FDA to Consider Expanding Indication for Carotid Stenting to Standard-Risk Surgical Patients

January 25, 2011 (Miami Beach, Florida) — Should patients at standard risk for adverse events from carotid endarterectomy be treated with carotid artery stenting? That is the question a Food and Drug Administration (FDA) advisory panel will grapple with this Wednesday as panel members gather to make recommendations and vote on an expanded indication for the RX Acculink Carotid Stent System (Abbott, Abbott Park, IL) [1].

Currently, the RX Acculink stent is approved for use in patients requiring carotid revascularization who are at high risk for adverse events from carotid endarterectomy. These high-risk patients must also have a reference vessel diameter ranging from 4.0 mm to 9.0 mm at the target lesion and be symptomatic with a stenosis of the common or internal carotid artery >50%. The stent is also approved in high-risk patients without neurological symptoms but who have a stenosis of the common or internal carotid artery >80%.

Based on data from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), Abbott is looking to expand the indication of the RX Acculink stent to include patients at standard risk for adverse events from carotid surgery. Patients must meet the same criteria as high-risk patients, but the company is also seeking approval for use in asymptomatic patients with a stenosis >70%, as opposed to >80% with the current indication.

“The CREST study gave us a tremendous amount of data, some of which will be presented to the FDA,” Dr James Benenati (Baptist Heart and Vascular Institute, Miami, FL), president of the Society of Interventional Radiologists (SIR), told Heartwire last week at the International Symposium on Endovascular Therapy (ISET) 2011. “Basically, in carotid stenting in general, we know that for high-risk symptomatic patients, the FDA has approved this procedure. What many of us in the interventional community are looking for is an expansion. We believe there are data suggesting that, in patients in all risk stratifications, stenting is safe and effective, and the differences between endarterectomy and stenting in all patient subgroups are basically very, very small.”

Based on the FDA briefing materials, the hopes of Benenati and others in the interventional community are supported by the agency. According to an executive summary released early by the FDA, the new “proposed indications are supported by a primary analysis of the CREST trial data and by multiple important secondary and tertiary analyses.”

Treating Asymptomatic Patients

Although large portions of the FDA document are blacked out and won't be made public until Wednesday during the advisory panel meeting, the agency notes that primary-end-point event rates are lower than acceptable event rates proposed by the American Heart Association (AHA) guidelines for carotid revascularization. For example, the combined end point of perioperative death and stroke in CREST was 5.9% for carotid stenting and 2.4% for carotid endarterectomy in symptomatic patients, lower than the AHA-acceptable standard of 6%, although it's close to the limit for carotid stenting. In asymptomatic patients, the AHA-proposed limit for perioperative death and stroke is 3%, and in CREST both the carotid stenting and endarterectomy arms fell below this limit (2.5% vs 1.3%, respectively).

Speaking at ISET last week, however, were some who believed that asymptomatic patients shouldn't be treated with stents or surgery at all but rather with medical therapy. In an interview with Heartwire, Dr Anthony Comerota (University of Michigan, Ann Arbor) said that the “overwhelming majority” of patients in the US who undergo carotid stenting do not have any symptoms. Good medical management—such as high-dose statin therapy, good blood-pressure control, management of diabetes, and good platelet inhibition—can reduce the risk of stroke, and carotid endarterectomy, as well as carotid stenting, should be best left to highly selected patients, said Comerota.

Speaking at ISET, Comerota said that 97% of carotid-etiology strokes occur in patients with symptomatic disease, and yet 2005 data showed that more than 90% of carotid revascularization procedures were performed in asymptomatic patients. The reason this is important is that the biological characteristics of symptomatic and asymptomatic plaque differ significantly, with symptomatic plaque being more unstable, showing evidence of subintimal hemorrhage and thrombus within the lumen.

Benenati agreed, saying that while candidates for surgery should also be candidates for carotid stenting, not every patient is a candidate for revascularization.

“I wouldn't advocate that everybody gets a carotid stent, nor would I advocate that every carotid stenosis be treated with stent or surgery,” he told Heartwire. “One of the great things that all the carotid stent trials have brought to light is that there are some groups of patients that might do better with medical therapy. For example, asymptomatic patients, high- and low-risk, with stenosis less than 70% or 80%, will probably do fine with medical therapy.”

The Primary End Point in CREST

Although the expanded RX Acculink indication is based on data from CREST, Comerota took issue with the study, saying that the design incorporated an “inherent fallacy” that was part of conventional thinking at the time the trial was started. The primary end point was a composite of clinical stroke, MI, or death during the periprocedural period plus ipsilateral stroke on the vessel that was treated, with patients followed out to four years. At the time, perioperative MI was thought to be a very important problem, Comerota told Heartwire, one that led to a significantly higher death rate at six months.

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"This has turned out not to be the case," he said. "An asymptomatic myocardial infarction, a troponin leak, is not associated with an increased mortality risk and is not associated prognostically with an increased mortality risk over the next four or five years. So now we have a major trial equating an elevation in cardiac enzymes with stroke or death. That clearly is inappropriate, but when enthusiasts of carotid angioplasty and stenting want to present their side of the story, they’ll say there is no difference because of the higher myocardial infarction rate [with surgery]. Myocardial infarction didn’t alter the quality of life of patients down the road, whereas stroke, even minor stroke, altered the quality of life significantly."

In CREST, as reported previously by heartwire, there was no significant difference in the combined end point of stroke, MI, or death within the periprocedural period (7.2% for carotid stenting vs 6.8% for endarterectomy; p=0.51), but stroke rates were higher in the stenting arm, while rates of MI were higher among the surgical patients.

Based on the FDA documents, the advisory panel will discuss the appropriateness of including MI in the primary end point, as well as its definition and impact on the primary end point. In addition, they will debate the clinical significance and severity of cranial nerve injury, which occurred in 5.2% of patients treated with endarterectomy.

First the FDA Hurdle, Next the CMS

At the end of the day, even if the FDA advisory panel votes to approve the expanded indication for the RX Acculink stent to include standard-risk surgical patients, the Centers for Medicare and Medicaid Services (CMS) still need to green-light reimbursement. Currently, Medicare coverage is confined to patients at high risk for carotid endarterectomy who have symptomatic carotid artery stenosis ≥70%, as long as stenting is performed using FDA-approved systems with embolic-protection devices and at CMS-approved facilities. The CMS also covers carotid stenting in patients if they are a high-risk endarterectomy patient with lesser degrees of symptomatic carotid artery stenosis (50% to 70%) or at high risk for endarterectomy with asymptomatic carotid artery stenosis ≥80%, but only if they are participating in pre- or postapproval studies.

To heartwire, Benenati said the day is coming when clinical centers performing carotid stenting will need to receive accreditation. The Intersocietal Commission for the Accreditation of Carotid Stenting Procedures, in support of numerous societies, including SIR, is seeking to establish minimum requirements and recommendations for facilities performing carotid stenting.

"I'm a strong advocate, as is the society, that not every physician who does endovascular therapy should be doing carotid stenting," said Benenati. "Carotid stenting is a skill that's learned--it takes repetition and dedicated continuing medical education. Also, the facility where the carotid stenting takes place is critically important, too."

Benenati reports serving as the chief medical officer of Northpoint Domain and consulting for or serving on the advisory boards of Abbott, Amaranth Medical, Biosphere, Cordis, Endovention, and WL Gore. Comerota reports speaking for or receiving honoraria from Bristol-Myers Squibb, Covidien, Otsuka, Sanofi-Aventis, Servier; ZymoGenetics; consulting for or serving on the advisory boards of Aastrom, AngioDynamics, Convatec, Cook, Covidien, Bristol-Myers Squibb, Talecris; and receiving research support from Aastrom, Abbott Vascular, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, BSN, Colorado Prevention Center, CVRx, eV3, Johnson & Johnson, Lombard Medical, Medtronic, the National Institutes of Health, Pfizer, Sanofi-Aventis, Schering-Plough, and Talecris.

References