FDA INSIGHTS

The Cordis Carotid Stent System Panel Hearing

A recap of the groundbreaking FDA advisory panel session that concluded with a recommendation of approval with conditions for CAS.

BY MATT PESOTSKI, ASSOCIATE EDITOR

After nearly 10 hours of discussion and deliberation, the FDA Circulatory System Devices Panel on April 21 voted 6 to 5 in favor of recommending approval with conditions for the Cordis Carotid System (Cordis Endovascular, a Johnson & Johnson company, Miami, FL). The panel, which was heterogeneously mixed in regard to medical specialty, levied its decision based on extensive testimony from Cordis representatives and investigators, FDA employees, physicians on behalf of their respective societies, and each other.

With months of anticipation leading up to the hearing, the morning began with a buzzing energy circulating throughout the small hotel conference room crowd. By lunch, however, it was clear that the panel and audience members would likely have to endure until the evening hours for the long-awaited decision. The duration of the hearing and the resultant frustration were justified, as this was arguably one of the most groundbreaking and controversial such votes since the CDRH began conducting panel meetings, and as such was not something to be hurried or cut short.

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What began as a difficult decision was only made more so by hours of delicate discourse, which debated far more than simply the non-inferiority of carotid artery stenting (CAS) using the Cordis system as compared to carotid endarterectomy. The day's discussions also encompassed the definition of "high-risk patients" and at several points diverged into the validity of performing carotid endarterectomy on certain asymptomatic patients, which has been considered the standard of care for years. One audience member was overheard questioning whether the panel would next debate the use of the death penalty in Texas. These side arguments perhaps took valuable time away from issues such as the data regarding these asymptomatic patients and the conditions for approval, which were hurriedly discussed in the hours after the panel was scheduled to adjourn.

When the dust had settled, the majority of the voting members had decided that Cordis' Carotid Stent System, which consists of the Precise Nitinol Self-Expanding Stent and the AngioGuard Emboli Capture Guidewire, should be considered "non-inferior" to carotid endarterectomy, the question the panel was convened to answer, and recommended approval with conditions. The conditions stipulated were: (1) that the patient information brochure be revised in several specific ways; (2) that the post-marketing study proposal be amended to require an evaluation by an independent neurologist at 30 days postprocedure for the 1,000 patients to be enrolled, as well as at the annual exams for patients currently enrolled in the IDE study; (3) that the indication include a cautionary note regarding the potential for increased risk of adverse events in instances of difficulty deploying the embolic protection device properly; and (4) modifying the indication for use to include treatment of patients requiring carotid revascularization and having specific anatomic or medical comorbid conditions, consistent with the selection criteria used for the clinical study. Cordis agreed to work with the FDA to complete each of the conditions.

THE OPEN PUBLIC SESSIONS

At two points during the hearing, the panel and audience members heard from members of the public via presentations or letters read aloud. Particularly note-

worthy among these were statements made by physicians on behalf of their respective societies in expression of their views on CAS and its approval. Janette D. Durham, MD, the President of the Society for Interventional Radiology, stated that 90% of interventional radiologists are interested in CAS, and that the Society believes the evidence supports its approval as a treatment option. Regarding the providing of required training, Dr. Durham expressed that hospitals alone should be responsible, not industry.

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Kenneth Rosenfeld, MD, and William A. Gray, MD, on behalf of the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, respectively, each voiced their "strongest support" of CAS approval, as well as the need for rigorous but not prohibitive training prior to performance. J. Michael Bacharach, MD, speaking for the Society for Vascular Medicine and Biology, also asserted full support and emphasized the need for proper training. Speaking on behalf of the American Academy of Neurology, Daniel F. Hanley, MD, stressed the importance of the PMA process, offering support for the decision of the panel without prediction or presumption of what it might be. Of utmost importance, he said, was that competency requirements should be extensive and included in the labeling. Among Dr. Hanley's suggestions were that physicians conduct at least 100 cerebral angiograms prior to performing CAS, and overall that neurology, carotid, and stroke treatment experience be required, rather than a CME-type means of education.

Rod White, MD, read a letter from Richard M. Green, MD, President of the Society for Vascular Surgery (SVS). Although the SVS believes endarterectomy is appropriate for the majority of patients with carotid artery stenoses and indications for intervention, it supports the judicious use of CAS in what it terms "bona fide 'high-risk' patients." The definition of "high-risk patients" as used in the SAPPHIRE Trial is not, he states, uniformly accepted by all vascular surgeons, and should be determined via a collaborative decision-making process including multiple physicians and a surgeon who performs carotid endarterectomy. The SVS further stated that it would like to see collaboration among the interested professional societies in regard to training, competency, and credentialing, but that to date, such action has not been observed. Finally, Dr. Green asserted his disagreement with the proposition of an arbitrary minimum of diagnostic cerebral angiograms as a credentialing prerequisite, naming several reasons for its not being an acceptable means of determining qualification.

THE CORDIS DATA PRESENTATION

The sponsor presentation was given by Sidney A. Cohen, MD, PhD, Cordis' Group Director for Clinical Research, and Ken Ouriel, MD, Chairman, Division of Surgery and Department of Vascular Surgery for The Cleveland Clinic Foundation, who served as one of SAPPHIRE's investigators. Dr. Cohen first reviewed the background of Cordis' US FEASIBILITY, CASCADE, and SAPPHIRE trials, stroke and carotid disease, and the current standard of care and its related trials (NASCET, ACAS, ECST, and the VA Cooperative Study, etc.). He then provided detailed descriptions of the devices used in each of the Cordis studies and gave an overview of the PMA clinical data before turning the podium over to Dr. Ouriel.

Dr. Ouriel's presentation encompassed the SAPPHIRE Trial's study design, highlighting primary endpoints, patient flow, the statistical analysis plan, outcomes, and differences from previous carotid trials. The most notable of these differences was the inclusion of myocardial infarction (MI) as part of SAPPHIRE's primary endpoint. Several reasons for adding MI were given, including that it leads to disability, death, prolonged hospitalization, and increased health care costs. Dr. Ouriel stated that in patients undergoing peripheral vascular surgery who sustain a non-Q–wave MI experienced a six-fold increase in mortality over 6 months, that perioperative MI predicts mortality at 1 year, and that there is a 27-fold increase of having another MI over the next 6 months. A complete description of the results of the SAPPHIRE Trial is beyond the scope of this article. A slideshow containing the presentation in its entirety can be found at www.fda.gov. Additional coverage can also be found in our September 2003 issue.

When Dr. Ouriel concluded, Dr. Cohen gave an outline of Cordis' CAS training system, which will include onsite instruction from CAS-experienced physicians, online training, and simulator modeling. This program would provide medical device training within a greater context of CAS. Individual hospitals would be responsible for the determination of credentialing and allowances for physicians to perform CAS. SAPPHIRE's postmarketing surveillance is designed to enroll 1,000 patients and to compare clinical outcomes with historical control data from

(Continued on page 80)

SIR 2004

The 29th Annual Scientific Meeting of the Society of Interventional Radiology (SIR) was held in Phoenix, AZ, March 25-30, 2004.

As part of its continuing mission to improve health and quality of life through the practice of vascular and interventional radiology, the SIR 2004 Annual Scientific Meeting featured a wide variety of panel discussions and presentations designed to address the topics and issues facing today's endovascular specialists engaged in the dynamic field of interventional radiology.

CAROTID STENTING DATA

During the half-day symposia, Mark Wholey, MD, presented data from the ARCHeR and SAPPHIRE trials, of which he was a principal investigator.

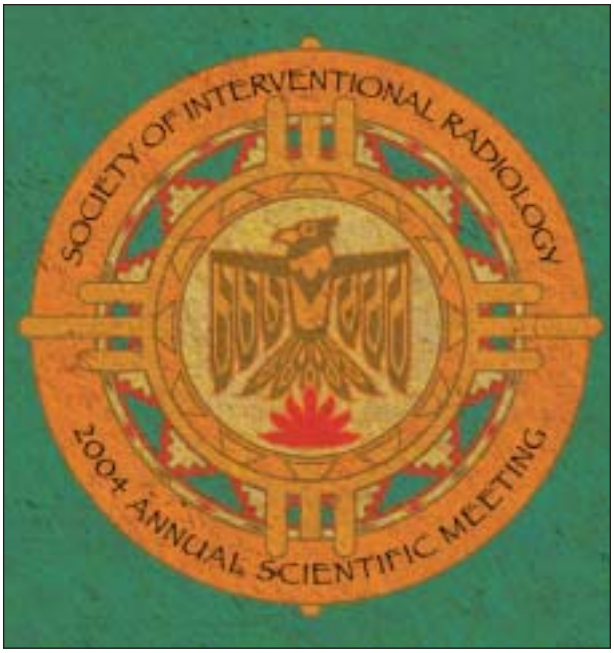
ARCHeR

Data showed that carotid stenting for stroke prevention is safe and effective in high-risk patients. The ARCHeR 1 trial used just the stent, the ARCHeR 2 trial included the stent plus embolic protection, and ARCHeR 3 used a newer version of the catheters for delivering the stent and embolic filter (rapid exchange system). The incidence of major stroke or death in the first 30 days was low in all trials: 3.8%, 2.5%, and 2.8% for ARCHeR 1, 2, and 3, respectively. At 1 year, the MAE rate was 8.3% and 10.2% for ARCHeR 1 and 2, respectively.

SAPPHIRE

In high-risk diabetic patients, data showed that carotid stenting to prevent stroke is safer than surgery. This finding is based on a study of 86 patients in the high-risk diabetic subset of the SAPPHIRE Trial. The primary endpoints of the study measured the 30-day MAE rate, and the 1-year MAE, which included the 30-day rate plus death and same-side stroke from 31 days to 1 year. The 30-day MAE, which included death, any stroke, or heart attack, was 4.8% for stenting and 22.7% for carotid surgery. However, the combination of the 30-day MAE rate with the same-side strokes and deaths due to stroke (neurologic death) from 31 days to 1 year resulted in an MAE rate of 4.8% for stenting versus 25% for surgery at 1 year.

Statistically significant differences at 1-year follow-up were also observed for stenting over surgery for heart attack (2.4% vs 18.2%) and major bleeding (4.8% vs 20.5%). The incidence of stroke in diabetic patients was lower in the stenting group (2.4%) compared to the surgery group (11.4%), but the difference was not statistically significant.



2004 GOLD MEDAL AWARD

The Gold Medal Award honors IR leaders who have led the way through education, research, clinical investigation, patient care, and Society involvement. The Gold Medal Honorees for 2004 are Franklin J. Miller, MD, Director of the HHT Clinic, Salt Lake City, UT, and Stewart R. Reuter, MD, JD, Professor Emeritus of Radiology at the University of Texas Health Science Center at San Antonio, Texas.

20TH ANNUAL DOTTER LECTURE

The 20th Annual Dotter Lecture entitled "Interventional Radiology Today: What Would Charles Dotter Say?" was presented by Anne C. Roberts, MD, Executive Vice Chair for the Department of Radiology at the University of California, San Diego School of Medicine, San Diego, California. The Annual Charles T. Dotter Lecture was established in 1984 to honor one of the founding fathers of interventional radiology.

2004 LEADERS IN INNOVATION AWARD

Constantin Cope, MD, was awarded the 2004 Leaders in Innovation Award, which recognizes an individual who has conceptualized and implemented an idea that has had an advantageous impact on the practice of interventional radiology. Dr. Cope is Professor of Radiology at the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

2004 GARY J. BECKER YOUNG INVESTIGATOR AWARD

Kamran Ahrar, MD, of the MD Anderson Cancer Center, Houston, Texas, was awarded the 2004 Gary J. Becker Young Investigator Award, which is awarded to a young interventional radiologist whose work best fits the ideal of promoting academic research.

RESTRUCTURING OF THE SIR FOUNDATION

The Board of Directors of the Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF) announced that the Foundation was reorganizing itself and adjusting its mission in an effort to better serve members of the SIR and the interventional radiology community. The new SIR Foundation will focus its energy on three main goals: (1) Building a clinical trials network for interventional radiology procedures; (2) Funding targeted research that more directly supports the clinical goals of interventional radiology; and (3) Securing the future by developing young investigators and strengthening the IR research community.

MEDICAL STUDENT MENTORING

Students were invited to attend the meeting at no charge, as well as participate in a 1-day mentoring event to accompany an established IR throughout the meeting to gain career insight, educational understanding, and the fundamentals of patient care. ■

(Continued from page 78)

SAPPHIRE in the early time period following approval, as well as to assess the effectiveness of the training program.

THE FDA CONCERNS

Throughout the hearing, the FDA raised several issues with regard to Cordis' study designs and executions. First, Cordis was unable to complete its proposed randomized study, primarily due to competing studies and the fact that many physicians were no longer willing to randomize patients. The FDA took further issue with Cordis' conducting statistical inferences for the prematurely halted randomized trial.

Because of an unsolicited amendment to the panel review submitted by Cordis on April 5, 2004, which described a sheath size upgrade (+1-F upsizing requirement) for the Precise RX (rapid exchange) stent due to air entrainment complaints (estimated event rate, 0.14%), the RX version was not reviewed for consideration during the hearing. The FDA also addressed a warning letter it sent to Cordis on April 1, 2004, which cited nonconformance with the Current Good Manufacturing Practice requirements at the company's manufacturing facilities. The stent system being reviewed by this panel, however, was not specifically mentioned in the letter.

Heng Li, an FDA statistician, presented some of the statistical issues raised by the SAPPHIRE Trial. He clarified the concerns regarding the randomized study, which he said was not conducted according to the original group sequential protocol, with no alternative protocol developed or described to the FDA prior to PMA submission. The protocol used by the sponsor was probably the most favorable choice for declaring non-inferiority, stated Mr. Li.

Also of concern was Cordis' implementation of the propensity score method, a set of statistical procedures designed to facilitate evaluation of treatment groups that are not necessarily comparable (ie, the non-randomized stent study vs the CEA arm of the randomized trial). This method reduces bias by balancing a set of chosen covariates; however, Mr. Li stated that it was not clear whether Cordis' analysis took full advantage of the method because certain key covariates (baseline demographics and angiographic data) were not used. The panel discussed these concerns and asked for feedback from the company. Drs. Cohen and Ouriel, as well as statistical experts, handled each concern quickly but carefully, providing solid, satisfactory answers to questions carrying potentially heavy consequences.

WHAT'S NEXT

In the coming weeks, Cordis must work closely with the FDA to address the conditions for approval and to finalize the labeling and complete the summary of safety and effectiveness data. This process often takes about 6 to 8 weeks, and approval may or may not be slowed by outstanding issues, such as any concerns associated with the FDA warning letter. It remains to be seen whether the conditions stipulated for this approval, most notably the postmarketing surveillance and training requirements, which could be considered fairly extensive, will be applied to every carotid stent system seeking approval. ■