

Worldwide CAS Practice in 2011

Comparing and contrasting the AHA, NICE, and ESVS guidelines.

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Stroke prevention is a major public health priority; best medical therapy for patients who are at risk of atherosclerosis reduces their risk of stroke. In patients with tight carotid artery stenosis, the risk of subsequent stroke is significantly reduced by removing the atherosclerotic plaque. Carotid endarterectomy (CEA) has been available for more than 50 years and has, to date, been the standard treatment for significant carotid stenosis in symptomatic and asymptomatic patients. Carotid artery stenting (CAS) is a new and effective treatment that avoids the pain and morbidity associated with surgery.

A number of trials have compared CAS with CEA, and although both procedures have a real risk of perioperative stroke, recent randomized trials have highlighted an increased risk of minor stroke with CAS and an increased risk of perioperative myocardial infarction with CEA. Cranial nerve injury and access site hematoma requiring return to the operating room or an unexpected increase in the level of care are significantly greater after CEA, while contrast related issues are a consideration for CAS.¹ Clinical trials have not yet provided clear evidence of superiority of either treatment for “standard operative risk” patients and have been criticized for their design, patient selection, and very variable physician training and credentialing.

This article describes the main messages of current guidelines for CAS from the European Society for Vascular Surgery (ESVS) (2009), the American Heart Association (AHA) (2011), and the UK National Institute for Clinical Excellence (NICE) (2011).²⁻⁵ The ESVS and the AHA guideline documents are large consensus documents covering a wide range of topics related to the management of carotid disease, whereas NICE guidelines are specific to CAS. The extracts in this article summarize the messages from these guidelines.

DISCUSSION

There is no international consensus on stenting for carotid artery disease. There has, however, been a gradual shift from CEA as the only option toward recognition that CAS has a real role to play in the treatment of a significant number of patients worldwide. The future role of CAS will depend on many factors. Currently, there is an expanding and improving worldwide experience of CAS.

Between 1998 and 2004, Goodney et al described a 149% increase in the number of CAS procedures performed in the United States as found in Medicare billing data.⁶

Thousands of mostly asymptomatic patients underwent CAS with independent neurological evaluation, participating in large, industry-funded registries; the excellent results of CAS from these registries equaled CEA and encouraged continuation of CAS, expanding practice and experience.⁷ This experience occurred at a time when CAS was only freely available in the United States for high-risk surgical patients. The majority of patients treated in the United States at the time were asymptomatic, both within randomized trials such as SAPHIRE, where two-thirds were asymptomatic, and industry-sponsored registries. Gray et al reported that 5,558 out of 6,319 (88%) patients undergoing CAS as part of the EXACT and CAPTURE 2 registries were asymptomatic.^{7,8}

After the CREST trial results, the US Food and Drug Administration panel voted in favor of expanding the indication for CAS from high-risk only to standard-surgical-risk patients in January 2011.⁹ It seems likely, therefore, that CAS will be increasingly adopted as a viable alternative to CEA unless new trials report adverse results. This acknowledged, there are no current trials in progress or likely to commence that deal with symptomatic populations. Ongoing trials (ACST-2, SPACE 2, ACT 1) and the proposed CREST 2 deal exclusively with asymptomatic patients, and in CREST, this population

ESVS GUIDELINES 2009²**Indications for CAS**

Symptomatic patients

- Available evidence from randomized controlled trials (RCTs) suggests that for symptomatic patients, surgery is currently the best option (grade A).
- Midterm stroke prevention after successful CAS is similar to CEA (grade A).
- CAS should be offered to symptomatic patients if they are at high risk for CEA, in high-volume centers with documented low periprocedural stroke and death rates, or inside a randomized controlled trial (grade C).

Asymptomatic patients

- It is advisable to offer CAS to asymptomatic patients only in high-volume centers with documented low periprocedural stroke and death rates or within well-conducted clinical trials (grade C).
- CAS should not be offered to asymptomatic high-risk patients if the peri-interventional complication rate is > 3% (grade C).

CAS Procedure

The team

- The decision to undertake CAS is best made by a multidisciplinary team.
- Validated training programs should be developed (grade B).

Periprocedure

- The presence of an anesthesiologist or another physician capable of maintaining adequate hemodynamic control is mandatory.

- CAS should be performed under dual-antiplatelet treatment with aspirin and clopidogrel (grade A). Dual-antiplatelet treatment should start before CAS and continue for 3 months after the stenting procedure (grade C).
- Cerebral protection devices are probably beneficial (grade C).

The grade of recommendation for these guidelines is based on available level of evidence (Appendix A, page 54 of this article).

Comments on the ESVS Guidelines

These guidelines were developed by a working group of 30, of whom 22 have a surgical background. The evidence at that time strongly favored CEA, and a 2007 Cochrane Collaboration meta-analysis showed a significantly lower risk of stroke and death with surgery compared to stenting (odds ratio, 1.39; 95% confidence interval, 1.05–1.84; $P = .02$).¹⁰ Future improvements in CAS results were thought to be likely and, despite the grade A recommendation for CEA, supported randomization in the large randomized controlled trials that were underway at that time (ICSS and CREST). CAS was thought to be more appropriate for surgically inaccessible lesions and after previous neck surgery or irradiation (ie, in traditionally high-surgical-risk populations). A small number of nonevidence-based recommendations are included, such as that a physician independent of the performance of the CAS procedure capable of maintaining hemodynamic control be present. Since hemodynamic perturbation can be anticipated during a CAS procedure, both the team and the operator(s) (and/or a separate physician not involved with the procedure such as an anesthesiologist) should be well-versed in, and prepared for, managing this possible eventuality.

has very comparable all stroke/death outcomes for CEA and CAS in the intermediate term. Longer-term data will help inform future decision making.

For asymptomatic patients, the three sets of current guidelines acknowledge the need for further studies and recommend undertaking CAS within well-conducted trials. This is largely because the importance of longer-term data in these patients is clinically very relevant. These patients are generally offered carotid intervention because they are expected to have a reasonable life expectancy. The original trials of CEA versus best medical therapy as conceptualized at the time when ACAS and ACST were recruiting, demonstrated that unselected asymptomatic patients generally need to live on average 5 years before they can reap the rewards of carotid intervention for their asymptomatic lesions.

Figures such as these may ultimately change in light of current concepts of best medical therapy but as yet remain speculative.

ACST-2 is currently recruiting patients. It is a large multicenter randomized trial comparing CAS and CEA in patients who have been asymptomatic for at least 6 months and in whom both procedures are technically feasible when there is substantial uncertainty about which procedure to offer. It is a government-funded rather than industry-funded trial that plans to recruit more than 5,000 patients, half of whom will be allocated to undergo CAS, and in which operators can use their preferred techniques and all available CE Marked stents and embolic protection devices on the market.

Both the ESVS and AHA guidelines make strong recommendations for dual-antiplatelet therapy in the peri-

AHA GUIDELINES 2011³**Indications for CAS**

Symptomatic patients

- CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by > 70% as documented by noninvasive imaging or > 50% as documented by catheter angiography and where the anticipated rate of periprocedural stroke or mortality is < 6% (class I recommendation, level of evidence B).

Asymptomatic patients

- Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (class IIb recommendation, level of evidence B).

CAS Procedure

The team

- No specific recommendations on the makeup of the team but state that all recommendations for carotid revascularization “assume that operators are experienced, having successfully performed the procedures in > 20 cases with proper technique and a low complication rate based on independent neurological evaluation before and after each procedure.”

Periprocedure

- Dual-antiplatelet therapy with aspirin plus clopidogrel is recommended before and for a minimum of 30 days after CAS (class I recommendation, level of evidence C).

- Embolic protection device deployment during CAS can be beneficial to reduce the risk of stroke when the risk of vascular injury is low (class IIa recommendation, level of evidence C).

The grade of recommendation for these guidelines is based on available level of evidence (Appendix B, page 54 of this article).

Comments on the AHA Guidelines

Both surgery and CAS receive a class I recommendation, but the level of evidence was stronger for surgery (level A) than for CAS (level B). The level I recommendation for CAS reflects a subtle but significant shift in international opinion after publication of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) results in 2010. There was no significant difference in the primary endpoint of any stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization (CAS = 7.2% vs CEA = 6.8%; $P = .51$).¹¹ These guidelines also pave the way for undertaking CREST II, a trial in asymptomatic patients that plans to compare intervention (with either CEA or CAS) versus medical treatment alone. Embolic protection devices are recommended, although the level of evidence upon which these recommendations are based is limited simply because there have been no randomized trials of protected versus unprotected CAS based on clinical outcome events. A recent meta-analysis demonstrates that CAS with embolic protection is superior to unprotected CAS, reaching superiority in the year 2004, the relative risk stabilizing at around 0.6 in the year 2005.¹² The FDA does not explicitly demand the use of embolic protection but CMS will not reimburse CAS performed without embolic protection.

operative period with aspirin and clopidogrel (grade A and class I, respectively). The AHA recommends therapy for a minimum of 1 month; the ESVS recommends 3 months. The published literature supports dual-antiplatelet therapy after CAS, but the optimum duration of therapy remains to be seen. McKevitt et al demonstrated an excess risk of neurological complications when aspirin and heparin were used for 24 hours compared to aspirin and clopidogrel for 28 days; the trial was terminated early as a result (25% vs 0%; $P = .02$).¹³ Dalainas et al similarly reported a significant difference in neurological complications with dual antiplatelets in the form of aspirin and ticlopidine versus aspirin and 24 hours of intravenous heparin (16% vs 2%; $P < .05$).¹⁴

SUMMARY

The guidelines reviewed here reflect the opinion that CAS may become a real alternative to CEA for most patients. Summary recommendations from the Australia and New Zealand Carotid Stenting Guidelines Committee first suggest, “[the] evidence from randomized controlled trials indicates that, at present, a cautious approach should be taken to recommending carotid artery stenting—*festina lente* (hasten slowly).” They then continue, “stenting warrants consideration in younger patients (< 70 years of age) and [in] those with symptomatic severe carotid stenosis unsuitable for endarterectomy.” Stenting for asymptomatic disease is supported where the clinician considers revascularization to be appropriate but within randomized trials.¹⁵

NICE GUIDELINE 2011^{4,5}**Indications for CAS**

Symptomatic patients

- Current evidence on the safety and efficacy of carotid stent placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit or research.
- During the consent process, clinicians should ensure that patients understand the risk of stroke and other complications associated with this procedure. Clinicians should also ensure that patients understand the reasons for advising carotid artery stent placement rather than endarterectomy in their particular case.

Asymptomatic patients

- Current evidence on the safety of carotid artery stent placement for asymptomatic extracranial carotid stenosis shows well-documented risks—in particular, the risk of stroke. The evidence on efficacy is inadequate in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit, or research.
- NICE encourages clinicians either to enter patients into the ACST-2 trial (Asymptomatic Carotid Artery Surgery Trial-2) (www.acst.org.uk) or to submit data to the Endovascular Carotid Register, which is run by the British Society of Interventional Radiology and the Vascular Society of Great Britain and Ireland (www.bsir.org and www.vascularsociety.org.uk, respectively).

CAS Procedure

The team

- Patient selection should be carried out by a multidisciplinary team, which should include an interventional radiologist or a neuroradiologist, a vascular surgeon, and a physician with specialist interest in stroke.
- This procedure should only be carried out by clinicians with specific training and expertise in the technique who regularly perform complex endovascular interventions. The Royal College of Radiologists has produced training standards.

Periprocedure

- No specific periprocedural management recommendations.

Comments on the NICE Guideline

The NICE guideline does not make explicit recommendations regarding selection of CAS versus CEA in symptomatic patients. They do, however, recommend that patients are counseled as to the reason CAS is recommended in their particular case. For asymptomatic patients in whom both CEA and CAS are appropriate, NICE specifically directs that patients should be considered for inclusion in the ACST-2 trial. This large, worldwide trial, funded by the United Kingdom government National Institute of Healthcare Research by comparing patients in whom both procedures are possible, aims to determine whether CAS is as good as or better than CEA in mid- to long-term stroke prevention. In common with the ESVS guidelines, great emphasis is placed on the selection of cases for CAS by a multidisciplinary group that is able to offer both treatment options as appropriate.

In our summary, CAS for primary treatment of symptomatic standard-surgical-risk patients is supported by both the AHA and NICE guidelines, while the ESVS guidelines urge that CAS is restricted to high-surgical-risk symptomatic patients. The discrepancy between the AHA and NICE guidelines versus the ESVS guidelines might result from the fact that the AHA and NICE guidelines reflect balanced multidisciplinary team decision making, while the ESVS guidelines reflect the recommendations of a single specialty in the majority (ie, vascular surgery). Furthermore, the ESVS guidelines were published in 2009 and predate the results of CREST; arguably they are in need of updating. Regarding asymptomatic patients, all recommendations urge some degree of caution with respect to CAS and would support involvement in important ongoing trials. Effectively, the guidelines reviewed here reflect that CAS is clearly a very attractive option for

an increasing number of patients and that trials comparing both procedures should be welcomed, not feared. ■

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APPENDIX A. GRADE OF RECOMMENDATION FOR ESVS²

Grade	Recommendation
A	Based on the criterion of at least one randomized controlled clinical trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B	Based on well-conducted clinical studies but no good-quality randomized clinical trials on the topic of recommendation.
C	Based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities (ie, no applicable studies of good quality).

APPENDIX B. CLASSIFICATION OF RECOMMENDATIONS AND LEVEL OF EVIDENCE FOR AHA³

Class of Recommendation	Level of Evidence
Class I: Benefit >>> Risk • Procedure or treatment should be performed	Level A • Multiple populations evaluated • Data derived from multiple RCTs or meta-analysis
Class IIa: Benefit >> Risk • Additional studies with focused objectives needed • It is reasonable to perform the procedure	Level B • Limited populations evaluated • Data derived from a single RCT or nonrandomized study
Class IIb: Benefit > Risk • Additional studies with broad objectives needed; additional registry data would be helpful • Procedure may be considered	Level C • Very limited population evaluated • Only consensus opinion of experts, case studies, or standard of care
Class III: No Benefit • Procedure not helpful	
Class III: Harm • Excess cost without benefit or harmful	

Vascular, Bard Peripheral Vascular, Cordis Corporation, ev3 Inc., Gore & Associates, Medtronic Invatec, and Pyramed, and that she is a paid consultant to Abbott Vascular, ev3 Inc., Medtronic Invatec, and Gore & Associates. Dr. Macdonald may be reached at sumaira.macdonald@nuth.nhs.uk.

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