

Quality assurance guidelines for the performance of carotid stenting:

European Standards adopted and modified by CIRSE in cooperation with the Society of Interventional Radiology (SIR) Standards of Practice Committee.

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Introduction:

Carotid artery stenting (CAS) is a relatively new endovascular treatment for patients with carotid disease. The provision of guidelines and standards of practice are difficult not least because refinements in technique and evolution in technology are ongoing whilst the technique is being increasingly adopted into clinical practice. It is anticipated that more data regarding outcomes and complications will be published in the near future from many of the ongoing trials and registries. Accordingly, it is recommended that these guidelines therefore be updated within the next 24 months to remain applicable to contemporary medical practise.

Published Recommendations for Carotid Stenting:

Current recommendations are based on outcomes from the earliest randomized trials comparing endovascular carotid intervention (initially angioplasty alone and subsequently primary stenting) with carotid endarterectomy (CEA). At this time two were prematurely stopped (1, 2) and three trials mainly focussing on the symptomatic population were ongoing (3, 4, 5).

The recommendations from advisory bodies are presented in chronological order;

The American Heart Association Science Advisory Councils' statements with respect to carotid stenting and angioplasty date from 1998 and are as follows (6):

“Despite several large studies...there is still debate about its relative efficacy and applicability compared with surgery, primarily because long-term patency after PTA (angioplasty) is limited by restenosis...” The final statement of this document was: “At this point, with few exceptions, use of carotid stenting should be limited to well-designed, well-controlled randomized studies with careful, dispassionate oversight.”

This recommendation is based largely on the results of carotid angioplasty only and since this time a substantial body of experience has developed. Six randomized trials comparing CEA and CAS reported from 1998 onwards.

In 2001 a consensus of opinion leaders concluded (7):

“Carotid bifurcation angioplasty and stenting should not undergo widespread practice, which should await results of randomized trials. Carotid bifurcation angioplasty and stenting is currently appropriate treatment for patients at high risk of

surgery in experienced centers. Carotid bifurcation angioplasty is not generally appropriate for patients at low risk”.

In 2002, an Intercollegiate Working Party for Stroke (Royal College of Physicians, London, United Kingdom) produced guidelines on secondary stroke prevention as part of the National Clinical Guidelines for Stroke (8). It was stated that: “Carotid angioplasty or stenting is an alternative to surgery but should only be carried out in centers with a proven low complication rate”. This was a grade A recommendation and reflected an early subtle change in emphasis. There was no stipulation that carotid stenting must be limited to trials or to patients deemed to be at high surgical risk.

The European Stroke Initiative Recommendations for Stroke Management-Update 2003 (9) suggested with respect to asymptomatic disease:

“The use of carotid angioplasty and stenting should be limited to well-designed, well-conducted, randomized trials”. The specific recommendations were;

1. Carotid percutaneous transluminal angioplasty may be performed for patients with contra-indications to endarterectomy or with stenosis at surgically inaccessible sites (Level-IV).
2. Carotid percutaneous transluminal angioplasty and stenting may be indicated for patients with re-stenosis after initial endarterectomy or stenosis following radiation (Level IV).
3. Patients should receive a combination of clopidogrel and aspirin immediately before, during and at least 1 month after stenting (Level IV).

With respect to asymptomatic disease it was concluded:

“Carotid angioplasty, with or without stenting, is not routinely recommended for patients with asymptomatic carotid stenosis. It may be considered in the context of randomized clinical trials”.

Despite these cautionary notes, current systematic reviews have indicated equivalence between the two treatment modalities.

A contemporary meta-analysis (published in 2005) compared one-month composite rates of stroke or death, all stroke, disabling stroke, myocardial infarction, cranial nerve injury, and major bleeding and one-year rates of both minor and major ipsilateral stroke. The 30-day stroke and death rates associated with CAS and CEA were not significantly different. Lower rates of myocardial infarction and cranial nerve injury were observed with CAS compared with CEA (10).

A Cochrane Systematic Review of CAS published slightly earlier (2004) concluded that CEA and CAS had similar early risks of death and stroke and similar long-term benefits, but that the substantial heterogeneity in the evaluated studies rendered overall estimates of effect somewhat unreliable. It was stated that because two trials had been stopped early due to safety concerns, there was a potential overestimate of the risks of endovascular treatment. Endovascular treatment appeared to avoid completely the risk of cranial neuropathy, although there was some uncertainty about the potential for restenosis to develop and cause recurrent stroke. The final

comments were that the current evidence did not support a widespread change *in practice* away from recommending CEA as the treatment of choice for suitable carotid artery stenosis but that there was a strong case to continue recruitment in the current randomized trials comparing CAS and CEA (11).

Indications and Contraindications:

Definitions:

A high-grade stenosis is a $\geq 70\%$ stenosis by NASCET criteria (equivalent to a $\geq 85\%$ stenosis by ECST criteria).

Acceptable Indications:

Symptomatic:

1. Symptomatic high-grade stenosis in a patient suitable for surgery in an experienced unit that can demonstrate good outcomes.
2. Symptomatic high-grade stenosis that is relatively inaccessible surgically i.e. high bifurcation that may require mandibular disarticulation and would expose the patient to increased risk of postoperative cranial neuropathy.
3. Symptomatic high-grade stenosis in a patient with significant medical co-morbidity that may render the patient a high risk for surgery.
4. Symptomatic severe stenosis and one of the following conditions:
 - a. Significant tandem lesion that may require endovascular therapy.
 - b. Radiation-induced stenosis.
 - c. Restenosis after CEA .
 - d. Stenosis secondary to arterial dissection.
 - e. Stenosis secondary to fibromuscular dysplasia.
 - f. Stenosis secondary to Takayasu arteritis.
5. Pseudoaneurysm.
6. Refusal to undergo CEA after appropriate informed consent.
7. Patient with symptoms attributable to global hypoperfusion. Guidance from a neurologist with an interest in stroke prevention or stroke physician is helpful.

Asymptomatic:

1. Combined bilateral stenoses of the internal carotid arteries $\geq 160\%$ in a patient who is awaiting cardiac surgery (coronary artery bypass grafting or valve replacement). The evidence-base to support this intervention is limited.
2. Units that can demonstrate independently reviewed good outcomes compared to CEA may offer CAS to younger male patients with a rapidly progressing high-grade asymptomatic lesion plus/minus cerebral infarction on computerised tomography (CT) of brain in light of the Asymptomatic Carotid Surgery Trial (ACST) results (12).

Relative contraindications:

1. High-grade stenosis in a patient whose symptoms may be attributable to an alternative embolic source i.e. atrial fibrillation, patent foramen ovale, mechanical heart valves etc
2. Symptomatic high-grade stenosis in a patient with a significant contraindication to angiography.

Symptomatic high-grade stenosis associated with an intracranial vascular malformation is a challenging clinical scenario and there are no data to guide practice.

Treatment of symptomatic high-grade stenosis in patients with recent cerebral infarction remains controversial. Conventional wisdom dictates that surgery be delayed ≥ 6 weeks but recent work may challenge these preconceptions. Whilst the optimal period of benefit for intervention for a patient presenting with TIA is considered to be within two weeks, timing of intervention following cerebral infarction documented on cross-sectional imaging of brain is unclear for both CEA and CAS (13, 14, 15).

Absolute contraindications:

1. A high-grade stenosis that cannot be safely reached or crossed by an endovascular approach.

The presence of angiographically visible intraluminal thrombus associated with a high-grade carotid stenosis presents some technically challenging aspects to an endovascular procedure. Whilst this type of lesion may theoretically be safely treated if flow-reversal is employed as a means of cerebral protection there are limited data to support practice. Secondly, it must be noted that neither duplex ultrasonography nor digital subtraction angiography can reliably identify intraluminal thrombus.

Appendix I gives the current study design, inclusion, exclusion criteria, patient involvement and primary outcomes for the ongoing randomized trials of CAS versus CEA.

Training, Qualifications and responsibilities of personnel:

A multidisciplinary approach provides a supportive environment for patient and involved clinician. This may include stroke physicians or neurologists with an interest in stroke prevention, surgeons with expertise in carotid endarterectomy and interventionists with expertise in carotid stenting, regardless of their speciality.

The team as a whole must ensure that they have between them:

-A thorough knowledge of cerebrovascular anatomy, hemodynamics, physiology and pathophysiology.

-Knowledge of both clinical and imaging evaluations. The appreciation of the strengths and limitations of different imaging modalities involved in patient assessment is important and the clinical manifestations of the disease process and its natural history must be understood.

-An appreciation of the risks and benefits of carotid stenting relative to best medical therapy and to CEA.

-An understanding of procedural pharmacological support.

-The ability to provide appropriate endovascular management of vascular complications related to carotid stenting.

-The ability to provide immediate basic life support and treatment of any cardiac arrhythmia complicating carotid stenting. This includes trained personnel, equipment and pharmacotherapeutics.

-An understanding of radiation physics and safety, including the principles of radiation biology, radiation monitoring requirements of personnel and the hazards of radiation exposure for both patient and personnel.

Independent review and data collection are recommended.

Adequate training and experience are absolute prerequisites for the performance of any procedure which carries a risk of stroke. The neurological complication rate associated with cerebral angiography is higher for inexperienced operators (16, 17). Operator risk factors for stroke/transient ischemic attack complications of cerebral angiography include increased procedure and fluoroscopy time, increased numbers of catheters used, and performance of arch aortography (18, 19). In the Asymptomatic Carotid Atherosclerosis Study (ACAS), the rate of stroke complicating diagnostic cerebral angiography prior to surgery in patients with asymptomatic disease was approximately 1.2%, largely reflecting the risk of selective carotid injections. This may be higher than the risk of stroke from the stenosis itself for many asymptomatic patients (20, 21).

Unique and distinct learning curves exist for carotid stenting per se and separately for the use of cerebral protection devices (22). CAVATAS clearly demonstrated the effect of experience on the rate of adverse procedural events both for CEA and CAS (3). Large single center experiences of carotid stenting show a similar pattern (23, 24). It is unclear what the minimum number of procedures constituting any such learning curve is. The accrual of numbers of cases alone do not necessarily equate with technical competence but a minimum of fifty cases has been suggested (55).

The Royal College of Radiologists (RCR) provide curricula for structured training in clinical radiology in the United Kingdom. Competence is based on index procedure numbers. A trainee wishing to train in Vascular/Interventional Radiology or Interventional Neuroradiology must do so within a recognised accredited programme which are approved by the RCR. It is recommended that for a full-time vascular or neurointerventionist, 1-2 years should be dedicated to subspeciality training. For a Vascular/Interventional radiologist, a minimum of 150 diagnostic angiograms must be performed (including “peripheral, central and selective”). Carotid stenting is not specifically mentioned. An Interventional Neuroradiologist should participate in at least 80 neuroradiological interventional procedures of which a substantial proportion will be for intracranial vascular lesions. The trainee must be the first operator in at least a third of cases. Again, carotid stenting is not separately mentioned. The trainee does not currently qualify with a separate accreditation in Interventional Radiology or Interventional Neuroradiology. In the UK, cardiologists are expected to perform a minimum of 150 percutaneous coronary interventions prior to taking up a substantive (consultant) post in interventional cardiology.

There is ongoing debate regarding the requirement to have basic experience in selective cerebral angiography prior to treating patients with CAS. The American Association of Neurological Surgery (AANS), the Congress of Neurological Surgeons (CNS), and the AANS/CNS Cerebrovascular Section, American Society of Interventional and Therapeutic Neuroradiology (ASITN) and American Society of Neuroradiology (ASN) unanimously endorse that diagnostic cervicocerebral angiography be performed in 100 cases prior to learning intervention i.e. as a pre-requisite for entry into an Accreditation Council for Graduate Medical Education (ACGME) approved residency/fellowship programme in Endovascular Surgical Neuroradiology (26, 27). However the Society for Cardiovascular Angiography and Interventions (SCAI), Society for Vascular Medicine and Biology (SVMB) and Society for Vascular Surgery suggest that such a requirement would lead to unnecessary procedures (28), but does recommend that at least 30 cervicocerebral angiograms are performed at some stage prior to undertaking CAS.

The training guidelines of The American Heart Association (AHA), American College of Cardiology (ACC), Society for Vascular Surgery (SVS), SIR, ASNR and the ASITN require 100 diagnostic angiograms be performed regardless of the vascular bed (26). For the coronary circulation the ACC require 300 diagnostic angiograms prior to accreditation.

These figures may be difficult to achieve in the current climate where the majority of diagnostic carotid work prior to carotid endarterectomy is non-invasive. Most selective cervicocerebral catheterisations are performed for assessment of and/or interventions in the cerebral circulation. The demographics of this patient population

and risks of selective catheterisations are largely different from those with stenotic disease at the carotid bifurcation.

Thirty-two of 134 CREST-credentialed interventionists to date have been vascular surgeons or neurosurgeons. As these surgeons had performed well in the lead-in to the trial it was concluded that 10-30 CAS cases per surgeon be devoted to training (29). It was recognised, however, that these individuals had already acquired basic skills in catheter and guide-wire manipulation. Surgeons in the USA wishing to undergo endovascular training are required to perform at least 100 catheterisations (half of which should be selective catheterisations) and 50 therapeutic interventions. It is recommended that the trainee act as primary interventionist in at least half of these procedures. In addition at least 25 percutaneous arterial cannulations should be performed (30).

In the United Kingdom, a three-staged training programme for carotid stenting exists and similar models exist in mainland Europe.

This includes attendance at a carotid-stenting study day, a visit by the whole interventional team (to include nurses and radiographers) to a high-throughput center and the performance of carotid stenting procedures under the tutelage of an experienced proctor. It is then usually at the discretion of the proctor to suggest when the interventionist may proceed without further supervision. However, it has been advocated, certainly in the UK, that the performance of the procedure by two experienced interventionists is advisable. This provides a supportive environment in the early stages and is an attractive concept for a procedure which has such a potentially devastating complication profile.

In order to perform carotid stenting within the International Carotid Stenting Study (ICSS), the interventionist must have completed a carotid-stenting training programme (31).

Support for the concept of proctorship comes from The Kennedy report which was produced after the poor outcome of pediatric cardiac surgery in Bristol in the UK. The Summary of the Bristol Royal Infirmary Inquiry concluded (32).

“Where surgeons or other clinicians undertake an invasive clinical procedure for the first time, they should be properly trained and directly supervised, if the procedure is already established. In the case of a new, untried invasive clinical procedure they must seek permission from the local research ethics committee for permission. Patients are entitled to know what experience the surgeon or clinician has before giving consent”.

With respect to the management of the “learning curve” it was suggested that private preparation, visiting centers of excellence and observing there, assisting an experienced surgeon at an operation, attending workshops and the invitation of experts to operate or assist the surgeon at their own centre be employed.

The Safety and Efficacy Register of New Interventional Procedures (SERNIP), whose work is now covered by the National Institute of Clinical Excellence (NICE) in the UK, provided guidelines on the introduction of new procedures;

“Training needs to take into consideration all professionals who will be involved in the new procedure. This includes junior medical staff, nursing staff, allied health and support staff who may be involved in the sterilising or setting up of the equipment (33).

There is currently no procedure-based competence assessment for any endovascular procedure. The attainment of target numbers may be appropriate if the limitations of this means of evaluation are accepted. It is clear that training and credentialing standards for CAS should encompass all of the recognized traditional components of any invasive, high-risk intervention. Most important of which is perhaps the demonstration of the competence of an individual to meet acceptable outcomes.

Maintenance of competence:

Low-volume throughput is associated with a higher procedural stroke rate for surgeons performing endarterectomy and on this basis, some advocate that regionalisation should be considered for endarterectomy and that surgeons with low volumes should not provide the service (34-38).

There is no reason to believe that these concerns may not also apply to interventionists performing carotid stenting, although the absolute numbers of procedures which must be performed annually to maintain competence is not documented. Within ICSS, surgeons must have performed 50 endarterectomies as first operator (which may include supervised cases in training) and be operating on 10 carotids a year minimally. The minimal annual figures for stenting are not suggested although ten proctored CAS cases are the minimum entry-requirement into ICSS. These cases will be included in the ICSS dataset but may be analysed as a subset to reflect learning curve issues. It is recommended that a center does not begin a programme unless it can provide a sufficient number of cases per year for the interventionist to remain proficient. At least 10 cases a year would constitute a basic minimum.

The General Medical Council (GMC) provides guidelines for maintaining good medical practice in the UK and these may easily be extrapolated to suit mainland Europe (39). Aspects of the maintenance of good medical practice include;

- standards of performance
- internal and external medical and clinical audit
- effective quality assurance

It is stated;

“Effective clinical teams should be prepared to test themselves against others providing similar care, to see where they stand and to learn from this. This testing can be quite informal - for example, through visits, discussions, and comparing results with colleagues. It may also be more formal - for example, through external review leading to accreditation for training”.

DOCUMENTATION:**Consent:**

For the patient and referring clinician to be able to make informed choices about treatment options, accurate local data on the morbidity and mortality of stenting, endarterectomy and medical therapy should be available (40). Informed consent should be taken in compliance with institutional policy and be consistent with the International Code of Medical Ethics declared at the Geneva Convention in 1949, approved by the World Medical Association. Approval from the appropriate local research ethics committee (or multi-center research ethics committee for studies involving more than two sites) must be sought prior to recruiting patients to CAS trials.

The main risks are stroke and death. Puncture site complications may be less of an issue with the use of closure devices. Allergic reactions to iodinated contrast are relatively uncommon and unless they result in severe anaphylaxis, are often easily managed without lasting clinical sequelae. Contrast induced nephrotoxicity may be avoided by the judicious use of a periprocedural nephrotoxicity protocol in at-risk patients, for example, in diabetics with documented renal impairment. This may include hydration, the use of iso-osmolar non-ionic contrast (such as iodixanol) and/or the use of oral n-acetylcysteine (41). Cardiac arrhythmia may still be encountered despite the use of atropine or glycopyrrolate to prevent adverse bradyarrhythmias following endovascular manipulation of the carotid bulb.

Documentation:

The results and outcomes of all CAS procedures should be monitored on a continuous basis. Records should be kept of immediate and long-term outcomes and of the number and types of complications. Technical procedural data and imaging details should be kept in accordance with the data protection act. At least 30-days of clinical follow-up are required for appropriate quality assurance. Outside of CAS trials, data should be submitted to national registries where possible.

Specifications of the procedure:

Technical requirements:

The minimum facility requirements include:

-An angiographic suite with sufficient space to allow positioning of patient-monitoring equipment whilst providing sufficient space for circulating staff to move without contaminating the sterile field. Road-mapping (real-time digital subtraction) is a huge advantage. Facilities for accurate calibrated angiography to allow appropriate sizing of stents and protection devices are a bonus. Alternatively, diameter measurements of the CCA may be made on ultrasound in order to size the stent although measurements of the distal ICA for placement of a protection device may not be possible in all patients using ultrasound.

- A high-resolution image intensifier and imaging chain with the ability to acquire and store images digitally. Imaging and recording must be consistent with the ALARA principle regarding radiation dose (As Low As Reasonably Achievable).
- Adequate equipment for periprocedural physiological monitoring, including equipment for cardiopulmonary resuscitation and temporary cardiac pacing.
- Immediate access to computed tomography (CT) or magnetic resonance imaging (MRI) to allow investigation of suspected complications i.e. intracranial embolization.
- Immediate access to neuro-rescue skills

Success and complication rates:

With respect to technical success, there is insufficient evidence in the carotid artery for a scientific definition, compared with the peripheral vasculature, renal or coronary arteries.

From the coronary literature, technical success for angioplasty/stenting has been redefined as a decrease in stenosis to <20% (42, 43). However, the degree of stenosis in the extracranial carotid artery is essentially a surrogate marker of the degree of emboligenic risk posed by the plaque burden, rather than a cause of symptoms relating to hemodynamic compromise per se. It is unknown what degree of correction of carotid stenosis is necessary to reduce the risk of embolization, but control of the embolic source is fundamental. Accepting a higher degree of residual stenosis may lead to a higher rate of restenosis, although the clinical impact and significance of restenosis, which may largely be due to intimal hyperplasia, may be minimal (44, 45). In the absence of definitive scientific evidence, an improvement of the stenosis by at least 20% with a final residual stenosis of <50% by NASCET criteria would be a pragmatic approach (46). Comparisons of long-term outcome and restenosis between centers using different definitions of technical success may be possible if clear records are kept.

It is recommended that a validated stroke assessment scale be employed both to assess the patient pre-procedurally (residual deficit is of critical importance as there is little rationale for intervening in a severely disabled patient) and post-procedurally. As noted above, independent review is recommended. A functional scale such as the Modified Rankin Scale may be employed to assess the patient pre-procedurally (**Table I**) (47). Post-procedurally, both the duration and the severity of neurological complication are important. The National Institute of Health Stroke Scale (NIHSS) (48) provides a validated assessment tool in the acute setting.

Definitions of neurological complications: Appendix III

Differentiation between outcomes and complications in symptomatic and asymptomatic populations is critical. The risks and consequently risk-benefit ratios in these very different populations are discrepant.

THRESHOLDS:

Because of the recognized learning curve associated with CAS, complications will be more frequent when the procedure is performed by less experienced practitioners. To account for the level of physician experience with respect to CEA, an ad hoc committee of the AHA Stroke Council (49) proposed that a “beginning surgeon be assigned 100 trouble-free cases as a theoretical statistical basis”. This means that 75 cases would be added proportionately by indication categories to a beginning surgeon’s 25 cases to form a statistical basis of 100 total cases. The number of trouble-free cases is then decreased by the number of actual cases until the practitioner has performed 100 cases. With this system, an inexperienced practitioner would be considered to have a 5% complication rate, rather than 50%, if 5 of the initial 10 cases were complicated. Relatively high thresholds have been set for the complications associated with CAS (46). If this is not assured, excessive complications might continue without triggering a review. For the performance of CAS, 30 trouble-free cases could be assigned (to include patients in both the symptomatic and the asymptomatic categories) (80) (**Table II**).

CAS; EXECUTIVE SUMMARY:

Indications:

- Symptomatic patients with high-grade stenoses who are surgical candidates in centers that can demonstrate good independently reviewed outcomes
- Symptomatic patients with high-grade stenoses who present a high surgical risk on the basis of anatomical or co-morbid factors
- Asymptomatic patients with bilateral high-grade carotid stenoses awaiting CABG
- Asymptomatic patients fitting ACST criteria in centers that can demonstrate good independently reviewed outcomes

Absolute Contraindications:

- A lesion that cannot be safely reached or crossed by endovascular means

Training:

- The interventional team as a whole must be proficient in clinical review, procedural risk-benefit analysis, imaging, patient monitoring, pharmacological support, technical expertise, rescue procedures to include basic life support and neurorescue skills
- Learning curves are relevant to each stage of CAS i.e. patient selection and the use of protection devices; a minimum of 50 cases is suggested
- Training programmes and proctoring aim to limit complications during the interventionists' learning curve
- Maintenance of competence mandates sufficient throughput and low-volume centers may have a higher complication rate
- Thresholds are set such that an audit is triggered if a high complication rate is encountered
- 30 trouble free cases may be assigned to inexperienced interventionists for initial statistical analysis so that patients in inexperienced centers can be appropriately consented

Consent:

- Accurate local data on outcomes must be provided such that the patient and referring clinician can make an informed choice about treatment options.

Independent review and data collection is recommended

Table I: Modified Rankin Scale:

| SCORE | DESCRIPTION |
|--------------|---|
| 0 | No symptoms at all |
| 1 | No significant disability; able to carry out all usual activities. |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Slight disability; unable to carry out all previous activities, but able to look after own affairs with assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

Total (0-6)=

**Table II (46):
Thresholds for Indications, Technical Success and Complications in High-Risk Patients:
(See Appendix II for commentary on thresholds versus incidences of complications).**

| Neurological Complication | Complication Threshold | |
|---------------------------|--------------------------|-------------------------|
| | Asymptomatic Patient (%) | Symptomatic Patient (%) |
| Minor transient deficit | * | * |
| Major transient deficit | * | * |
| Minor reversible stroke | 3.5 | 6 |
| Major reversible stroke | 2 | 3 |
| Minor permanent stroke | 3 | 4.5 |
| Major permanent stroke | 2 | 3 |
| Death | 0‡ | 0‡ |

Indications

Meets the indications listed above 100%

Technical Success** 90%

Key

* At present there are insufficient data available to suggest thresholds for transient deficits after CAS. These data should be recorded and used to inform future revisions of this document.

**Technical success may be arbitrarily defined as satisfactory stent placement with <30% residual stenosis and safe retrieval of any protection device utilized during the procedure.

‡ All deaths should be reviewed

References:

1. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N et al (1998). Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: A stopped trial. *Journal of Vascular Surgery* 28:326-334.
2. Alberts MJ (2001). Results of a multicenter prospective ransomised trial of carotid artery stenting versus carotid endarterectomy. *Stroke* 32:325.
3. CAVATAS investigators (2001). Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Lancet* 357:1729-1737.
4. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L (2001). Carotid Angioplasty and Stenting versus Carotid Endarterectomy a randomized trial in a community hospital. *The Journal of American College Cardiology* 38:1589-1995.
5. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ et al; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected Carotid-Artery Stenting Versus Endareterectomy in High-Risk Patients. *New England Journal of Medicine* 351:1491-1501.
6. Bettmann MA, Katzen BT, Whisnant J, Brant-Zawadzki M, Broderick JP, Furlan AJ, et al (1998). Carotid stenting and angioplasty: a statement for healthcare professionals from the Councils on Cardiovascular Radiology, Stroke, Cardio-Thoracic and Vascular Surgery, Epidemiology, and Prevention, and Clinical Cardiology, American Heart Association. *Circulation* 97: 121-123.
7. Veith FJ, Amor M, Ohki T, Beebe HG, Bell PR, Bolia A et al (2001). Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. *J Vasc Surg* 33:S111-6.
8. Intercollegiate Working Party for Stroke (2002). National Clinical Guidelines for Stroke. Section 11.3: Secondary prevention-update. Copyright to Royal College of Physicians, London.
9. The European Stroke Initiative Executive Committee and EUSI Writing Committee (2003). European Stroke Initiative Recommendations for Stroke Management-Update 2003. *Cerebrovasc Dis* 16:311-337.
10. Qureshi AI, Kirmani JF, Divani AA, Hobson RW II (2005). Carotid Angioplasty with or without Stent Placement versus Carotid Endarterectomy for Treatment of Carotid Stenosis: A Meta-analysis. *Neurosurgery* 56:1171-1181.
11. Coward LJ, Featherstone RL, Brown MM (2004). Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev*. (2):CD000515.

12. Halliday A, Mansfield A, Marro J, Peto CD, Peto R, Potter J, Thomas D; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. *Lancet* 2004;363:1491-1502.
Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial.
13. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ (2004); Carotid Endarterectomy Trialists Collaboration. *Lancet*;363:915-924.
14. Welsh S, Mead G, Chant H, Picton A, O'Neill PA, McCollum CN (2004). Early carotid surgery in acute stroke: a multicentre randomized pilot study. *Cerebrovasc Dis* 18:200-205.
15. Zaidat OO, Alexander MJ, Suarez JI, Tarr RW, Selman WR, Enterline DS, et al (2004). Early carotid artery stenting and angioplasty in patients with acute ischemic stroke. *Neurosurgery* 55:1237-1243.
16. Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera L (2003). Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. *Radiology* 227:522-528.
17. McIvor J, Steiner TJ, Perkin GD, Greenhalgh RM, Rose FC (1987). Neurological morbidity of arch angiography in cerebrovascular disease. The influence of contrast medium and the radiologist. *Br J Radiol* 60:117-122.
18. Mani RL, Eisenberg RL (1978). Complications of catheter cerebral angiography: analysis of 5,000 procedures. III. Assessment of arteries injected, contrast medium used, duration of procedure, and age of patient. *AJR* 131:871-874.
19. Dagirmanjian A, Davis DA, Rothfus WE, Goldberg AL, Deeb ZL (2000). Detection of clinically silent intracranial emboli ipsilateral to internal carotid artery occlusions during cerebral angiography. *AJR* 174:367-369.
20. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (1995). Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 275:1421-1428.
21. Olin JW, Fonseca C, Childs MB, Piedmonte MR, Hertzner NR, Young JR (1998). The natural history of asymptomatic moderate internal carotid artery stenosis by duplex ultrasound. *Vasc Med* 3:101-108.
22. Cremonesi A, Manetti R, Setacci F, Setacci C, Castriota F (2003). Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. *Stroke* 34:1936-1941.
23. Complications following carotid angioplasty and carotid stenting in patients with symptomatic carotid artery disease. *Cerebrovasc Dis* 17:28-34.

24. Roubin GS, New G, Iyer SS, Vitek JJ, Al-Mubarak N, Liu MW, et al (2001). Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation*. 103(4):532-7.
25. Ahmadi R, Willfort A, Lang W, Schillinger M, Alt E, Gschwandtner ME, et al (2001). Carotid artery stenting: effect of learning curve and immediate-term morphological outcome. *J Endovasc Ther* 8:539-546.
26. Connors JJ, 3rd, Sacks D, Furlan AJ, Selman WR, Russell EJ, Stieg PE, et al. Training, competency, and credentialing standards for diagnostic cervicocerebral angiography, carotid stenting, and cerebrovascular intervention. *AJNR Am J Neuroradiol* 2004;25(10):1732-41.
27. Barr JD, Connors JJ, 3rd, Sacks D, Wojak JC, Becker GJ, Cardella JF, et al. Quality improvement guidelines for the performance of cervical carotid angioplasty and stent placement. *AJNR Am J Neuroradiol* 2003;24(10):2020-34.
28. Rosenfield KM. Clinical competence statement on carotid stenting: training and credentialing for carotid stenting--multispecialty consensus recommendations. *J Vasc Surg* 2005;41(1):160-8.
29. Hobson RW 2nd, Howard VJ, Roubin GS, Ferguson RD, Brott TG, Howard G, et al (2004): Credentialing of surgeons as interventionalists for carotid artery stenting: experience from the lead-in phase of CREST. *J Vasc Surg* 40: 952-957
30. White RA, Hodgson KJ, Ahn SS, Hobson RW, 2nd, Veith FJ. Endovascular interventions training and credentialing for vascular surgeons. *J Vasc Surg* 1999;29(1):177-86.
31. Featherstone RL, Brown MM, Coward LJ; ICSS Investigators (2004). International carotid stenting study: protocol for a randomized clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. *Cerebrovasc Dis* 18:69-74
32. Final Report Summary of the Bristol Royal Infirmary Inquiry; http://www.bristol-inquiry.org.uk/final_report/
33. Model Policy for the Safe Introduction of New Interventional Procedures Into Clinical Practice (2003). A model policy for Area Health Services and Other Public Health Organisations. Oct 2003.
34. Hannan EL, Popp AJ, Tranmer B, Fuestel P, Waldman J, Shah D (1998). Relationship between provider volume and mortality for carotid endarterectomies in New York State. *Stroke* 29:2292-2297.
35. Pearce WH, Parker MA, Feinglass J, Ujiki M, Manheim LM (1999). The importance of surgeon volume and training in outcomes in vascular surgical procedures. *J Vasc Surg* 29:768-776.

36. O'Neill L, Lanska DJ, Hartz A (2000). Surgeon characteristics associated with mortality and morbidity following carotid endarterectomy. *Neurology* 55:773-781.
37. Cowan JA, Dimick JB, Thompson BG, Stanley JC, Upchurch GR (2002). Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. *J Am Coll Surg* 195:814-821.
38. Feasby TE, Quan H, Ghali WA (2002). Hospital and surgeon determinants of carotid endarterectomy outcomes. *Arch Neurol* 59:1877-1881.
39. <http://www.gmc-uk.org/standards/mgmp.htm>
40. Consent issues in the management of cerebrovascular diseases (1999): A Position Paper of the American Academy of Neurology Ethics and Humanities Subcommittee. *Neurology* 53:9-11.
41. Erdogan A, Davidson CJ (2003). Recent clinical trials of iodixanol. *Rev Cardiovasc Med* 4 Suppl 5:S43-50.
42. Ryan TJ, Bauman WB, Kennedy JW (1993). Revised guidelines for percutaneous transluminal coronary angioplasty: A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Angioplasty). *Circulation* 88:2987-3007.
43. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, et al (2001); ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines): A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 2239i-2239ixvi.
44. Christiaans MH, Ernst JM, Suttorp MJ, van den Berg JC, Overtoom TT, Kelder JC, et al (2003); Antonius Carotid Endarterectomy, Angioplasty and Stenting Study Group. Restenosis after carotid angioplasty and stenting: a follow-up study with duplex ultrasonography. *Eur J Vasc Endovasc Surg* 26:141-144.
45. Lal BK, Hobson RW 2nd, Goldstein J, Geohagan M, Chakhtoura E, Pappas PJ, et al (2003). In-stent recurrent stenosis after carotid artery stenting: life table analysis and clinical experience. *J Vasc Surg* 38:1162-1169.
46. Barr JD, Connors JJ 3rd, Sacks D, Wojak JC, Becker GJ, Cardella JF, et al (2003); American Society of Interventional and Therapeutic Neuroradiology; American Society of Neuroradiology; Society of Interventional Radiology. Quality improvement guidelines for the performance of cervical carotid angioplasty and stent placement. *J Vasc Interv Radiol* 14:S321-S335
47. Bonita R, Beaglehole R (1988). Modification of Rankin Scale: "Recovery of Motor Function After Stroke". *Stroke* 19:1497-1500.

48. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al (1989). Measurement of acute cerebral infarction: a clinical examination scale. *Stroke* 20:964-970.

49. Beebe HG, Clagett GP, DeWeese JA, Moore WS, Robertson JT, Sandok B, et al (1989). Assessing risk associated with carotid endarterectomy. A statement for health professionals by an Ad Hoc Committee on Carotid Surgery Standards of the Stroke Council, American Heart Association. *Circulation* 79:472-473.

APPENDIX I

Inclusion and Exclusion Criteria for the Ongoing Randomized Trials of CAS versus CEA:

ICSS (CAVATAS-2) - International Carotid Stenting Study

Study Design: Open, prospective, randomized, multicenter trial.

Inclusion Criteria: Patients older than 40 years with symptomatic severe ($\geq 70\%$), whose carotid stenoses are suitable for primary stenting and surgical endarterectomy, who are able to begin treatment as soon as possible after randomization, and who have no indication or contraindication to either treatment will be eligible.

A recent amended to protocol has been the inclusion of lower degrees of stenosis ($>50\%$ NASCET, equivalent to $>70\%$ ECST).

Exclusion Criteria: Patients who have had a major stroke with minimal recovery of function in the territory of the artery in question, who are unsuitable for stenting due to tortuous anatomy proximal or distal to the stenosis, the presence of a visible thrombus, proximal carotid artery stenotic disease, pseudo-occlusion, high stenosis, or rigid neck, who are medically unfit for surgery, or who have a life expectancy < 2 years will be excluded.

Primary Outcome: Incidence of mortality and debilitating (modified Rankin score (MRS) < 3 for 30 days after onset) stroke.

SPACE - Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy

Study Design: Prospective, randomized, independently-controlled, multicenter trial.

Inclusion Criteria: Patients with severe carotid stenosis ($\geq 70\%$ by Duplex sonography, $\geq 50\%$ by NASCET criteria, or $\geq 70\%$ by ECST criteria) who have experienced amaurosis fugax, TIA, prolonged reversible ischemic neurological deficit (PRIND), or other mild stroke within 180 days of randomization, amaurosis fugax, or non-disabling stroke (mod. Rankin ≤ 3) occurring within 180 days will be eligible.

Exclusion Criteria: Pregnant females, and persons with a history of intracranial bleeding within 90 days of randomization, who have a confirmed arteriovenous malformation or aneurysm, who have a serious comorbid illness limiting life expectancy < 2 years, who have an uncontrolled coagulopathy, who have any contraindication for heparin, aspirin, clopidogrel, or contrast media, who have stenosis or dissection of the common and/or internal carotid arteries, who have stenosis following surgical or endovascular pretreatment, whose stenoses result from radiation therapy, fibromuscular dysplasia, or endovascular thrombosis, who have tandem stenoses (if the distal stenosis is the more severe), who have other planned surgical interventions, or who have any comorbid condition that, in the opinion of the investigator, would interfere with the study, will be excluded.

Primary Outcome: 30-day incidence of ipsilateral cerebrovascular events (cerebral infarction and/or hemorrhage with symptoms lasting for more than 24 hours); 30-day mortality.

EVA-3S Endarterectomy Versus Angioplasty in patients with Severe Symptomatic carotid Stenosis

Study Design: Prospective Randomized Open Blinded End-point (PROBE) Study.

Inclusion Criteria: Patients presenting within 4 months of ischemic cerebral or retinal stroke will be eligible.

Patient Involvement: Eligible patients will be randomized to undergo either carotid endarterectomy or angioplasty with stenting. The use of cerebral protection is mandatory. Angioplasty patients will receive either ticlopidine or clopidogrel for 1 month after the procedure. Patients in both groups will receive follow-up visits at 1 month, 6 months, and every 6 months thereafter for 2 - 4 years. Duplex scans will be performed at the time of the procedure, and every 6 months for the duration of the study. Patients in the angioplasty group will undergo blood draws at 15 days and 1 month, and a simple cervical radiogram at 2 years after the procedure.

Primary Outcome: All mortality and all recurrence of stroke within 30 days, all ipsilateral stroke within 2 - 4 years.

CREST - Carotid Revascularization Endarterectomy versus Stent Trial

Study Design: Prospective, randomized, clinical trial on lower risk patients.

Inclusion Criteria: Patients who have experienced a TIA, amaurosis fugax (AF), or non-disabling stroke within the past 180 days, and who have an ipsilateral carotid stenosis > 50% by angiography or 70% by ultrasound will be eligible.

A recent amendment to protocol has been the inclusion of patients with asymptomatic stenoses > 80% by ultrasound.

Exclusion Criteria: Patients who have comorbid conditions that interfere with the evaluation of endpoints, that are known to interfere with the completion of CEA or CAS, or that affect the likelihood of survival for the 4-year study period, will be excluded.

Patient Involvement: Eligible patients will be randomized to undergo either CAS or CEA. All will receive aspirin, antiplatelet therapy, treatment for hypertension, and management of other stroke risk factors. Follow-up will last four years.

Primary Outcome: Death, stroke, or myocardial infarction at 30 days postoperatively; ipsilateral stroke at 60 days post-operatively.

APPENDIX II: Thresholds and incidences of complications.

Pertaining to **Table II**, inappropriate comparison of the thresholds in **Table II** to the reported incidences of complications after CEA might lead to the erroneous conclusion that higher rates of neurological complications are acceptable for CAS compared to lower rates for CEA.

- a. A “threshold” is not intended to represent the desirable incidence of complications but rather implies a complication rate that is **significantly above** the expected rate of complications, such that an audit be conducted to examine the cause of this unexpectedly high incidence of complications.
- b. These thresholds are **significantly higher** than the complication rates for CEA published in NASCET and ACAS. These trials included low-risk patients. The thresholds pertain **only** to high-risk patients i.e those listed in “Indications” above, for symptomatic patients points 1-3.
- c. The thresholds are comparable with the incidences of complications resulting from CEA performed on similar high-risk patients (74).
- d. The definitions of neurological complications on which these thresholds are based differ from those utilized in many reported series. No accepted, standardized reporting methodology exists, but the definitions chosen should be applicable to a broad range of cerebrovascular interventions and surgery. Thresholds pertain to complications occurring within 30 days of the procedure.
- e. Thresholds for the reversible stroke categories are based on the expectation that reversible deficits are likely to be slightly more common than permanent strokes. It is appreciated that there are, as yet, no adequate scientific data to confirm this.

APPENDIX III; Definitions of neurological complications (46)

Neurological complication:

Neurological deterioration evidenced by an increase in the NIHSS score of one or more points.

Transient deficit (Transient Ischemic Attack, TIA):

A neurological complication which is fully resolved within 24 hours.

Reversible Stroke: (reversible ischemic neurological deficit (RIND))

A neurological complication having a duration of more than 24 hours and up to 30 days.

Permanent Stroke

A neurological complication having a duration of more than 30 days.

Minor Deficit:

Neurological deterioration evidenced by an increase of the NIHSS score of less than four points without the presence of aphasia or hemianopsia.

Major Deficit:

Neurological deterioration evidenced by an increase of the NIHSS score of four or more points or the presence of aphasia or hemianopsia.