Topical Reviews

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What Is the Current Status of Invasive Treatment of Extracranial Carotid Artery Disease?

A. Ross Naylor, MD, FRCS

Abstract—Year 2011 sees the publication of US guidelines that recommend expanding indications for carotid artery stenting into “average-risk” patients, whereas guidelines from Australia/New Zealand largely do not. This article reviews the status of invasive treatment of carotid disease and highlights 2 controversial issues that were not really addressed in these guidelines: (1) a lack of emphasis on the importance of intervening rapidly after transient ischemic attack/minor stroke; and (2) why continue to recommend that only “highly selected” asymptomatic patients should undergo intervention when virtually no-one pays any attention? (Stroke. 2011;42:2080-2085.)

Key Words: asymptomatic carotid stenosis ▪ carotid endarterectomy ▪ interventional radiology ▪ stents ▪ symptomatic carotid stenosis

“There are no facts, only interpretations”
—Friedrich Nietzsche

Regardless of prejudices or affiliations, few could dispute that 2011 is a landmark year in the treatment of carotid disease. Previous guidelines have concluded that carotid artery stenting (CAS) was appropriate in “high risk” for carotid endarterectomy (CEA) symptomatic patients but not “average-risk” patients. This changed when the Food and Drug Administration Circulatory System Devices Panel recommended that; “the benefits of the RX Acculink® Carotid Stent system in symptomatic/asymptomatic patients at standard-risk for adverse events from CEA outweighed the risks.”1 The momentum toward CAS continued with 2011 guidelines from the American Heart Association (AHA) and American Stroke Association (ASA)2,3 and a 14 Inter-Societal Panel.4 Each recommended that CAS indications be expanded to include “average-risk” patients, a decision based on the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST).5 However, these recommendations are at variance with 2011 Australia/New Zealand guidelines, which advise against CAS in asymptomatic patients at the same time as only slightly expanding indications in symptomatic patients.6

Trials and Tribulations

Thirteen randomized trials (7480 patients) provide the evidence base for these guidelines. Some were methodologically flawed; many were criticized (usually after publication); early studies did not have access to dedicated stents, protection devices, or dual-antiplatelet therapy; end points changed to include “chemical” myocardial infarction (MI); there were interdisciplinary “turf wars” and a perception that North American colleagues sometimes view data from elsewhere as being inferior. Six trials stopped prematurely (1 blocked from publication by its sponsor) and because each stopped on a “premature low,” this was another potential source of bias.
So, despite the AHA/ASA2 referencing CREST,5 at the same time as ignoring the International Carotid Stenting Study (ICSS7; still the largest randomized trial in symptomatic patients), was it reasonable to expand the indications for CAS?

What Do We Know?

Thirty-Day Death/Stroke
Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S), Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), ICSS, and CREST randomized 5938 (80%) of the 7480 patients. The Carotid Stent Trialists Collaboration (CSTC) meta-analyzed data from EVA-3S, SPACE, and ICSS, observing that the 30-day death/stroke rate was significantly higher after CAS (8.9%) versus 5.8% after CEA (OR, 1.53; 95% CI, 1.2 to 1.95).8 A similar trend was present in CREST, in which 30-day death/stroke in symptomatic patients was 6.0% versus 3.2% after CEA (OR, 1.9; 95% CI, 1.1 to 3.4; \( P = 0.02 \)).5 When symptomatic patients from CREST were combined with CSTC data, CAS incurred a near 2-fold excess risk of stroke/death (OR, 1.7; 95% CI, 1.2 to 2.4). A similar trend was also evident in asymptomatic patients in CREST with a 30-day death/stroke rate of 2.5% after CAS versus 1.4% after CEA (OR, 1.9; 95% CI, 0.8 to 4.4; \( P = 0.15 \)).5 Accordingly, 1 consistent finding across all randomized studies was that CAS was associated with a doubling of the risk of procedural death/stroke.

Midterm Stroke
EVA-3S, SPACE, and CREST found that patients undergoing CAS not having a procedural stroke had similar rates of late ipsilateral stroke compared with CEA (2% to 3% at 4 years), suggesting that CAS was durable. Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) reported increased rates of TIA/stroke, but this was primarily in patients who underwent angioplasty.9

Restenosis
Randomized trials consistently report significantly higher rates of restenosis after CAS, but these have not translated into increased rates of late ipsilateral stroke.9

“High-Risk” Patients
“High risk” refers to CEA (not stroke) and to qualify, patients had to have a 50% to 99% symptomatic stenosis or an 80% to 99% asymptomatic stenosis plus 1 of the following: significant cardiac disease; severe pulmonary disease; age >80 years; contralateral occlusion; contralateral laryngeal nerve palsy; previous radical neck surgery/neck radiotherapy; or recurrent stenosis after CEA.

In symptomatic patients, several “high-risk” factors for CEA are also “high risk” for stroke, making it reasonable to preferentially offer CAS, perhaps even accepting a slightly increased procedural risk. However, none of these factors are recognized as being “high risk” for stroke in asymptomatic patients and the 3% risk threshold must be retained. Accordingly, although CAS may be considered in “high risk for CEA” symptomatic patients, most asymptomatic patients should probably be treated conservatively unless interventionists have an audited 30-day death/stroke rate of ≤3%. This is not the type of patient for CAS practitioners to work off their learning curve.

“Alternate” End Points
Several trials introduced alternate end points generating considerable controversy. In reality, most will only assume importance if the difference in procedural stroke risk is small (eg, the 1% difference in asymptomatic patients in CREST5). However, should the absolute difference in stroke risk become greater, these alternate end points will assume lesser importance.

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Table 1. 2011 Guidelines for CEA and CAS

<table>
<thead>
<tr>
<th>Average-risk, 50%–69%</th>
<th>Class I/Level B</th>
<th>CAS (Class I/Level B)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA/stroke &lt;6 mo</td>
<td>CEA</td>
<td>CAS (Class I/Level B)*</td>
</tr>
<tr>
<td>Average-risk, 70%–99%</td>
<td>CEA (Class I/Level A)</td>
<td>CAS (Class I/Level B)</td>
</tr>
<tr>
<td>TIA/stroke &lt;6 mo</td>
<td>CEA (Class I/Level A)</td>
<td>CAS (Class I/Level B)</td>
</tr>
<tr>
<td>“High risk for CEA” 70%–99%</td>
<td>CAS (Class IIb/Level B)</td>
<td>CAS (Class IIb/Level B)</td>
</tr>
<tr>
<td>TIA/stroke &lt;6 mo</td>
<td>CAS (Class IIb/Level B)</td>
<td>CAS (Class IIb/Level B)</td>
</tr>
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</table>

Average risk, asymptomatic

| 60%–99% (angiography) | CEA (Class IIa/Level A) | CAS (Class IIa/Level A) |
| 70%–99% (noninvasive) | CAS (Class IIb/Level B)† | CAS (Class IIb/Level B)† |

“High risk for CEA, asymptomatic

| 60%–99% (angiography) | CAS role “uncertain” (Class IIb/Level C) | Effectiveness of revascularization versus medical therapy in “high risk” for CEA/CAS not well established (Class IIb/Level B) |
| 70%–99% (noninvasive) | CAS (Class IIb/Level B)† | CAS (Class IIb/Level B)† |

CEA indicates carotid endarterectomy; CAS, carotid artery stenting; AHA/ASA, American Heart Association/American Stroke Association; TIA, transient ischemic attack.

*Fifty percent to 99% (angiography, not noninvasive).
†Highly selected asymptomatic patients.

So, despite the AHA/ASA2 referencing CREST,5 at the same time as ignoring the International Carotid Stenting Study (ICSS7; still the largest randomized trial in symptomatic patients), was it reasonable to expand the indications for CAS?
importance, because the key issue is (and always will be) stroke prevention.

**“Chemical” MI**

Surgeons and neurologists share concerns over the inclusion of “chemical” MI within the primary end point, largely because they believe it is not equivalent in status to death or stroke. Without its inclusion, CEA would have proved superior to CAS in symptomatic patients within CREST. However, if “chemical” MI does confer a poorer prognosis, this is important to know. Unfortunately, this subject has inappropriately dominated debates and it is probably better to wait until CREST reports on whether “chemical” MI increases midterm mortality rates before undertaking major changes in practice.

**Silent MRI Lesions**

A systematic review found that CAS was associated with a 6-fold increase in new ischemic brain lesions on postoperative MRI and this was corroborated in the ICSS MRI substudy in which 50% of patients undergoing CAS developed new brain lesions compared with 17% after CEA (OR, 5.2; 95% CI, 2.8 to 9.8; \( P < 0.0001 \)). Patients undergoing CAS were 6 times more likely to have persisting lesions at 1 month (OR, 5.9; 95% CI, 2.3 to 15.6; \( P = 0.0003 \)). Like with “chemical” MI, this is another emotive subject and presumably reflects the greater embolic burden observed during CAS (despite protection devices) compared with CEA. To date, few studies have determined whether these MRI lesions are associated with impaired cognition/dementia, but these are urgently required.

**Cranial Nerve Injury**

Surgeons have been guilty of underestimating the importance of cranial nerve injuries, whereas interventionists have been guilty of overemphasizing their significance. Randomized trials report cranial nerve injury rates of 6% to 9% after CEA; however, there is little information about the prevalence of persisting cranial nerve injuries (which can be just as disabling as a stroke). CREST will rectify this in the near future.

**Quality of Life**

CREST reported that major/minor strokes were associated with a significant deterioration in physical and mental health at 1 year, whereas “chemical” MI was not. This is an important observation because many interventionists have argued that most strokes after CAS are minor and of no long-term consequence.

**Do We Have Answers to the Important Questions?**

Two important issues were largely ignored in the 2011 guidelines: (1) inadequate emphasis on the importance of intervening rapidly after symptom onset; and (2) why recommend that only “highly selected” asymptomatic patients should undergo CAS/CEA when virtually no-one pays any attention?

**Time Is Brain!**

Every national guideline retains a 6-month threshold for being “recently symptomatic,” but there is now compelling evidence that this is obsolete. US guidelines recommend that “when revascularization is indicated in patients with TIA/stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery.” Unfortunately, this statement is rather weak and, apart from observing that CEA conferred greater benefit if performed within 2 weeks, neither guideline emphasized the importance of intervening in the hyperacute period. Moreover, neither guideline provided information on what constituted “contraindications to early intervention.” This was left to the discretion of the surgeon/interventionist and will almost certainly be ignored, largely because of the belief that delays to treatment reduce procedural risks. What few are then willing to accept is that although delays may make the surgeon/interventionist appear good (on league tables), this is at the expense of the highest risk patients who experience their stroke before having any realistic prospect of undergoing CEA/CAS.

Table 2 details rates of stroke in the hyperacute period after having a TIA/less minor stroke. Conventional teaching describes rates of 1% to 2% at 7 days and 2% to 4% at 30 days (ie, no impetus for change), but meta-analyses using “face-to-face” follow-up suggest that the risks may be 6 times higher with 50% of strokes destined to occur within 7 days happening within the first 24 hours. In addition, the risk of recurrent stroke within 7 days of the index TIA in patients with a significant carotid stenosis may be as high as 20%. Surgeons/interventionists may argue that they never see such high rates of recurrent stroke in their practice, but this is because most patients will have had their stroke before having any chance of being seen and undergoing treatment. Accordingly, these are compelling data for driving changes in future AHA/ASA guidelines. In the United Kingdom, the National
times more likely to have a procedural stroke (than patients undergoing CEA) if they underwent treatment within 14 days of the most recent symptom (OR, 2.7; 95% CI, 1.4 to 5.5). It is, therefore, possible that CEA might prove (for now) to be safer in the hyperacute period, whereas CAS becomes preferred thereafter. Given the data in Tables 2 and 3, most of us would probably want to be treated as soon as possible. We should therefore ensure that exactly the same standards apply to our patients.

Table 3. Effect of Delays to Surgery on 5-Y Stroke Prevention*

<table>
<thead>
<tr>
<th></th>
<th>ARR at 5 Y</th>
<th>CVA/1000/5 Y</th>
<th>ARR at 5 Y</th>
<th>CVA/1000</th>
<th>ARR at 5 Y</th>
<th>CVA/1000</th>
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</thead>
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<tr>
<td><strong>Males</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;2 wks</td>
<td>15.2%</td>
<td>152</td>
<td>23.3%</td>
<td>233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4 wks</td>
<td>6.8%</td>
<td>68</td>
<td>23.8%</td>
<td>238</td>
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<tr>
<td>4–12 wks</td>
<td>5.0%</td>
<td>50</td>
<td>18.3%</td>
<td>183</td>
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<td></td>
</tr>
<tr>
<td>&gt;12 wks</td>
<td>6.3%</td>
<td>63</td>
<td>20.4%</td>
<td>204</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 wks</td>
<td>13.8%</td>
<td>138</td>
<td>41.7%</td>
<td>417</td>
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<tr>
<td>2–4 wks</td>
<td>−5.7%</td>
<td>NB</td>
<td>6.6%</td>
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<tr>
<td>4–12 wks</td>
<td>−2.2%</td>
<td>NB</td>
<td>−2.2%</td>
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<td>−21.7%</td>
<td>NB</td>
<td>−2.4%</td>
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</table>

ARR indicates absolute risk reduction; CVA/1000 at 5 Y, ipsilateral strokes prevented at 5 y per 1000 carotid endarterectomies; NB, no benefit.

*Reanalysis of Carotid Endarterectomy Trialists Collaboration (CETC) data.20

Institute for Clinical Excellence18 now recommends that CEA be undertaken within 14 days of the index event (some health authorities are using this as a criterion for reimbursement as well as a marker of quality), whereas the UK Department of Health’s “Strategy for Stroke” has recommended that by 2017, services should be reconfigured so that surgery can be undertaken within 14 days of the index event.19

The benefits of intervening early were also evident in a meta-analysis of patients randomized within European Carotid Surgery Trial (ECST), North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the Veterans Administration Trials20 (Table 3), which showed that the longer the delay to treatment, the greater the possibility that little (or no) benefit would accrue to the patient (especially in females and those with 50% to 69% stenoses).

One reason for being reluctant to perform expedited CEA/CAS in patients with TIA is a worry that this might increase procedural risks and render the doctor vulnerable to uncritical censure. This is understandable and needs addressing within future guidelines because an alternative analysis of the Carotid Endarterectomy Trialists Collaboration (CETC) data suggests that surgeons who operate within 2 weeks with a 10% death/stroke rate may actually prevent more strokes in the long term (through rapid intervention) than if they delayed intervening for >4 weeks and then operated with a 0% risk.13 Patients with minor stroke or major stroke with rapid recovery may also benefit from early intervention (because they also have high rates of early recurrent stroke).21 Some surgeons/interventionists harbor concerns that rapid treatment in this type of patient will increase the risk of hemorrhagic transformation. Although the available evidence does not support this opinion,13 any future studies on this subject should carefully evaluate the risks of undertaking expedited CEA with specific regard to size of infarction and preoperative National Institutes of Health Stroke Scale scores.

Accordingly, the key issue not addressed in the guidelines was whether CEA or CAS was safer in the hyperacute period. The CSTC observed that patients undergoing CAS were 3

Idealism, Realism, and a Touch of Cynicism

Many believe that treating huge numbers of asymptomatic patients will significantly reduce the burden of stroke driven by the mantra that strokes occurring without a preceding TIA could have been prevented by prophylactic CEA/CAS.22 Unfortunately, such a policy will have little impact on the overall burden of stroke. Even if one could identify every patient with a 60% to 99% asymptomatic stenosis and then perform CEA/CAS with risks similar to those in Asymptomatic Carotid Atherosclerosis Study (ACAS), 95% of strokes will still occur.23 This is because only 8% to 10% of strokes involve a previously asymptomatic severe stenosis. This fact, along with evidence of a declining stroke risk in medically treated patients, is leading to increasing conservatism in the management of asymptomatic disease.

The 2006 guidelines recommended that CEA was appropriate in “highly selected” patients with a “high-grade” asymptomatic stenosis, the phrase “highly selected” being retained in the 2011 AHA/ASA guidelines.3 Interestingly, neither guideline recommended that interventions in asymptomatic patients should be directed toward patients aged <75 years (as was advocated in the 2005 American Academy of Neurology Guidelines24), primarily because of the absence of proven benefit from intervening in older patients. The AHA/ASA14-Society Guidelines3,4 did, however, concede that “the benefits of surgery may be lower than anticipated from historical studies” and that “CREST was never powered for subgroup analyses based on symptom status.” Despite these caveats, both guidelines still recommended that CAS might be considered “in highly-selected” asymptomatic patients.

Accordingly, the real message from the guidelines was that only “highly selected” patients needed treatment. Unfortunately, the interpreted message will be that any “average-risk” patient benefits. Moreover, anyone trying to determine what is meant by “highly selected” will only find the following advice: “selection of asymptomatic patients for carotid revascularization should be guided by assessment of comorbid conditions, life-expectancy and other individual factors.” In reality, this will have little effect on selection and the element of restraint being advocated will be ignored. Given that 122 986 patients with asymptomatic disease underwent CEA/CAS in the United States in 200525 (92% of carotid revascularizations that year), there is little evidence of surgeons/interventionists being “highly selective” and little confidence that selection criteria will change in the future. In fact, 1 consequence of the guidelines/Food and Drug Administration Panel ruling might be an unwarranted increase.

The recommendation that interventions should be targeted within smaller cohorts of high-risk patients is important. If
one assumes that the 1995 ACAS data remain representative in 2011, the following observations can be made. With a procedural risk of 2.3%, CEA confers an absolute risk reduction of 5.9% in ipsilateral stroke at 5 years, meaning that 17 procedures need to be performed to prevent 1 ipsilateral stroke at 5 years, but only 59 ipsilateral strokes will be prevented at 5 years per 1000 CEA (ie, 941 out of 1000 interventions were ultimately unnecessary). If the procedural risk were reduced to 0, only 82 ipsilateral strokes would be prevented at 5 years (ie, 92% of interventions were still unnecessary (918/1000)). To put this into context; if one assumes that CEA/CAS was performed with a 2.3% risk in 2005, US health providers spent $2.1 billion on ultimately unnecessary CAS/CEA interventions. US health providers spent $2.1 billion in 2005 on ultimately unnecessary CAS/CAS interventions.

However, this assumes that ACAS remains as relevant in 2011 as in 1995. If not, the 2011 guidelines are fundamentally compromised. The Figure details the annual risk of stroke in asymptomatic patients treated medically stratified for publication year and degree of stenosis. There is an obvious sustained decline in annual stroke risk across all stenosis thresholds. This has continued since ACAS published and is also evident within randomized and nonrandomized studies. In 1995, ACAS reported a 17.5% 5-year risk of “any” stroke (3.5% per annum [pa]) in medically treated patients. By 2004, the risk of “any” stroke in Years 1 to 5 of Asymptomatic Carotid Surgery Trial (ACST) had fallen to 11.8% (2.4% pa), whereas in Years 6 to 10, the risk of “any” stroke had decreased to 7.2% (1.4% pa). In 1995, ACAS reported 5-year risks of “ipsilateral” stroke of 11.0% (2.2% pa). By 2004, the 5-year risk in ACST was 5.3% (1.1% pa), whereas in Years 6 to 10, the risk of “ipsilateral stroke” decreased to 3.6% (0.7% pa).

The data from the Figure do not demand that all interventions in asymptomatic patients should stop. They are, however, evidence against perpetuating the current “one-size-fits-all” strategy. To date, most surgeons/interventionists have ignored recommendations that only “highly selected” asymptomatic patients should be offered CEA/CAS, probably because there is no clarity regarding what this term means. In addition (and contrary to popular opinion), CREST has not resolved the asymptomatic debate because it was never powered to do so. However, the consequences of recommending that CAS is now appropriate in “average-risk” patients are far reaching. Notwithstanding the syndrome of “trial fatigue,” there is a desperate need for a randomized trial comparing CEA with CAS, which also includes an adequately powered third limb for best medical therapy, which should include assessments of whether transcranial Doppler detected embolization, stenosis progression, biomarkers, silent CT/MRI infarcts, computerized plaque analysis, MRI plaque hemorrhage, circle of Willis patency, and so on, can identify a “high-risk for stroke” cohort in whom to target interventions. Perhaps US health providers might consider that a fraction of the $2 billion spent annually on unnecessary interventions is a worthwhile investment to resolve this issue.

Disclosures

None.

References


Naylor
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7. ICSS Investigators. Carotid artery stenting compared with endarterect-
9. Economoupolous KP, Sergentanis TN, Tsigouali G, Mariolos AD, Stavenandis C. Carotid artery stenting versus carotid endarterectomy: compre-
40. Nicolaidis AN, Ekkadis SK, Griffin M, Sabeti M, Dhanji S, Tegos T, et al. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemi-
44. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsi-
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