The Rise of the Registry

Of signal importance in carotid artery stenting.

BY WILLIAM A. GRAY, MD

It is axiomatic in medical research that randomized control study is the highest-quality scientific study that can be performed and provides the highest level of data for medical decision making. Today, two critically important randomized carotid artery stent (CAS) trials are in process in the US, both in standard-surgical-risk patients. Specifically, the NIH Carotid Revascularization Endarterectomy versus Stent Trial (CREST), which started randomizing in 2000, is examining outcomes in both symptomatic and asymptomatic patients with severe carotid disease assigned to either carotid endarterectomy (CEA) or CAS in a 1:1 ratio. There are more than 1,900 patients in CREST, and it is projected to achieve its 2,500 patient goal by mid-2008 at the current rate of enrollment. In addition, the Carotid Stenting versus Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I) trial, which began enrollment in 2005, is dedicated to studying the asymptomatic carotid stenosis patient and is randomizing to CAS and CEA in a 3:1 ratio. There are now approximately 400 patients in the study with a goal of approximately 1,800 patients. These two trials, in addition to the International Carotid Stent Study (ICSS) being performed in approximately 50 centers around the world, will provide further direction as to the utility of CAS in the standard-surgical-risk patient.

In the high-surgical-risk population, an already completed randomized trial (SAPPHIRE), along with several registry studies that were able to leverage some of the SAPPHIRE randomized data, has already led to FDA approval of five CAS stent and filter systems for both symptomatic and asymptomatic patients. The first of these regulatory approvals, the Guidant (now Abbott Vascular, Santa Clara, CA) Acculink and Accunet, was in August 2004. Unfortunately, on the 3-year anniversary of this first device approval in the US, and in spite of two separate national coverage decision deliberations, the Centers for Medicare and Medicaid Services (CMS) have only approved reimbursement for symptomatic patients at high surgical risk, leaving aside the asymptomatic patients for whom there are approved devices but no coverage.

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This gap between US regulatory and coverage policy presents the field of carotid stenting with two significant problems: first, how to gain the asymptomatic patient at increased surgical risk access to this already FDA-approved therapy and second, how to improve current outcomes through next-generation technique or device iteration, which is the typical march of interventional technology. The measured diffusion of CAS, constrained by limited CMS coverage, has made it difficult to understand the mechanisms of stroke during CAS in broad populations of patients, so that targeting device improvements has been slowed, which creates a bit of a self-fulfilling prophecy: continued outcomes predicated on legacy devices.

Enter the postmarket surveillance (PMS) registry. As a condition of device approvals, the FDA will mandate that the device experience be monitored outside of the clinical trial setting postapproval, generally to assess the occurrence of any rare or unanticipated device events. In the case of CAS, these PMS registries were also meant to judge the capability of the training programs provided to novice

operators. In several cases, these registries have been extended to further refine our understanding of CAS outcomes; they have also provided an avenue for patients to gain access to this technology. Published reports from both CAPTURE (Carotid RX Acculink RX/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events)[1] and CASES (Carotid Artery Stenting with Emboli Protection Surveillance Post-Marketing Study)[2] registries have shown no unanticipated device events and outcomes comparable to or better than the pivotal trials that led to device approval, which is confirmation of the training programs adequacy.

These registries are also rich sources of important data regarding CAS. It is useful to remember that the pivotal trials that led to FDA device approval typically enrolled 300 to 500 patients, not generally enough to perform meaningful subset analysis. The number of patients in various PMS registries is now well over 10,000, easily representing the largest prospective collection of data in carotid therapy—medical, surgical, or endovascular—ever assembled. With neurologist-audited results and adjudicated outcomes, these data are robust enough to not only make salient observations regarding the broad results in CAS but also allow the characterization of predictors of outcomes. They have demonstrated a relationship of age, previous symptomatic status, and certain procedural and operator characteristics to outcomes in CAS. Future publication will also detail the timing, location, and characterization of stroke in CAS, as well as the relationship of gender, diabetes, etc, to outcomes. With these and other analyses of registry data, there will be a clearer picture of who may be the best candidate for CAS and where improvements are possible to lower rates of adverse outcomes for all patients. This information can be challenging to harvest from randomized trials meant to compare two therapies, rather than examine predictive components of one.

These registry results have also demonstrated a temporal improvement in CAS outcomes. When comparing CAPTURE to registries that followed it (even with the same devices), one can see a gradual but steady progression of improvement in the outcomes of many, if not all, of the subsets of patients undergoing CAS in the 3 years since device approval. This level of data providing detailed analysis in carotid revascularization and documented improvement over time is unprecedented and not available in the >50-year experience with CEA.

Recently, the outcomes of CAS in the EVA-3S study[3] have raised concerns regarding the viability of this therapy in symptomatic patients. While it is easy to disparage the conduct of the trial and the experience of the operators, lacking any randomized data from the US on which to reflect, the data from these PMS registries have legitimized the EVA-3S critiques and have the supported ongoing investigation (CREST) in this population.

As these results continue to improve, the basis for the exclusion of these patients from coverage of endovascular carotid therapy becomes less clear, especially since surgery continues to be performed and covered without nearly the scale and scope of outcome data in this population. The general concerns regarding the asymptomatic patient at high risk for surgery have been the lack of data on survival (ie, will they live long enough to benefit from the intervention?) and the need to achieve the American Heart Association's guideline 30-day death and stroke rates of ≤3%. However, these rates have been established based on data from standard-risk patients with carotid stenosis, and it could be reasonably argued, based on natural history study in the patients with medical comorbidities, that outcomes are worse without carotid revascularization in this cohort than in otherwise healthy patients. It nevertheless remains a standard to be reckoned with. The most recent data available from these CAS registries, still being analyzed, appear to suggest that survival and outcome rates may be in an acceptable range. If so, they could serve as the basis for a request to CMS to reopen the national coverage determination process on CAS in the asymptomatic high-surgical-risk patient.

While the randomized trials such as ACT I and CREST will be critical in developing the comparative data for CAS and CEA in the standard-surgical-risk patient and should be supported whenever possible, the CAS registry data, both previous and future, will continue to provide important insights into this therapy, as well as provide the basis for device improvements, technique refinements, medical decision making, and coverage for our patients in need of a surgical alternative. ■

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