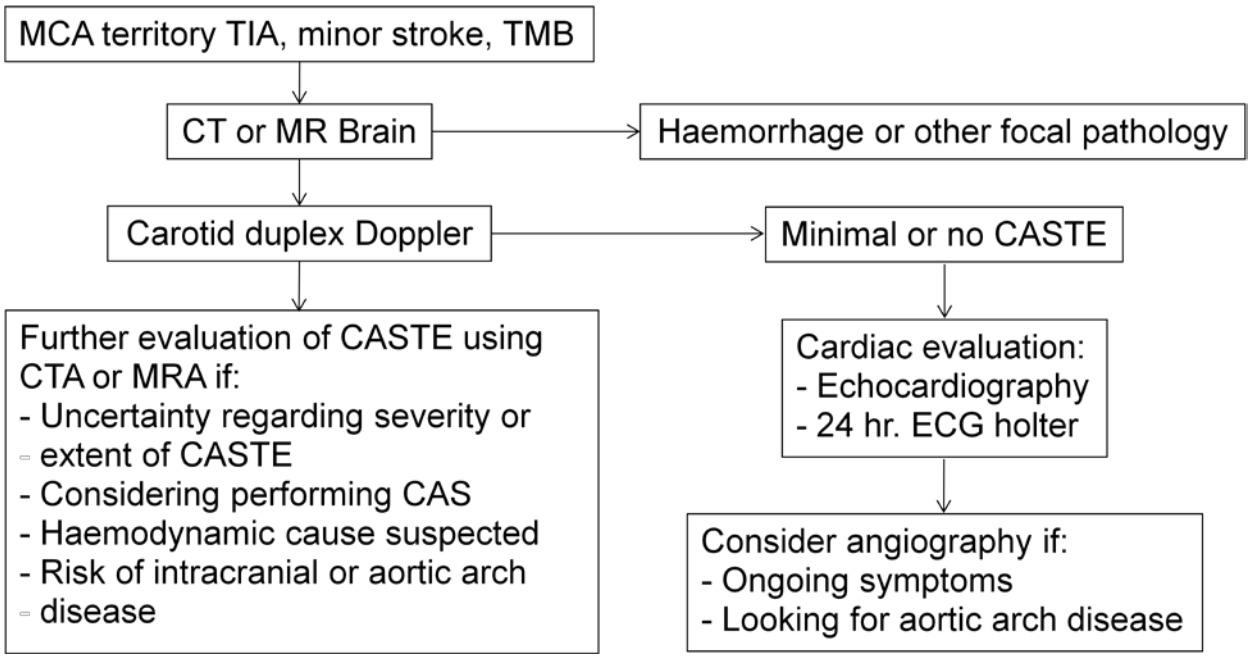
Other recommendations:

- In patients with any transient or permanent focal hemispheric neurological symptoms, brain imaging is required. Recommendations in this regard fall outside the scope of this guideline (Class 1, Level of Evidence C).
- Ultrasound plaque characterisation (plaque echogenicity, surface morphology, presence of plaque ulcers) may be useful in determining the risk of stroke and might be of value in management decisions (Class 2b, Level of Evidence B).
- Evaluation of cerebral blood flow and cerebral function are currently not routinely used in the evaluation and management of patients with extra-cranial arterial occlusive disease (Class 2b, Level of Evidence C).

Future:

Better methods of determining plaque stability such as high resolution ultrasound imaging (with ultrasound contrast materials) and PET scanning are currently being evaluated.

Recommended diagnostic algorithm in patients with minor or stable focal hemispheric neurological deficits:



MCA: Middle Cerebral Artery; TIA: Transient Ischaemic Attack, TMB: Transient Monocular Blindness; CASTE: Carotid Artery Stenosis; CAS: Carotid Angioplasty and Stenosis

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C. Overview of symptomatic trials

Dr Ruan Botha

Fisher remarked in a 1951 publication that “regular investigation of the internal carotid artery will reveal pathological processes which are among the most important causes of hemiplegia.” The typical symptoms was also accurately described.[1]

At a meeting held in January 1959 in Washington DC, under the direction of Michael E. DeBakey, plans were formulated for the development of a cooperative study of cerebrovascular insufficiency due to extra cranial vascular occlusive disease. The principal goal of this study was to determine the efficacy of arterial reconstructive surgery in the treatment of cerebrovascular disease caused by surgically accessible lesions in the arteries of the neck and upper portion of the thorax.[2]

An interim progress report on 1225 patients demonstrated statistically significant differences at 42 months which suggested that surgical treatment was beneficial for unilateral carotid artery stenosis in patients with transient attacks or mild to moderate neurological deficits.[3] Comparison of the numbers of surviving, asymptomatic patients in the two arms of the series appeared to favour patients having undergone carotid artery surgery (non-surgical: 28.2% vs. surgical: 46.6%; p = 0.001).[4]

The justification for performing a carotid endarterectomy in patients presenting with carotid territory TIAs depends on four factors, which seldom can be ascertained with certainty in an individual, but which in general need to be present:

1) The presence of a stenotic plaque/lesion at the origin of the internal carotid artery which is the probable cause for the preceding TIA, usually by being a source of embolism but also very occasionally by reduction in arterial blood flow.
2) No other pathology (arterial or cardiac), or other general disorder (e.g. polycythaemia, arteritis, etc) is as, or more likely to have been the cause of the focal neurological symptoms.
3) The lesion is likely to cause further TIAs and/or more importantly, cerebral infarction.
4) The long-term risk of stroke without surgery is greater than the long-term risk with surgery to which needs to be added the risk of preceding invasive investigations – which is rarely required.[5]

The three major trials evaluating the benefits of carotid endarterectomy (CEA) in patients with preceding carotid territory symptoms are:

- The Veterans Affairs Cooperative Study which included 189 men within 120 days of the onset of symptoms. At a mean follow-up of 11.9 months, there was a significant reduction in stroke or crescendo TIAs in patients who underwent CEA (7.7%) compared with patients not offered this surgery (19.4%), an absolute risk reduction (ARR) of 11.7% (p=0.011). The benefit of surgery was more profound

in patients with a internal carotid artery stenosis greater than 70% (absolute risk reduction, 17.7%; p = 0.004).[6]

- In the European Carotid Surgery Trial (ECST) 3024 men and woman of any age who had symptoms during the previous 6 months were randomly assigned to undergo CEA (60%) or control (40%). In patients with a greater than 80% carotid artery stenosis, the 3 year ARR for individuals undergoing CEA was 11.6%.[7]
- The North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported in 1991 on 659 patients who had suffered a non-disabling stroke within the 120 days before entry to the study and who had a carotid artery stenosis of between 70 and 99 %. Life-table estimates of the cumulative risk of any ipsilateral stroke at two years was 26 % in the 331 medically treated patients and 9 % in the 328 patients undergoing CEA – an ARR (±SE) of 17±3.5 % (p<0.001).[8]

  The following factors in patients undergoing CEA were found to increase the risk of perioperative stroke or death:

  - Contralateral carotid occlusion
  - Left-sided carotid disease
  - Taking less than 650 mg of aspirin per day
  - The absence of a history of myocardial infarction or angina
  - An ipsilateral ischaemic cerebral lesion present on computed tomography or magnetic resonance imaging
  - A history of diabetes mellitus
  - A diastolic blood pressure above 90 mm Hg.

  On the other hand the following characteristics were associated with greater long-term benefits from the CEA:

  - The male sex
  - A recent stroke
  - Recent hemispheric symptoms
  - Taking 650 mg or more of aspirin per day.

  Patients with severe stenosis (>70 %) had a durable benefit from CEA at eight years of follow-up.[9]

The pooled data from the above trials revealed that surgery was of marginal benefit in those patients with symptomatic 50–69% stenosis (1549 patients, ARR 4·6%, p=0·04), was highly beneficial in those with 70% stenosis or greater (1095, 16·0%, p<0·001) and was not beneficial in those near-occlusion.[10]

Recommendations:

- Aggressive atherosclerotic risk reducing therapy is indicated in all patients with a symptomatic. (Class 1, Level of Evidence A)

  This entails:

  - Aspirin 75-325mg/d (Class 1, Level of Evidence A)
  - Good blood pressure control (primarily using ACE/ARB, target blood pressure in non diabetic patients < 140/90) (Class 1, Level of Evidence A)
  - Tight glucose control (HBA1c < 7%) (Class 1, Level of Evidence A)
  - The stroke prevention benefit, however, of intensive glucose-lowering therapy to a glycosylated haemoglobin A1c level < 7.0% has not been established.
  - HMG CoA reductase inhibitors (statins) with a target total cholesterol of < 4.2 mmol/L and an LDL < 2.2 mmol/L (Class 1, Level of Evidence B).

- Smoking cessation is indicated in all patients with atherosclerotic carotid artery stenosis. (Class 1, Level of Evidence B)

- CEA or carotid artery angioplasty and stenting (CAS) is not indicated in patients presenting with a symptomatic carotid artery stenosis of less than 50%. (Class 1, Level of Evidence A)

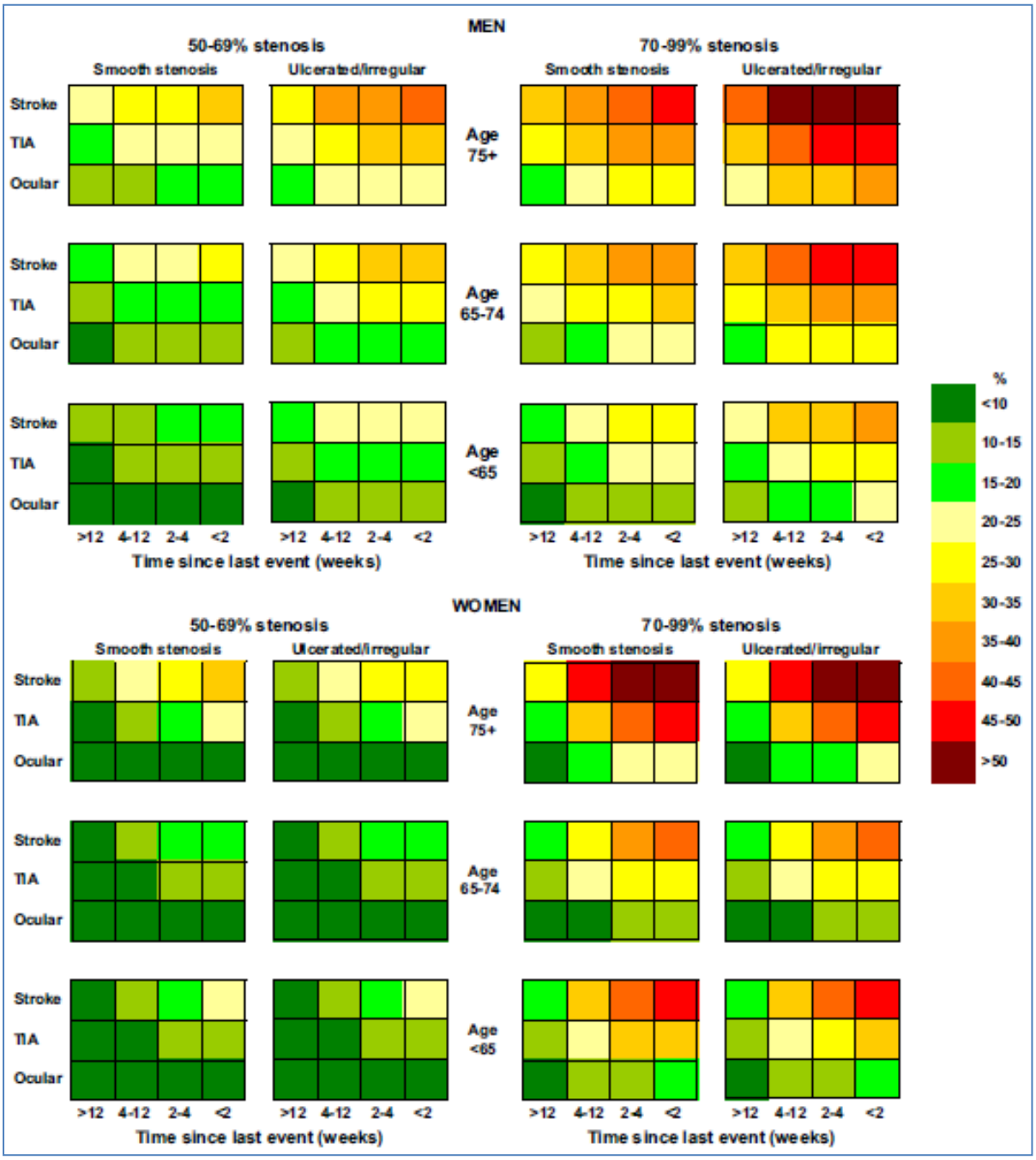
- CEA or CAS is indicated in patients with a greater than 50% symptomatic (non-disabling ischaemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax) carotid stenosis, if the surgeon's peri-operative stroke/death rate is <6%. (Class 1, Level of Evidence A)

  Additional considerations:

  - Further risk stratification using criteria as the patient's age, gender, the presence of plaque ulceration, plaque echolucency, the presence of bilateral carotid artery stenosis, type of index event and time from index event using data such as published by Rothwell (see below) is highly recommended.
  - Outcomes in older patients (age ≥70 years), favour CEA compared to CAS.
  - Concomitant high anatomic or medical risk favours CAS.
  - The intervention should be performed within 2 weeks of the patient's symptoms having occurred. (Class 2a, Level of Evidence B)
  - CEA can be done with the aid of either local or general anaesthesia (Class 2a, Level of Evidence B), selective shunting (Class 2a, Level of Evidence C) and non reversal of Heparin (Class 2a, Level of Evidence B). Patch angioplasty should usually be considered but particularly in women. (Class 2a, Level of Evidence B)

- CAS should be done using dual antiplatelet therapy (Aspirin and clopidogrel - at least 1 month after carotid stent placement and preferably for 3 months) (Class 2a, Level of Evidence C) and cerebral protection devices are probably beneficial (Class 2a, Level of Evidence C).

Figure: The 5 year risk of developing a stroke in the presence of a symptomatic carotid artery stenosis:



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D. Early management of TIA/stroke

Kris Michalowski

Acute anti-thrombotic treatment

The current data does not support early anticoagulation used to improving outcomes after acute ischaemic stroke. The majority of patients should however receive aspirin within 48 hours of a stroke, but overall effects of are modest. Aspirin should not be considered as an alternative to thrombolysis

Early interventions

Thrombolysis with intravenous or intra-arterial rtPA (recombinant tissue plasminogen activator) results in the higher levels of neurological recovery if used promptly following the onset of acute ischaemic stroke (ideally less than 4 hours and no benefit if given after 6 to 8 hours). The survival rates are no better than no thrombolysis as a consequence of an increased risk of conversion to haemorrhagic stroke.

- Intravenous (IV) thrombolysis:

  rtPA is recommended for thrombolytic therapy in ischaemic stroke if administered within 3 hours of stroke onset. Hemorrhagic transformation of the infarction remains the primary concern and occurs in 5.2% of patients after intravenous thrombolysis. Many patients who could benefit from rtPA are not offered it and there is evidence that rtPA could benefit many more patients who do not meet current criteria. Twenty six randomized trials of a thrombolytic agent compared with a control in patients with definite ischaemic stroke were analyzed in a Cochrane review. Data of 7152 patients, testing different thrombolytic agents was included. The majority of the data came from trials testing rtPA (11trials with 3977 patients; 56%). Most data came from trials that started treatment up to 6 hours after stroke onset. Very few patients were aged >80 years. Overall, among the selected population of patients included in the trials, infusion of rtPa significantly reduced the proportion of patients with poor outcomes after stroke. This overall benefit was apparent despite a statistically non-significant increase in deaths, mostly attributable to intracranial haemorrhage. The current data is insufficient to determine the risk-benefit ratio in clinically important subgroup of patients, especially those aged >80 years, but also by vascular risk factors and medical history, brain scan appearances, stroke subtype, or latest time for benefit.

- Intraarterial (IA) thrombolysis:

  Is also potentially associated with a reduction in mortality and an improvement in favourable outcomes after stroke, but also associated with increased risk of haemorrhagic complications. The combination of IV and IA therapy is being

tested, to allow for early treatment of stroke with IV while resources to deliver IA therapy are organized. At this stage there is insufficient data to make recommendation for the use of IA therapy outside randomized clinical trials.

- Mechanical embolectomy and other endovascular procedures:
  Endovascular and other adjunctive mechanical thrombolytic methods including laser, intraarterial suction devices, snares, angioplasty, and clot-retrieval devices have been extensively described. In some cases, these devices have been used in conjunction with rtPA. None of the methods of mechanical thromolysis have been adequately tested to draw conclusion about efficacy.

CEA or CAS if used for appropriate carotid artery lesions reduces the risk of further embolic stroke most effectively if performed soon after the herald cerebral or ocular ischaemic event. Current data suggests that such procedures should be undertaken ideally within 14 days of the index event.

Early CEA after thrombolysis has been suggested. Currently, the number of patients who would qualify for early CEA after thrombolysis is very small. The largest published cohort of 450 patients who received thrombolysis in two prospectively collected databases reported only 10 patients who underwent CEA with no major complications.

Recommendations:

- Anticoagulants (e.g. heparin, low molecular weight heparin, Warfarin; etc.) should not be used other than for other indications such as thromboprophylaxis. (Class 1, Level of Evidence B).
- The majority of patients < 80 years of age with an ischaemic stroke who present within 3 hours of the onset of symptoms should be urgently evaluated for treatment with intravenous rtPA. (Class 2a, Level of Evidence C)
- Brain imaging using CT or MRI is required to guide the selection of acute interventions to treat patients with stroke. (Class 1, Level of Evidence C)
- Early CEA following thrombolysis seems to be safe (Class 2b, Level of Evidence C)

Areas of Uncertainty

- Brain imaging by MRI in the acute ischaemic stroke setting.
- The time window for the use of thrombolysis might be extended to 6 to 9 hours for IV treatment with rtPA.

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E. Timing of carotid artery interventions

James Tunnicliffe

Index neurological events include TIA, amaurosis fugax (AF), crescendo TIA, stroke in evolution and completed stroke. For the purposes of this guideline, these events will be considered in 2 groups: stable or unstable. It is implicit that an isilateral carotid stenosis ≥ 60% (using NASCET criteria) is present, and that all patients will receive be receiving best medical therapy (BMT).

Stable Index Events (TIA, AF, Completed Stroke)

The early risk of developing a stroke after an index event has been grossly underestimated in the past. Furthermore, the risk is predictable with some degree of accuracy depending on factors such as: the patients age, gender, the presence of plaque ulceration and echolucency, Bilateral carotid artery stenosis as a risk factor is well established as is the fact that ocular events carry a lower risk of subsequent stroke than do cerebral ischaemic events. This risk is highest immediately after the index event, and falls exponentially with time. In females the benefit of carotid interventions is lost more rapidly than in men, such that intervention in females after 2 weeks from the event no longer carries any benefit when assessed at 5 years. In males the advantage of intervention is still present at 5 years if intervention is carried out within twelve weeks of the index event.

Overall, early intervention will prevent many more strokes than later intervention, but only if the intervention can be performed within acceptable risk levels.

Recommendations:

- Intervention should be carried out on the next available operating list. (Class 1, Level of Evidence B)
- No intervention in females if more than 2 weeks have elapsed since the index event. (Class 1, Level of Evidence A)
- No intervention in males if more than 12 weeks have elapsed since index the event. (Class 1, Level of Evidence A)

Unstable Index Event (Stroke in Evolution or Crescendo TIA):

If seen after 3 hours from onset of the index event thrombolysis is not considered. The natural history of these events is dismal, with stroke in evolution carrying a 17% stroke rate, and a 20% stroke and death rate. Crescendo TIA carries rates of 7% and 11% respectively. Early intervention in these cases has a mortality of 4 – 6% and a

stroke rate of 6%. Thus early intervention is risky, but can significantly reduce the stroke and death rates.

Recommendations:

- If within 3 hours from onset of the index event consider thrombolysis. (Class 2, Level of Evidence B)
- If more than 3 hours from onset of the index event intervention should be carried out as soon as possible. (Class 2, Level of Evidence C)

Unresolved Issues

- The role of thrombolysis for acute stroke and the role of stroke units.

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F. Case selection – Carotid endarterectomy (CEA) versus carotid angioplasty and stenting (CAS)

Martin Veller

The value of addressing atherosclerotic disease in the common carotid artery bifurcation, in selected patients, was established from studies in which carotid endarterectomy (CEA) was compared to a non-intervention. Since these studies were published endovascular therapies have developed to such an extent that outcomes similar to CEA can be obtained with carotid artery angioplasty and stenting (CAS). By early 2011, at least 13 studies comparing CEA to CAS, evaluating more than 7000 mostly symptomatic subjects have been published. The largest of these, the International Carotid Stenting Study (ICSS) and Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) were published in 2010. Since then the data has been summarised in 6 meta-analyses.

- The Carotid Trialist Collaboration used the individual patient data from 3 studies (EVA-3S, SPACE, ICSS) including 3433 symptomatic patients to evaluate the 120-day post intervention outcomes in an intention-to-treat analysis:
  - The patient baseline data in both groups was similar.
  - The average time to treatment was 30 days.
  - CAS had a statistically higher rate of the combined endpoints *stroke or death* (8.9% vs. 5.8%; risk ratio 1.53: 95%CI 1.20-1.95) and of the endpoint *any stroke* (8.2% vs. 4.9%; risk ratio 1.66: 95%CI 1.28-2.15).
  - A tendency to a higher rate for *disabling stroke* (4.8% vs. 3.7%; risk ratio 1.27: 95%CI 0.92-1.74) and *all cause mortality* (1.9% vs. 1.3%; risk ratio 1.44: 95%CI 0.84-2.47) was also found for CAS.
  - In the per-protocol-analysis the outcomes for CAS were worse than in the intention to treat analysis.
  - No difference in the rate of symptomatic myocardial infarction was noted in these patients, but CEA was associated with a 14 times higher rate of cranial nerve palsy (6.0%) and a higher rate of haematoma.
  - In a subgroup analysis, most of the differences between the two modalities of treatment were found in patients over the age of 70 years.
- The meta-analysis by Murad et al. evaluated the 30 day data of 13 studies with 7484 patients of whom approximately 80% were symptomatic.
  - These studies demonstrated significant heterogeneity.
  - CAS was associated with an increased risk of *any stroke* (6.2% vs. 4.1%; relative risk 1.45: 95%CI 1.06-1.99) and a decrease risk of *periprocedural myocardial infarction* (0.7% vs. 1.7%; relative risk 0.43: 95%CI 0.26-0.71) and

a statistically non significant increase in *mortality* (1.2% vs. 0.09%; relative risk 1.40: 95%CI 0.85-2.33).

- The meta-analysis by Guay evaluated the 4 studies (CREST, EVA-3S, ICSS, SAPPHIRE) in which there was a high level of use of cerebral protection devices as these studies demonstrated a low level of heterogeneity.
    - The 30 day data in these 5012 patients demonstrated that the stroke rate was lower in patients undergoing CEA (5.6% vs. 2.8%; risk ratio 0.5: 95%CI 0.38-0.67; NNT 37: 95%CI 29-55) but that the rate of myocardial infarction was higher (0.9 vs. 1.8%; risk ration 2.16: 95%CI 1.32-3.54; NNH 96: 95%CI 44-341).
    - The mortality rate was not statistically different.

Age appears to be a significant predictor of unfavourable outcome related to CAS in both the CREST as well as the combined data from the ICSS, Space and EVA-3S studies. The cut-off consistently lies in the region between 70 and 75 years.

The 4 year follow-up from the CREST study suggest that both treatments have similar durable outcomes but the long-term data from CAVATAS is not as good in the CAS group. This suggests that stenting is an essential component of the endovascular treatment.

A criticism of many of the studies favouring CEA is that the experience of the CAS operators in these studies is low. In the CREST study in which only experienced operators were invited to recruit patients, the rate of the combined primary endpoints was similar. CAS was however associated with a higher rate of peri- and post-procedural symptomatic stroke or death at 4 years (6.4% vs. 4.7%) while the predominately peri-procedural asymptomatic myocardial infarction rate was lower (1.1% vs. 2.3%).

The essential differences between the two treatment modalities are that CAS results in a lower rate of myocardial infarctions, of which the majority are non-ST segment infarcts, and that CEA has a lower rate of symptomatic peri-procedural stroke. In addition, the ICSS-MRI study (n=231) suggests that the rate of asymptomatic MRI detected ischaemic lesions in the CAS group is also substantially higher (46% vs. 14%; hazard ratio 5.24: 95%CI 2.6-10.5). Much debate has therefore ensued asking if asymptomatic myocardial infarction and asymptomatic cerebral infarction are of equal consequence. In the ICSS patient quality of life was better in patients who had had a myocardial infarct compared to patients who had a stroke.

Protocol defined subgroup analysis of the CREST study's primary endpoints has demonstrated that:

- Women undergoing CAS have a trend towards a higher rate of the primary endpoints (stroke, death and MI) compared to women undergoing CEA – 8.9%

versus 6.7% (HR 1.35, 0.82-2.23) – while no difference was found in men – 6.2% versus 6.8% (HR 0.99, 0.66-1.46).

- An increasing risk for stroke after CAS in older patients. CEA and CAS had equivalent efficacy at approximately 70 years of age but the risk of the primary endpoint occurring with CAS increased by a factor of 1.77 (95% CI 1.38-2.28) per 10 year increment while there was no increment in patients undergoing CEA.

Uncertainties

The time from onset of symptoms to procedure being undertaken in the published studies is longer than currently recommended. What impact more urgent intervention will have in such symptomatic patients is uncertain. The higher rate of ischaemic cerebral events in CAS may become more pronounced.

Recommendations:

- CEA and CAS have a similar short and medium term outcome in patients less than 70 years of age, who present with non-disabling stroke, transient focal hemispheric ischaemic neurological symptoms or with transient monocular blindness who have a 70% or greater stenosis in the origin of the ICA (Class 1; level of evidence B).
- CEA should be the first choice of treatment in patients: older than 70 years, when the ICA stenosis is less than 70% or when asymptomatic disease is being treated, unless the carotid artery bifurcation is difficult to access, or if there is evidence of contralateral cranial nerve injury or any other local factors that would preclude safe CEA. Prior to using CAS for these reasons, a careful re-evaluation of benefit of intervention is desirable (Class 2a; level of evidence A).

Future:

Current treatment is expected to have low complication rates. In the CREST the 30 day adverse event rate for CEA was 2.3%. Endovascular therapies will evolve but whether these will succeed in reducing the risk of ischaemic cerebral injury as a result of the therapeutic intervention is unknown.

Pharmacological developments have resulted in a reduction of the risk of stroke in patients with asymptomatic carotid artery stenosis. The need for new studies looking at not only the type of intervention but also including a medical arm is therefore apparent.

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G. Antiplatelet therapy during intervention

Charl Dreyer

It is well established that irrespective of why the patient is at high risk of developing serious vascular events (non-fatal myocardial infarction, non-fatal stroke or death from a vascular cause) and irrespective of the age, blood pressure, sex or presence of diabetes, the proportional reduction in risk is about 25% in those taking antiplatelet therapy in the long term. The dose required to achieve this is between 75 mg and 325 mg per day.[1] In the acute stroke setting there is good evidence to support initiating antiplatelet therapy as soon as possible after an acute ischaemic stroke is suspected, thus complimenting the long- term antiplatelet usage, with the net benefit being the greatest in the first month of starting after acute stroke.[2,3]

The only significant evidence for the use of other antiplatelet drug instead of Aspirin exists for clopidogrel which at best may be slightly more effective than Aspirin.[4]

In the MATCH[5] and CHARISMA[6] studies the addition of clopidogrel to Aspirin in the high-risk group (recent ischaemic stroke or transient ischaemic attack) resulted in a non-significant reduction in major vascular events at the price of increased life threatening major bleeding and can therefore not be advocated.

In the ESPRIT trial (Aspirin plus dipyridamole versus Aspirin alone after cerebral ischaemia of arterial origin) and the European Stroke Prevention Trial (ESPS2)[7,8] the combination of slow release dipyridamole plus Aspirin showed some benefits over Aspirin alone and is thought to be a worthwhile alternative. The use of low-dose Aspirin however, did not reduce the Aspirin-related side effects.

Carotid Endarterectomy

Safety and efficacy of initiating Aspirin therapy pre-operatively in patients undergoing CEA has been well documented.[9] In addition, in the ACE trial the low-dose regimen of 81 to 325 mg was favoured to that of higher doses and it was also demonstrated that the drug should be taken for at least six months or life-long.[10]

Clopidogrel significantly increases the bleeding time and therefore the likelihood of peri-operative bleeding with resulting post-operative haematomas and prosthetic patch infections. In general then it would be wise to withhold Clopidogrel in the event of planned Carotid Endarterectomy. Whether to withdraw Clopidogrel depends on the reason why it was prescribed in the first place.

In a single study it has been demonstrated that high-grade embolisation following CEA which may result in peri-operative thrombotic stroke can be prevented not only by Dextran but by a single 75 mg pre-operative dose of Clopidogrel orally without the increased bleeding risk.[11]

Carotid Artery Stenting

The benefits of combined antiplatelet treatment in CAS using Aspirin and clopidogrel has been established. Dual antiplatelet therapy has a significant influence on reducing adverse neurological outcomes in the setting of CAS without increasing bleeding complications.[12,13] The routine use of two GP IIb/IIIa is actively discouraged due to the increased risk of bleeding.

Areas of Uncertainty

- Loading dose of Aspirin in the acute setting.
- Pre-intervention loading of clopidogrel and uncertainty about the dosage (as is practiced in coronary artery stenting).
- Pre-CEA use of single dose clopidogrel although convincing evidence exists from one reputable institute, verification is needed.

Relevant on-going trials

- The Aortic Arch-related Cerebral Hazard (ARCH) trial.
  The combination of Clopidogrel and Aspirin versus oral anticoagulant in preventing brain infarction, brain haemorrhage, MI, peripheral embolism and vascular death in patients with atherothrombosis of the aortic arch, and a recent cerebral or peripheral embolic event.
- The Secondary Prevention of Small Subcortical Strokes-3 (SPS 3) trial.
  The combination of Aspirin plus clopidogrel versus Aspirin alone, in the setting of active intensive blood pressure lowering specifically in patients diagnosed with a lacunar and small vessel disease subtype of stroke.
- The combination of Clopidogrel and Aspirin for the prevention of Early Recurrence in Acute Atherothrombotic Stroke (COMPRESS) trial.
  Comparing the combination of clopidogrel plus Aspirin with Aspirin alone for the prevention of recurrent ischaemic stroke on either 5-day diffusion-weighted imaging (DWI) or 30-day DWI/FLAIR.
- The Platelet-Orientated Inhibition in New Transient Ischaemic Attack (POINT) trial.
  This trial is evaluating Clopidogrel plus Aspirin compared with Aspirin alone preventing an ischaemic stroke or MI, or ischaemic vascular death within 90 days after a TIA.

Recommendations:

Anti-thrombotic therapy in patients with extra-cranial Carotid disease not undergoing intervention:

- For patients with a non-cardiac embolic ischaemic stroke or TIA, antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardio-vascular events and MI. This benefit is not established for the prevention of stroke in asymptomatic patients (primary prevention). (Class I, Level of Evidence A)
- Aspirin 81 mg to 325 mg per day as mono-therapy (Class I, Level of Evidence A), combination of Aspirin 25 mg and extended release dipyridamole 200 mg twice a day (Class I, Level of Evidence B), clopidogrel 75 mg mono-therapy (Class I, Level of Evidence B) are all accepted options for initial therapy but these should be individualised.
- The addition of clopidogrel to Aspirin increases the risk of haemorrhage and is not recommended for secondary prevention after ischaemic stroke or TIA. (Class 3, Level of Evidence A)
- For patients already on Aspirin having an ischaemic stroke, there is no evidence that increased doses of Aspirin adds additional benefit. No single agent or combination has been studied in patients who have had an event whilst receiving Aspirin. (Class 2b, Level of Evidence B)

Peri-procedural management: CEA

- Patients undergoing CEA: Aspirin 81 to 325 mg is recommended before CEA and continued indefinitely post-operative (Class I, Level of Evidence A).
- After the first month following Carotid Endarterectomy Aspirin 81 to 325 mg, Clopidogrel 75 mg per day or the combination of low-dose Aspirin 25 mg plus extended release dipyridamole 200 mg twice daily should be administered for long term prophylaxis against ischaemic cardio-vascular events.(Class I, Level of Evidence B).
- Single 75 mg Clopidogrel pre-operatively has shown to reduce the peri-operative embolic event rate. (Class I, Level of Evidence B).

Peri-procedural management: CAS

- Starting before and continuing for a minimum of 30 days after CAS, dual antiplatelet therapy with Aspirin 81 to 325 mg per day plus clopidogrel 75 mg per day is recommended. (Class I, Level of Evidence A)

- Ticlopodine, 250 mg twice daily may be given if clopidogrel intolerance exists. (Class I, Level of Evidence C)
- After the first month following CAS, Aspirin 81 to 325 mg per day, Clopidogrel 75 mg a day, or combination of low-dose Aspirin 25 mg plus extended release dipyridamole 200 mg twice daily should be administered for long term prophylaxis against ischaemic cardio-vascular events. (Class I, Level of Evidence B)

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H. Overview of asymptomatic trials

Martin Forlee

Seven randomised trials of carotid endarterectomy (CEA) for severe (> 50% stenosis), asymptomatic carotid stenosis compared to a non-interventional approach have been published. Three trials, namely the Veterans Affairs Co-operative Study[1] (VACS), the Asymptomatic Carotid Atherosclerosis Study[2] (ACAS) and the Asymptomatic Carotid Surgery Trial[3,4] (ACST) are methodologically most relevant to current practice. The 30 day peri-operative stroke and death rate ranged from 2.3% to 4.3%.

In VACS (n=444), benefit from CEA was only seen when TIA was included with any ipsilateral stoke.

In ACAS, (n=1662) the projected 5 year risk of **ipsilateral stroke and peri-operative stroke/death** was 5.1% for the surgical group and 11% for the medical group (ARR 5.9%, RRR 53%, 95% CI 0.22-0.72, p=0.004, NNT 19, 59 strokes prevented per 1000 CEA's). Benefit appeared after 10 months and became significant at 3 years. There was no significant benefit in preventing any territory stroke and peri-operative death or disabling/fatal strokes.

In ACST (n=3120), the main outcome was **any territory stroke and peri-operative stroke/death.** Projected 5 year estimates of risk were 6.4% for the surgical group and 11.8% for the medical group. (ARR 5.4%, RRR 46%, 95% CI 3-7.8%, p<0.0001, NNT 19, 54 strokes prevented per 1000 CEA's). Benefit appeared at 2 years and was significant at 5 years. There was a significant benefit in preventing fatal/disabling stroke. Benefit was maintained at 10 years[4].

A Cochrane review[5] combined the 3 studies and analysed 5223 patients with a mean follow-up of 3.3 years. The peri-operative stroke/death rate was 2.9%. CEA conferred a 29% relative risk reduction for peri-operative stroke/death and ipsilateral stroke (RR 0.71, 95% CI 0.55 to 0.90, P value 0.005). The RRR from CEA for peri-op stroke/death and any territory stroke was 31% (RR 0.69, CI 0.57 to 0.83, P value < 0.0001). The average annual absolute risk reduction was small, about 1% per annum.

Subgroup analyses are limited by relatively small numbers. The pooled data showed that CEA conferred significantly more benefit in men (RRR 51%) compared to women (RRR 4%). Younger patients (<68-75 years) derived more benefit than older patients while increasing degrees of stenosis had no effect on outcome.

The CREST[6] trial compared carotid endarterectomy to carotid angioplasty and stenting in symptomatic (n=1321) and asymptomatic (n=1181) patients. The primary endpoint was 30 day stroke/AMI/death For asymptomatic patients, despite more strokes occurring in the stenting group and more myocardial infarctions occurring in

the endarterectomy group, there were no statistically significant differences in peri-operative risks between the groups (CEA 3.6%, CAS 3.5%, HR 1.02, 95% CI 0.55-1.86, p=0.96).

Identifying the asymptomatic patient at high risk for cerebrovascular or retinal ischaemic (CORI) events has been difficult. The ACSRS[7] study was a prospective study of patients with asymptomatic carotid artery stenosis undergoing medical intervention alone. A number of baseline clinical characteristics and ultrasonic plaque features were shown to be independent predictors of subsequent ipsilateral CORI events. These included degree of stenosis, age, systolic blood pressure, smoking, raised creatinine, history of contralateral TIA, low gray scale medium, increased plaque area and plaque type 1, 2 and 3.

Strength of Data

In males less than 75 years old, CEA reduces the relative risk of stroke by about 50% over 5yrs, providing peri-operative stroke/death risk is less than 3%. The absolute risk reduction is small: 1% per annum.

Areas of Uncertainty

- The role of carotid angioplasty and stenting in the management of asymptomatic carotid stenosis.
- The effect that best medical therapy and a reduced annual risk of stroke has had on the benefit obtained from CEA.
- Identifying a subgroup of the asymptomatic patients that is at higher risk and who would benefit more from surgical intervention.

Future Direction

There are a number of ongoing/planned trials (ACT 1, ACST II, TACIT, SPACE II) comparing CEA to CAS in asymptomatic patients. The TACIT and SPACE II trials have also included a best medical therapy arm.

The ACSRS[7] trial has thrown some light on the high risk asymptomatic patient and more research is needed to define this group.

Recommendations

- Optimal medical therapy including intensive blood pressure and diabetes control, statins, antiplatelet and other risk factor modification needs to be instituted in all patients with asymptomatic carotid artery stenosis. (Class I, Level of Evidence A)
- Carotid endarterectomy may be considered in male patients, younger than 75 years old who are considered to be at high risk of ischaemic events based on clinical and ultrasonic plaque features, providing the peri-operative stroke/death risk is less than 3%. (Class 2a, Level of Evidence A)
- More data is required regarding the use of carotid angioplasty and stenting to treat asymptomatic patients and should not be utilized at this time, unless in the setting of a randomised controlled trial. (Class 2b, Level of Evidence B)

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I. When to treat haemodynamic cerebrovascular disease

Pradeep Mistry

Haemodynamic cerebrovascular disease or hypoperfusion syndrome is defined as an ischaemic stroke caused by hypoperfusion and not by emboli or a vasculopathy. The distinguishing feature of hypoperfusion syndrome is that blood flow towards a part of the brain is too low, resulting in ischaemia too an area of the brain or retina that is at a distance from the major vessels or blocked vessel. Hypoperfusion syndrome can be exacerbated by a decrease in regional blood pressure (proximal artery stenosis or occlusion secondary to emboli or atherothrombosis) or decreased systemic blood pressure (systemic hypotension or cardiac failure). Causes include carotid artery obstruction, vertebral artery obstruction, subclavian steal, low blood pressure, anaemia and occasionally intracranial diseases.

Clinical manifestations include limb shaking, signs of cognitive impairment and a large variety of precipitating circumstances of symptoms which include rising from a supine position, exercise, transition from a cold to a warm environment, having just consumed a meal, coughing, administration of antihypertensive drugs, or intensifying their dosage, or administration of other drugs that might lower blood pressure (e.g. sildenafil), bleeding, anaemia, episodes of loss of consciousness, monocular loss of vision after looking into bright light (retinal claudication), gradual deterioration of vision of one eye, with or without pain around the eye.

Clinical evaluation should include a check for orthostatic hypotension. Brain imaging should identify borderzone ischaemia, contrast angiography should be considered to assess collateral blood flow pathways and investigate the presence of stenosis in arteries important for collateral blood supply. Ophthalmological examination is valuable to check for venous stasis retinopathy and chronic ocular ischaemic syndrome particularly in patients in whom the external carotid artery–ophthalmic artery collateral pathway contributes to the collateral blood supply of the hemisphere ipsilateral to the ICA occlusion

Features associated with a **relatively low risk** of recurrent ischaemic stroke include retinal symptoms only with no symptoms of ischaemia of the brain and no recurrence of symptoms after documentation of the carotid artery occlusion. Features associated with a **relatively high risk** of recurrent ischaemic stroke include precipitating circumstances (rising, exercise, etc) causing symptoms indicative of a haemodynamic stroke, presence of leptomeningeal collateral blood supply from the posterior cerebral artery territory to the supply territory of the occluded ICA.and compromised blood flow in the supply territory of the occluded ICA, most convincingly shown by an increased oxygen extraction fraction measured with PET.

Recommendation: For anterior territory symptoms

- Patients with transient monocular blindness or retinal infarction due to haemodynamically induced disease who did not have signs or symptoms of cerebral ischaemia should probably not undergo invasive revascularisation procedures (Class 2a, Level of Evidence B), but should be treated with antithrombotic medication (Class 1, Level of Evidence B) and good control of risk factors (Class 1, Level of Evidence B).
- Patients who have had a TIA or mildly disabling ischaemic stroke with confirmed ICA occlusion should be treated with antithrombotic medication (Class 1, Level of Evidence B) and good control of risk factors (Class 1, Level of Evidence B).
- Bed rest in the acute stage might be considered in patients with precipitation of symptoms by a drop in blood pressure on rising, but is not of proven benefit. (Class 2a, Level of Evidence C)
- Tapering of antihypertensive drugs might be considered in patients with low blood pressure, particularly if symptoms are precipitated by a drop in blood pressure, but is not of proven benefit. (Class 2a, Level of Evidence C)
- Revascularisation procedures are not of proven benefit for the prevention of recurrent ischaemic symptoms or stroke, but might be considered in individual patients with compelling evidence for a haemodynamic cause of symptoms (Class 2a, Level of Evidence C). The surgery considered should only be performed on a single vessel to improve global cerebral perfusion (Class 1, Level of Evidence C).
- Revascularisation by PTA ± stenting, direct arterial reconstruction or extra-anatomic reconstruction in symptomatic patients with ischaemia of the anterior cerebral circulation caused by CCA or brachiocephalic artery is considered reasonable. (Class 2a, Level of Evidence C)
- In patients with a **chronic ocular ischaemic syndrome**, extracranial to intracranial bypass surgery or endarterectomy of a stenosis of the external carotid artery in the presence of an ICA occlusion can be considered to prevent blindness. (Class 2a, Level of Evidence C)
- Revascularisation is not of proven benefit for amelioration of **cognitive dysfunction** in patients with ICA occlusion, and should not be done solely for this reason. (Class 3, Level of Evidence C)

Recommendations: For vertebral artery symptoms:

- All patients with symptomatic vertebral artery disease should be subjected to standard atherosclerotic risk reducing therapy which includes pharmacological and lifestyle interventions. (Class 1, Level of Evidence A)

- Carotid-subclavian bypass is a reasonable intervention for patients with posterior cerebral or cerebellar ischaemia caused by subclavian artery stenosis or ischaemia. (Class 2a, Level of Evidence B)
- PTA ± stenting is a reasonable alternative in patients with posterior cerebral or cerebellar ischaemia caused by subclavian artery stenosis who are high risk for surgical complications. (Class 2a, Level of Evidence C)

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J. Non-artherosclerotic carotid disease

Tiago Fernandes

Takayasu's Arteritis

Takayasu's arteritis commonly affects the aortic arch branch vessels with both occlusive and more rarely aneurysmal disease. The symptoms caused by such involvement may include TIA's, stroke, amaurosis fugax and claudication of the upper limbs, mostly during the chronic stages of this condition.

The diagnosis of Takayasu's arteritis is usually made using clinical and radiological criteria (Ishikawa). Histological confirmation often does not yield a result. During the active phase of the disease inflammatory markers may be raised but during the quiescent or burnt out phase these markers may be normal. Radiologically these lesions are characterised by predominantly stenotic lesions. The course of the diseased remains variable and unpredictable. The mainstay of therapy is the use of high dose corticosteroids during the early active phase with rapid introduction of steroid-sparing strategies – most frequently with methotrexate but occasionally also using infliximab or cyclophosphamide. The aim is to reduce or halt the vascular wall inflammation – usually monitored by evaluating the ESR and CRP levels – which may require treatment for months if not years. During the burnt out phase there is not much value of these medications. Additional antiplatelet agents and statins are also recommended at least during the chronic phase of this disease.

Indications for intervention, based on sparse data, are similar to those for other vascular pathologies but ideally should only be performed once the active vasculitis has abated. While open surgical Intervention remains the gold standard, endovascular therapies have been described but supported with limited data. During the active phase of the disease it is difficult to establish where the inflammation starts and stops in a vessel and for this reason in the chronic phase it is hard to say where the inflammation might recur and therefore, there is no place for patch angioplasty, full interposition bypass grafting is recommended preferably from healthy to healthy vessel. The safety and efficacy of endovascular therapy in such circumstances is untested.

Recommendations

- Acute inflammatory Takayasu's arteritis of the aortic arch branches should be treated using effective immune-suppression. Steroid sparing strategies are currently favoured. Treatment should be continued until no biochemical evidence of inflammation exists, when these drugs should be withdrawn slowly, regularly monitoring the ESR and CRP. (Class 1; Level of Evidence B)

- Aspirin and statins are indicated life-long in patients with active or quiescent Takayasu's arteritis. (Class 1; Level of Evidence B)
- Interventions should only be considered while the arteritis is active if life threatening complications are found. (Class 1; Level of Evidence C)
- When such intervention is required, bypass surgery with exclusion of the diseases segments is favoured. (Class 2a; Level of Evidence C)
- The indications for interventions in the quiescent phase of this disease are similar to those for atherosclerotic disease. (Class 1; level of evidence C)

Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is an idiopathic dysplastic process that can affect all layers of the visceral and cervical medium sized arteries. There are four subtypes with medial fibroplasia being the commonest (75-80%). It is characterised by thinning of the media and concomitant collagen deposition in the vessel wall resulting in a "string of beads" appearance on angiography which in the cervical region usually affects the middle and distal thirds of the internal carotid artery. The degree of stenosis is not predictive of complications. Females are affected more frequently than males.

This condition is most frequently asymptomatic but in the carotid arteries can present with stroke, TIA, amaurosis fugax, dissection or aneurysmal disease. The diagnosis is made by imaging, catheter directed angiography would be the gold standard still; CTA and MRA are very useful but are limited in their ability to determine branch vessel involvement, duplex ultrasound is usually only used for post-operative surveillance. The renal arteries and cerebral circulation should be imaged, the former to look for renal artery stenosis and the latter to look for associated intracerebral aneurysms which is associated with FMD.

Asymptomatic patients should be given aspirin and need regular follow up. Symptomatic patients are treated according to the mechanism they present with. Stenotic lesions of the carotid arteries are treated with balloon angioplasty (± stenting) with the use of cerebral protection devices. Stenting is only advocated in dissections, tight stenosis (not amenable to angioplasty) and for flaps or aneurysms. There is limited experience treatment of the distal ICA at the base of the skull.

Recommendations

- Aspirin is indicated life-long in patients FMD. (Class 2b; level of evidence C)
- The indications for interventions are similar to those for atherosclerotic disease. (Class 1; level of evidence C)

Radiation induced carotid arteritis

Numerous individuals will undergo radiation therapy for head and neck malignancy's. A small subset will eventually go on to develop radiation induced carotid arteritis and stenosis subsequently.

The pathology in the early phase is characterised by intimal swelling and necrosis followed in the later stages with fibrosis with luminal occlusion predominantly due to intimal thickening. As a consequence of these two phases the first five years post radiation are characterised by thrombosis and embolisation and the latter phase is by occlusive disease. The condition is indistinct from atherosclerosis angiographically, the only differences being the wider distribution, the earlier age of onset and the absence of other atherosclerotic disease. The criteria for intervention are based on the criteria for carotid interventions for standard atherosclerotic disease. Most notably though open carotid repair is fraught with complications due to extensive fibrosis of the adjacent tissue and there is significant risk of cranial nerve damage. For this reason endovascular techniques are becoming popular but the risk of re-stenosis and thrombosis is considerable. Small series have however demonstrated favourable short-term outcomes while long-term data is sparse due to the limited lifespan caused by the underlying malignancy.

HIV and the Carotid Artery

HIV infection can cause both aneurysmal and occlusive disease. It is thought that both manifestations are due to a leucocytoclastic reaction starting in the vasovasorum which gradually extends to involve the whole vessel wall. It is unclear if the underlying vasculitis is due to the virus itself or as a result of the immune reaction that it elicits. Electron microscopy has however demonstrated virus particles in the walls of vessels suggesting the virus is the cause. If the vasculitis then involves the whole artery wall and in particular the endothelium, thrombotic occlusion can occur – particularly in the presence of a generalised hypercoagulable state, while weakening of the media results in aneurysmal disease. Aneurysms can occur anywhere within the vascular tree and can be multiple. It is also unclear whether such vascular pathologies are AIDS defining or not?

Patients taking protease inhibitors for HIV infections have greater intima media thicknesses compared to those taking non-nucleoside reverse transcriptase inhibitors (NNRTIs) or nucleoside reverse transcriptase inhibitors (NRIs), suggesting that such medication is associated with progression of atherosclerotic disease. Whether this progression of disease puts these patients at an increased risk of developing atherosclerotic disease which may result in a higher rate of cerebrovascular symptoms (TIA, or stroke) has however not been demonstrated. Protease inhibitors do contribute to the metabolic syndrome of insulin resistance, hypertension and dyslipidaemia.

Management of these conditions is similar to that for other arterial pathologies. The use of antiretroviral therapy is however controversial and some units still only commence therapy once the CD-4 count drops below 200. Aneurysmal disease is associated with a higher mortality than for occlusive disease and with more complications, most notably pneumonia and multiorgan failure. Currently carotid artery aneurysmal disease is preferentially treated by open repair and bypass. Saphenous vein conduits are preferred but numerous bypasses have been conducted using Dacron or PTFE grafts with good outcomes.

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K. Treatment of brachiocephalic artery disease

Cobus Vermaak

Brachiocephalic atherosclerotic disease (BAD) is a rare cause of embolic cerebrovascular accidents usually observed in conjunction with a tight stenosis (>75%) or an unstable plaque. BAD can be focal, multifocal, affect a single vessel or involve multiple vessels. Intervention is considered when a tight stenosis or unstable plaque is symptomatic: hemispheric cerebral event (TIA), vertebrobasilar insufficiency and steal syndromes (vertigo, nausea, ataxia), or upper limb ischaemia (claudication, embolisation, etc). Asymptomatic patients with a tight stenosis of the subclavian artery who are being considered for coronary artery bypass with the ipsilateral internal mammary artery may be considered for intervention. All other asymptomatic patients do not require intervention, even if they have a tight stenosis or reversal of flow in the vertebral artery.[1]

Options for intervention in BAD include bypass procedures (trans-thoracic and extra-thoracic), endovascular and hybrid interventions. Trans-thoracic procedures are generally only considered for “good risk” patients with multivessel disease, weighing the durability of such a procedure with peri-operative complications such as myocardial infarction, stroke, haemorrhage, respiratory failure, ventricular arrhythmias, infections, paralysis, hoarseness etc.

Bypass procedures are the norm when trans-thoracic procedures are considered, since endarterectomy should only be performed for focal lesions and indeed, such focal lesions are best treated with endovascular interventions. Significant plaque involving the ascending and transverse aorta precludes the application of partial occluding vascular clamps and therefore such trans-thoracic procedures should be performed using cardiopulmonary bypass. Short and long-term outcome as well as the complication rates for trans-thoracic revascularisation depends on patient selection and institutional experience. Even in high volume units, peri-operative mortality up to 8%, stroke rates up to 8% and a myocardial infarction rates up to 3% have been published since 1990.[2-4] Trans-thoracic procedures however have 5 and 10 year patency rates of >85%.[2-4]

Extra-thoracic procedures include carotid-subclavian transposition and bypass procedures such as: carotid-subclavian, axillo-axillary, subclavian-subclavian, carotid-carotid and carotid to contralateral subclavian bypass. Again, these procedures depend on patient selection, surgeon experience and unit volume. Perioperative stroke and myocardial infarction rates are lower when compared to the trans-thoracic procedures. The choice of conduit used for these procedures (synthetic vs. autologous vein) does not seem to affect outcome.[5,6]

Endovascular therapy of the brachiocephalic vessels is considered when favourable anatomy and lesion characteristics exist (stenotic, concentric, non-ulcerated, non-osteal lesions with suitable arch anatomy). The stroke risk in most series is less than 1% but increases when these procedures are performed in conjunction with

carotid endarterectomy or retrograde carotid artery stent placement. These outcomes are however expected to improve with advances in endovascular equipment and technique, including the use of low profile balloons.[7,8] There is not enough evidence to make a recommendation regarding the use of stents in the endovascular management of BAD. Most authors suggest the use of selective stenting according to lesion characteristic.

Long term patency of carotid subclavian bypass are superior to those of endovascular management of lesions involving the origin of the left subclavian artery in the few retrospective studies available.[9-11] Endovascular procedures remain attractive because of the reasonable initial success rates, low peri-operative complication rates and acceptable long-term results: 5 year patency rates in excess of 77%, irrespective whether a primary or selective stenting protocol was utilised.[12-14]

Recommendations:

- Only symptomatic brachiocephalic disease (tight stenosis, unstable plaque or occlusive) requires intervention. (Class1, Level of Evidence B)
- Endovascular management is usually recommended (Class IIa, Level of Evidence B), but needs to be individualized based on patient fitness, lesion characteristics and local expertise.
- Stenting is used selectively, based on lesion characteristic (Class IIb; level of Evidence C)
- Asymptomatic disease may require intervention should a stenosis of greater than 75% exist in the subclavian artery of a patient being considered for coronary artery bypass with the ipsilateral internal mammary artery. (Class IIb; level of Evidence B)

Uncertainties

The lack of evidence, variability in the lesions being considered, patient fitness, patient preference, centre volume, resource availability and physician preference makes it difficult to make quality recommendations.

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