A. Ross Naylor, MD

The recipient of the Gore & Associates 2012 Dedication to Analysis of Clinical Outcomes Award shares his perspective on the current assessment, treatment protocols, and clinical research for patients with carotid artery disease.

How do you decide when surgical, pharmacological, or stent-based intervention is the best course of action for treating carotid disease and preventing stroke?

In my carotid practice, the vast majority of patients are symptomatic (only about 15% are asymptomatic). In symptomatic patients, there has been a very strong national drive toward expedited intervention in recently symptomatic patients. In Leicester, almost 50% of symptomatic patients now undergo carotid endarterectomy (CEA) within 7 days of suffering their index event. At present, many interventional radiologists in the UK are reluctant to offer carotid artery stenting (CAS) within the hyperacute time period because evidence suggests that the procedural risks are significantly higher than after CEA. Of course, that may change as CAS technology improves and interventionists become more experienced.

I do not go actively hunting for patients with asymptomatic carotid disease. I explain to them that there is an ongoing controversy about how best to manage this condition and that the evidence suggests that the risk of stroke (on medical therapy) is probably declining. I do, however, point out that some patients will definitely benefit from intervention. If, after a full discussion of the risks and benefits, my asymptomatic patient wants to undergo CEA, that is fine (we do not currently offer CAS to asymptomatic patients), but I would not offer CEA to an asymptomatic patient who is older than 75 years. The available evidence would suggest that they gain no long-term benefit over taking medical therapy alone. In practice, the majority of my asymptomatic patients currently opt for medical therapy and ongoing clinical/ultrasound surveillance.

What do you think is the single greatest unanswered question pertaining to carotid revascularization?

Personally speaking, I think that it is absolutely essential that we identify criteria for defining patients who are at high risk for stroke with an asymptomatic carotid stenosis in whom we should target CEA or CAS. In the US, over 90% of carotid interventions are performed in asymptomatic patients (120,000 per year). However, if we assume that the 1995 ACAS (Asymptomatic Carotid Atherosclerosis Study) data still have any relevance in 2013 (although it probably does not), 95% of all carotid interventions in asymptomatic patients are ultimately unnecessary. Even if the procedural risk of CEA and CAS could be reduced to zero, 93% of all interventions would still be unnecessary.

For the United States, this means that approximately $2 billion is spent annually on procedures in asymptomatic individuals that will not benefit the patient. Exposing such large numbers of patients to an intervention that costs health providers so much yet benefits so few cannot be justified. There are a number of relatively easy imaging strategies that could be evaluated in a large prospective study including stenosis progression, silent infarcts on CT/MR, computerized plaque morphology algorithms, MR-diagnosed intraplaque hemorrhage, biomarkers (such as lipoprotein-associated phospholipase A2 activity), and spontaneous embolization using transcranial Doppler.

What is on your wish list for enhancements to the next generation of stent and embolic protection technology for CAS?

The key to preventing the most strokes (in the long-term) is to intervene as soon as possible after the onset of transient ischemic attack (TIA) or stroke. Delays to intervention may make the surgeon/interventionist look good in "league tables," but it confers little benefit to the patient. Accordingly, I would like to see attention being directed toward developing more generalizable and safe CAS technologies that can be used by many interventionists (not just a select few) in the hyperacute period after the onset of symptoms.

What is your imaging modality of choice for assessing carotid plaque morphology? How do you utilize this information in terms of clinical decision making?

My preferred imaging modality for plaque analysis is computerized Duplex ultrasound. Our group has been working in collaboration with Dr. Andrew Nicolaides to develop an imaging algorithm that can predict the presence of histologically unstable carotid plaque. If our findings can be corroborated in an independent cohort of patients, this could have important clinical implica-

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tions for identifying asymptomatic patients who are at a high risk for stroke in the outpatient department. To date, however, there have been a number of "false dawns," and very few centers currently have the confidence to base management decisions on plaque morphology (we don't).

What do you believe is the optimal time window in which suspected TIA patients must be evaluated and/or treated? How can this be better accomplished in hospitals across the globe?

Like many vascular centers, we previously believed that by offering CEA to our symptomatic patients within 6 months of symptom onset that we were somehow offering optimal treatment. As will be seen, such an attitude should be considered obsolete. There is now compelling evidence that the early risk of stroke (after a TIA/minor stroke) is much higher than previously thought (natural history studies are consistently suggesting a 10% risk at 7 days). In addition, the older randomized trials clearly showed that the sooner CEA was performed, the greater the number of strokes would be prevented.

I have heard many arguments against intervening in the hyperacute period, but none stand up to close scrutiny. For example, I have heard some say that the risks of intervening early are increased and will offset any benefit. In fact, if you reanalyze data from the ECST and NASCET trials, it becomes apparent that the surgeon who performs CEA within 14 days with a 10% procedural risk will still prevent more strokes than if the surgeon delayed CEA for 28 days and then operated with a 0% risk!

In Leicester, we completely reconfigured our service in 2008. We now run a 24/7 Rapid Access TIA Clinic, where there is single-visit Duplex and MR/CT imaging, and all patients start their risk factor medication in the clinic (ie, antiplatelets, statins). Anyone with a 50% to 99% stenosis is transferred directly to the vascular unit, where they undergo expedited CEA on the next available operating theater list (regardless of consultant ownership). Since this protocol was introduced, we have not observed a significant increase in the procedural risk (< 5% for interventions within 7 days), but we have observed that 10% to 15% of patients will have recurrent TIAs or strokes in the short time between being transferred from the clinic and undergoing surgery.

If it were me, I would want my operation performed as soon as possible after onset of symptoms by an experienced surgeon based on published outcome data. Shouldn't we offer a similar approach to all our patients?

What lessons were learned from evaluating the ABCD^2 score as a predictor of significant carotid disease in TIA patients, and what new directions are being pursued?

The ABCD^2 score predicts the likelihood of suffering a recurrent stroke in the early period after the index TIA. A higher ABCD^2 score does not, however, identify patients with clinically significant (50%–99%) carotid stenoses. In practice, most of the patients with low ABCD^2 scores are young or present with monocular blindness (both associated with lower stroke risks), but they still have a similar prevalence of carotid stenosis. Interestingly, recent research suggests that tissue injury (ie, infarction on CT/MR) is a much more powerful predictor of early recurrent stroke than the ABCD^2 score alone. When the two are combined, a high ABCD^2 score and an area of CT/MR infarction is associated with a 15% risk of stroke at 7 days.

What is the significance of antiplatelet function during carotid surgery? Is this very different than what occurs during CAS?

This is a very important and interesting question. We have a lot to learn from our CAS colleagues who have actively embraced the benefits of dual-antiplatelet therapy for both coronary and carotid interventions. Surgeons have been concerned that aspirin and clopidogrel will significantly increase the risk of major bleeding complications, which it can. It just so happens that there is a compromise.

Our group was one of the first to show that patients who are destined to have a high rate of embolization after CEA (50% will go on to suffer a thrombotic stroke) had platelets that were more sensitive to adenosine diphosphate (ADP). A randomized trial subsequently showed that regular aspirin plus 75 mg of clopidogrel the night before surgery significantly reduced postoperative embolization compared with aspirin plus placebo. We have now run the dual-antiplatelet protocol for nearly 7 years (800+ CEAs), and we have not encountered a single case of stroke due to postoperative carotid thrombosis. Interestingly, the combination of dual-antiplatelet therapy and a written protocol for treating post-CEA hypertension has virtually abolished major cardiac events as well.

The move of high-risk vascular interventions to higher-volume centers with greater experience has lowered the mortality rates for these procedures, but is there room for lower-volume centers to become up to date with the latest techniques in order to provide quality treatment to the growing elderly population?

The move toward higher-volume centers has been a controversial issue in the UK, but I believe that it will lead

to huge improvements in the care of vascular patients as a whole (we cannot just consider isolated disease subgroups in lower-volume centers). Dr. Matt Thompson's group in London has shown that high-volume vascular units have lower mortality rates following elective abdominal aortic aneurysm surgery; patients are less likely to be turned down for elective and emergency aneurysm surgery; patients are more likely to be offered endovascular aneurysm repair; they have better outcomes after CEA; and they are more likely to be offered limb salvage interventions.

The reasons for this volume-outcome relationship are multifactorial but probably relate to having a critical mass of consultants (surgeons and interventionists) and other specialized staff (anesthetists, intensive therapy unit, nurses) and access to expensive equipment (fenestrated devices, hybrid endovascular theaters) that is just not possible in the smaller-volume unit. In the UK, public surveys suggest that patients would be willing to travel for at least an hour beyond their local hospital in order to go to a center that offered better outcomes (as opposed to staying local). According to the St. George's data, such a policy would provide vascular coverage for up to 95% of the population.

What do you think are the instances in which a study must be a randomized trial, and in which instances are registries appropriate?

The asymptomatic controversy is a good case in point. I would have preferred that one or more of the ongoing randomized trials comparing CEA with CAS in asymptomatic patients would have a medical limb that was sufficiently powered to include an evaluation of those imaging parameters (as previously mentioned) that might be used to identify a high stroke risk cohort. Unfortunately, the two trials that plan to include a medical limb (SPACE-2 and CREST-2) are likely to have no funding for extra imaging studies, and they will continue to risk stratify based upon stenosis severity, which has already shown to be a failed approach in ACAS and ACST. In that situation, a large and carefully designed registry could provide vital information that could inform a future randomized trial between CEA and CAS. It just seems a shame that we will have to wait even longer before getting an answer. ■

A. Ross Naylor, MBChB, MD, FRCS(Ed), FRCS(Eng), is Professor of Vascular Surgery, Leicester Royal Infirmary; past President of the Vascular Society of Great Britain and Ireland; and Senior Editor of the European Journal of Vascular and Endovascular Surgery. *He has disclosed that he has no financial interests related to this article. Dr. Naylor may be reached at ross.naylor@uhl-tr.nhs.uk.*