Research Considerations in a Vacuum of CAS Access

What are the implications of future study in an environment with otherwise limited access to carotid stenting?

BY WILLIAM A. GRAY, MD

After the United States Food and Drug Administration (FDA) granted approval for the first of several carotid artery stent (CAS) systems for patients at high risk for carotid endarterectomy (CEA) in August 2004, the Centers for Medicare & Medicaid Services (CMS) agreed to cover symptomatic (but not asymptomatic) patients at high risk for CEA treated within an investigational device exemption (IDE), a 510(k) clearance study, or an FDA-mandated postmarket surveillance (PMS) study. Subsequently, nonmandated PMS studies were voluntarily extended by the manufacturers to further characterize CAS outcomes, several of which have published results (CAPTURE, CAPTURE 2, EXACT, and SAPPHIRE).[1-3] As a result of CMS and manufacturer actions, access to CAS, albeit more limited than the FDA-approved indications, was enabled, and more than 50,000 patients at high surgical risk have since been treated with a rigorous prospective collection of their outcomes. Not only has patient access been assured, but outcomes improved significantly as a result of this liberalization of availability and have achieved American Heart Association guideline standards. Additionally, the FDA has since extended the indications for CAS to the standard-surgical-risk population.

Today, however, most of the postapproval studies are closed or closing, and because there has been no interval expansion of CMS coverage, patient access to this technology has been severely constrained. Other than the high-surgical-risk, symptomatic patients, who are estimated to represent roughly 10% of the total carotid population, access will be limited to two device trials (ROADSTER [Silk Road Medical, Sunnyvale, CA] and SCAFFOLD [Gore & Associates, Flagstaff, AZ]) that are planning to enroll less than 500 patients combined and one remaining PMS (SAPPHIRE Worldwide [Cordis Corporation, Bridgewater, NJ]), all of which will likely be completed within 12 to 18 months.

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The Carotid Revascularization Endarterectomy Versus Stent Trial-2 (CREST-2) is in the preparatory phase of trial startup. It is meant to be a multiyear, multicenter, multimillion-dollar National Heart, Lung, and Blood Institute effort that will evaluate more than 2,000 asymptomatic standard-surgical-risk patients treated with optimal medical and lifestyle treatment (OMT) and randomize them to receive revascularization (CEA or CAS) or no revascularization. It is anticipated that approximately 500 to 600 patients will receive CAS in at least 75 centers—an average of six to eight patients per center over several years.

This confluence of circumstances leaves the field of CAS in the United States on the verge of a major trial

while simultaneously seeing access to the technology shrink to pre-FDA-approval numbers due to the lack of accompanying CMS coverage. It is fair to ask what the implication for the trial, and the field, is as a result of this curious condition. The purpose of this article is not to criticize CREST-2, which is a worthy and important trial that we need to support, but rather to consider the environment that this and other future trials may need to operate within.

FUTURE TRIAL CHALLENGES

From the standpoint of designing future trials, the lack of otherwise-active operators maintaining the skills they acquired in the past decade challenges the basic rule of equipoise. If two therapies are to be offered to a patient as reasonably equivalent alternatives in a randomized fashion, then the operators for those therapies must be equally expert so as not to bias the outcomes. In the case of CREST-2, the margins of efficacy required to determine superiority of CAS or CEA over medical therapy will be small, and if CAS outcomes are suboptimal as a result of limited patient access and operator experience, then the trial results can be irrevocably confounded. From a logistical standpoint, it is difficult to maintain and represent a CAS program when the only functioning ability to treat will be within a randomized trial setting in which up to 75% of patients referred might in fact receive an alternative therapy (50% OMT and 25% CEA); this will limit trial enrollment. Moreover, maintaining appropriate inventory and nursing/technician staff expertise is challenging at such low volumes.

The possibility of a patient to be treated by an operator who might be doing his or her first CAS procedure in several months, and only two or three procedures in a year, is suboptimal and has the potential to put the patient at higher risk.

As difficult as some of these design challenges may be for future study endeavors, equally problematic is the concept of undertaking research in a device therapy that has already achieved approval for the patient population being tested but does not have a reasonable degree of CMS coverage paired with it and, therefore, is severely restricted. A logical extension of the current situation is that CREST-2 might find the interventional CEA/CAS arm superior to medical therapy after the [up to] 10 years required to achieve its primary endpoint (several years of active enrollment [CREST-1 took 8 years to enroll] plus 4 years of follow-up). Then, because there is no new FDA indication coming out of CREST-2 and no ability to compare the outcomes between CAS and CEA (not enough patients for the anticipated low event rates), there may be no novel justification for CMS to extend coverage beyond what exists today. This is challenging, as patients will give up a choice of therapy and submit themselves to randomization with the expectation that the outcome will materially affect their, or others', subsequent access to the therapies being tested, when in fact there is no reason to expect this outcome in CAS, but it will be true in CEA and OMT. Patients who are subjects in trials are often remarkably and altruistically motivated by such considerations.

Moreover, industry support for devices in CAS will likely continue to contract. Already, Gore has discontinued production and sale of its flow-reversal device, and other manufacturers are contemplating similar moves with components of their CAS systems. This would limit the availability of device approaches within future trials and could materially affect outcomes.

COMMITMENT TO THE FUTURE

Research into the optimum treatment of carotid stenosis, whether symptomatic/asymptomatic or high/standard surgical risk, is really just in its early phases. Predictors of events in patients with asymptomatic plaques, defining the patient at low or high likelihood for neurologic events, reducing minor strokes in CAS procedures, reducing myocardial infarction in CEA operations, and defining OMT are worthy goals that will ultimately direct patient care and improve outcomes. It is the hope of CAS researchers that the prototypically incremental process of inquiry and discovery so important to progress in medicine will not be interrupted due to lack of availability, and that we might continue to make substantive contributions to managing this important and common clinical entity.

We further hope that the current level of patient access via reimbursement coverage can be addressed to ensure we can conduct all future research in CAS with adequate operator expertise, optimized patient outcomes, and continued advancement of technology. ■

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