SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

April 21, 2004

Gaithersburg Marriott
Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting
April 21, 2004

Attendees

Chairperson
Warren K. Laskey, M.D.
Uniformed Services University of the Health Sciences

Voting Members
Mitchell Krucoff, M.D.
Duke University Medical Center

William Maisel, M.D., M.P.H.
Brigham & Women's Hospital

Cynthia Tracy, M.D.
George Washington University

Christopher J. White, M.D.
Ochsner Clinic

Consultants
Gary M. Abrams, M.D.
San Francisco VA Medical Center

Anthony J. Comeroto, M.D.
Jobst Vascular Center

Kenneth E. Najarian, M.D.
University of Vermont College of Medicine

Gary Nicholas, M.D.
Lehigh Valley Hospital

Michael J. Pentecost, M.D.
Georgetown University Medical Center

Judah Z. Weinberger, M.D., Ph.D.
Columbia University

Industry Representative
Michael Morton
Carbomedics, Inc.

Consumer Representative
Allen Hughes, Ph.D.
George Mason University

Food and Drug Administration
Bram Zuckerman, M.D.
Director
Division of Cardiovascular Devices

Geretta Wood
Executive Secretary

Lisa Kennell, FDA Lead Reviewer
Ronald Weintraub, M.D., FDA Consultant
Heng Li, Ph.D., FDA Statistician

CALL TO ORDER

Panel Chair Warren K. Laskey, M.D., called the meeting to order at 9:06 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted to Mitchell Krucoff, M.D., and Christopher White, M.D., for their interests in firms that could be affected by the recommendations of the panel. A waiver had been previously granted for Judah Z. Weinberger, M.D., for his interest in firms that could be affected by the panel's recommendations. She noted that the Agency had taken into account other matters involving Anthony J. Comeroto, M.D., Mitchell Krucoff, M.D., Kenneth Najarian, M.D., Michael Pentecost, M.D., Cynthia Tracy, M.D., and Judah Z. Weinberger, M.D., who reported past or current interests involving firms at issue but in matters not related to the day's agenda; they could participate fully. Dr. Laskey then asked the panel members to introduce themselves.

Ms. Wood read the appointment to temporary voting status, which stated that Gary M. Abrams, M.D., Anthony J. Comeroto, M.D., Kenneth E. Najarian, M.D., Gary Nicholas, M.D., Michael J. Pentecost, M.D., and Judah Z. Weinberger, M.D., Ph.D., had been appointed temporary voting members for the duration of the meeting.

OPEN PUBLIC HEARING

Dr. Laskey read the Agency's statement on transparency of the device review process.

Janette Durham, M.D., President, Society of Interventional Radiology (SIR), described SIR's goals and membership. Ninety percent of SIR's members surveyed expressed interest in receiving training in carotid stenting. SIR supports approval of the technology. The sponsor's training program is sound. Only appropriately trained physicians should treat stroke patients. Procedural safety and effectiveness are equally important as device safety and effectiveness; the labeling must include training requirements. Hospitals and other institutions, not industry, are responsible for training. SIR has training guidelines for carotid stenting.

Dr. Kenneth Rosenfield, representing the American College of Cardiology (ACC) and Society for Cardiovascular Angiography and Interventions, participated in the sponsor's trial and supports carotid stenting. He described the goals and membership of ACC and SCAI. Both organizations support treatment and approaches that promise to improve or optimize care. Carotid angioplasty and stenting are innovative treatments that minimize invasiveness. Cardiologists deal with patients with multiple comorbidities; it is therefore important to have

minimally invasive treatment for these high-risk patients. The SAPPHIRE trial provides evidence to support carotid stenting for the patients included in the sponsor's trial.

William Gray, M.D., FACC, Director, Endovascular Care, Swedish Cardiovascular Research, stated that atherosclerosis is systemic and patient management is important. Carotid angioplasty is a new and promising technology. The Asymptomatic Carotid Atherosclerosis Study (ACAS) trial established the effectiveness of carotid endarterectomy (CEA), but no randomized trials compare the surgery to other therapies. CEA results are not as safe or effective as those seen in the SAPPHIRE trial, the first randomized controlled trial to explore any alternative to CEA. Compared with trials ratifying CEA as standard of care, carotid stenting data are much more extensive.

Dr. Rosenfield added that current data indicate that carotid stenting and dissection should be made available to patients who meet the SAPPHIRE trial's inclusion criteria. The remarkable results achieved with stenting will only be replicated through continued use of the procedure and careful patient selection. Competency in stenting includes cognitive, clinical, and technical skills. ACC and SCAI favor rigorous training and credentialing requirements. He referred the panel to longer comments he submitted to the Agency.

J. Michael Bacarach, M.D., MPH, FACC, an interventional medicine specialist and SAPPHIRE trial investigator representing the **Society of Vascular Medicine and Biology,** noted that the many comorbid conditions of patients who have carotid atherosclerosis make treatment risky. Carotid angioplasty with embolic protection makes treatment of those patients possible. It is an appropriate first-line therapy for high-risk patients. The procedure should not be broadly adopted without responsible and adequate training.

Daniel Hanley, M.D., a stroke physician and neurologist representing the **American Academy of Neurology,** emphasized the importance of the panel meeting and referred the panel to the Academy's white paper on stroke treatment. The Academy has not had the opportunity to comment on the treatment before the panel, but will be doing so soon. In reviewing this treatment approach, it is important to apply lessons from coronary angiography. The panel must consider brain outcomes. The procedure must be performed by practitioners with demonstrated technical and cognitive competence. Stroke is the most feared medical complication; the standards for performance should be at least as stringent as for coronary angiography. Treatment in coronary angiography alone, however, does not prepare practitioners to insert carotid stents.

Short CME courses or simulations do not substitute for brain vascular angiography training. The standard that will best protect patient well-being is the current established medical therapy for stroke. Comparisons with treatment not requiring stent placement should be considered.

SPONSOR PRESENTATION

Sidney A. Cohen, M.D., Ph.D., Group Director, Clinical Research, Cordis Corporation, summarized the sponsor's agenda and reviewed the requested indication. Two studies—the U.S. feasibility study and the SAPPHIRE pivotal study—demonstrated the noninferiority of carotid artery stent (CAS) to CEA at 1 year. CAS resulted in improved outcomes for MI and reinterventions as well as a significant decrease in cranial nerve injuries. The Agency issued a warning letter concerning Good Manufacturing Practices (GMP) to Cordis on April 1; the sponsor is working with the Agency to resolve the issues raised in the letter.

Dr. Cohen presented epidemiologic data on stroke and carotid artery disease. CEA has a 50-year history of technique development and refinement. It is currently the standard of care, and up to 200,000 procedures are performed annually in the United States, 20 percent of which are on high-risk patients. The studies that led to CEA's acceptance as the standard of care (North American Symptomatic Carotid Endarterectomy Trial [NASCET] and ACAS) were performed on a patient population that does not match the population that currently undergoes the procedure. Patients considered high risk for CEA (as defined by NASCET and ACAS ineligibility) constitute up to 50 percent of patients in the published studies. Actual CEA mortality is higher than in the ACAS and NASCET studies. Up to 75 percent of patients undergoing CEA are asymptomatic. Incidence of stroke at 360 days is flat but increases for patients with 80 percent occlusion or greater; only one-third of the patients in the ACAS trial had that level of stenosis. CAS is less invasive than CEA and is useful in patients for whom CEA is technically demanding for anatomic reasons or as a result of comorbidities.

The Cordis precise nitinol stent system comprises two devices (1) a stent and delivery catheter and (2) the Angioguard emboli protection device. The stent comes in a variety of sizes. Dr. Cohen described the stent delivery system and noted that the PMA is based on clinical data from a total of 1,619 patients from the CASCADE study in Europe, the U.S. feasibility study, and the SAPPHIRE study.

The CASCADE study was a nonrandomized trial involving 121 patients with 1-year follow-up. It evaluated the safety and performance of the SMART stent with or without the Angioguard emboli capture device in patients with high-grade carotid artery stenosis. CAS was found to be feasible for the treatment of carotid stenosis. The Angioguard device functioned well and appeared to reduce the risk of distal embolization, resulting in fewer strokes: At 30 days, 3.2 percent of patients in whom the procedure was performed with the Angioguard experienced ipsilateral stroke, compared with 8.9 patients who did not have Angioguard protection.

The U.S. feasibility study was a nonrandomized, prospective, 33-center trial that involved 261 patients, 176 of whom received a stent and 85 of whom received the Cordis stent with Angioguard protection. Follow-up lasted 3 years. The study assessed the feasibility of CAS in the treatment of obstructive carotid artery disease. A secondary goal was to assess and standardize optimal operator techniques for a pivotal trial. The primary endpoint was major adverse events (MAE) defined as death, stroke, and MI). Secondary endpoints were major clinical events, patency, and neurological assessments. At 3 years, 21.8 percent of patients had experienced MAE: 8.7 percent had experienced stroke, and 13.9 percent had died. The study demonstrated feasibility of CAS with the Cordis stent system. Use of Angioguard appeared to reduce the incidence of stroke.

Conclusions from the supportive studies allowed refinement of the CAS system, including a reduction in profile from 7 French to 5.5 French and other design improvements. The data supported the benefit of Angioguard in reducing stroke and the feasibility of CAS.

Ken Ouriel, M.D., Cleveland Clinic, presented the results of the SAPPHIRE study. The trial compared the safety and effectiveness of carotid stenting with emboli protection to CEA in the treatment of carotid artery disease in high-risk patients. A total of 2,294 patients were referred for evaluation of carotid artery disease; a panel of physicians (consisting of an interventionalist, surgeon, and neurologist at each site) concurred that 747 of those patients met the inclusion criteria for the study. Of those 747 patients, 334 were deemed suitable for either CEA or stenting; they were randomized to either a CAS or a CEA arm. Each arm had 167 patients. Of the remaining patients, those deemed at unacceptable risk for CEA received CAS treatment (n=406). Those deemed at unacceptable risk for CAS received CEA (n=7).

The primary endpoint was death from any cause, any stroke, and MI at 30 days and death and ipsilateral stroke between day 31 and day 360 postprocedure. A key difference between the

SAPPHIRE study and the other two studies was its inclusion of MI as an endpoint. MI leads to disability, death, prolonged hospitalization, and increased health care costs. It is a key safety endpoint in interventional trials, and it is a strong surrogate for long-term mortality after vascular surgical procedures. MI is also a primary endpoint for other CAS trials.

The SAPPHIRE study was designed as a noninferiority trial comparing CAS and CEA. The expected 1-year primary endpoint rate was 14 percent, the allowable delta was 3 percent, and statistical power was 90 percent. The expected sample size was 600 to 800 patients. The sponsor planned to use a triangular test interim analysis method, which involved performing statistical analysis every 100 patients. Results would permit stopping the trial when noninferiority was demonstrated.

The sponsor changed its analysis plan. The first two 100-patient interim analyses were omitted because results on a sample size of fewer than 300 patients would be unconvincing. By fall 2001, it was clear that enrollment would not exceed 400 patients because of competing trials. A final analysis was planned when enrollment ceased. The sequential method, as outlined to the Agency, allows for these changes. The first analysis, therefore, was the final analysis, because no previous interim analyses were performed.

Dr. Ouriel listed the inclusion and exclusion criteria and demographic data on the randomized patients. Procedural success rates for stent delivery, device, and Angioguard deployment were high. Of the 334 randomized patients, 310 received treatment; patient outcome data are based on intent-to-treat analysis. Results (Kaplan-Meier analysis) demonstrated no statistically significant differences in outcomes between CEA and CAS patients, although the results showed a trend in favor of stenting. The SAPPHIRE study demonstrated that CAS was noninferior to CEA.

At the Agency's request, the sponsor conducted retrospective interim testing at 100, 200, 300, and 334 patients. The results led to the same conclusion of noninferiority and would have permitted stopping the trial at that point regardless of the total number of patients enrolled. Rates of all MAE, stroke, and death were comparable in both arms.

Data on patients in the nonrandomized stent arm (the "stent registry") were compared with data from the CEA randomized arm, following the sponsor's consultation with the Agency in March 2003. The method adjusted for differences in baseline demographics because patients in the randomized CEA group had fewer high-risk characteristics than patients in the

nonrandomized stent arm. The sponsor could not adjust for angiographic parameters because the CEA arm lacked those data. Results for the primary endpoint of MAE at 360 days (Kaplan-Meier analysis) demonstrated noninferiority to CEA.

Although the study was not powered for subgroup analyses, the sponsor presented analyses for symptomatic and asymptomatic patients. Asymptomatic patients who received stents had lower MAE rates at 30 and 360 days than asymptomatic CEA patients. Symptomatic CAS patients had similar MAE rates to symptomatic CEA patients at 30 days and 360 days. Outcomes in the SAPPHIRE trial compare favorably with outcomes from other trials in cranial nerve injury and ipsilateral stroke for both symptomatic and asymptomatic patients. All surgeons participating in the trial were highly experienced in CEA.

In summary, the randomized arm of the SAPPHIRE study demonstrated that CAS is noninferior to CEA, and data suggest trends toward statistically significantly lower rates of major ipsilateral stroke, MI, target lesion revascularization, and restenosis. The primary endpoint was achieved. CAS resulted in a significant decrease in cranial nerve injuries. In the subgroup analyses, asymptomatic CAS patients had significant improvement at 360 days compared with asymptomatic CEA patients (50 percent reduction in MAE). MAE rates at 360 days were similar for symptomatic CAS and CEA patients. Outcomes for 30-day ipsilateral stroke overlap those from the NASCET and ACAS studies. In the nonrandomized CAS arm, outcomes were noninferior to those in the randomized CEA arm. Patients who are at too high risk for surgery are not necessarily at too high risk for stenting, whether symptomatic or asymptomatic.

The sponsor's training program will consist of online didactic training, training at regional educational centers, and onsite training at facilities involving experienced physician proctors. It will include 34 hours of training with exposure to a minimum of 15 cases.

The sponsor's postmarketing surveillance plan will compare clinical outcomes with historical control data from the SAPPHIRE trial. It will quantify patient outcomes and confirm the adequacy of physician training. It is a multicenter, prospective, nonrandomized, open-label study on at least 1,000 patients who have de novo or restenotic lesions. Inclusion criteria are based on the label indications. The primary endpoint is the 30-day composite of MAE (all death and all stroke). Follow-up data include neurologic examinations at discharge and 30 days and clinical events through discharge, as assessed at a 30-day postprocedure office visit and 9-month

telephone follow-up. Electronic data capture will expedite review of outcomes, and data analysis will include a stopping rule.

No multicenter randomized studies define outcomes in patients at high medical or surgical risk. The SAPPHIRE study provides an objective comparison of CEA, the current interventional standard of care, with CAS, a less invasive approach to therapy. The sponsor is seeking the following indication:

> *The Cordis [Carotid Stent System is] indicated for use in the treatment of carotid artery disease in high-risk patients. High-risk is defined as patients with neurological symptoms (one or more TIAs or one or more completed strokes) and >50% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram; and patients without neurological symptoms and >80% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram. Symptomatic and asymptomatic patients must also have one or more condition(s) that place them at high risk for carotid endarterectomy.*

FDA PRESENTATION

Lisa Kennell, FDA Lead Reviewer, introduced the FDA presenters and thanked the review team. She described the device and provided nonclinical data. The stent will be provided in diameters ranging from 5 to 10 mm, both tapered and straight. The sponsor also makes a Rapid Exchange (RX) configuration that is compatible with 0.014 inch guidewires; however, that configuration was not under consideration at the meeting due to reported adverse events. The Agency will continue to work with the sponsor to resolve this issue.

Since the sponsor's first submission for the device, many changes have been made to the device design, materials, sizes, and profile. The most significant changes are the introduction of the Angioguard embolic protection device, the lowered profile of the device, and the RX configuration.

The sponsor terminated the pivotal trial early, citing too many competing studies, physicians' reluctance to randomize, and surgeons' unwillingness to refer patients. The competing studies involved Cordis's own devices and were facilitated by Cordis in that the sponsor provided each investigator with a letter of authorization to allow FDA to access the Cordis file for background information. Cordis also supplied most of the investigators with a copy of the feasibility protocol as well as the case report forms and consent that were developed for that study. Most investigators opted to follow the protocol with little modification, but Cordis was not privy to interactions between the single investigators and FDA. Following PMA regulations, Cordis coordinated with 34 of 36 of the investigators to obtain their 30-day data for inclusion in the PMA.

The engineering and biocompatibility reviews are satisfactory; the sterilization review is ongoing, but the Agency does not anticipate issues. The many changes to the device design raise other issues. The RX configuration was approved without clinical data, but FDA may have to reconsider that decision in light of the reported adverse events. Finally, FDA investigators noted serious GMP noncompliance issues. Systemic problems were noted at many facilities. These will need to be corrected before approval can be granted for the device. The Agency issued a warning letter for GMP violations on April 1.

Heng Li, Ph.D., FDA Statistical Reviewer, summarized the randomized trial statistical analysis. The randomized clinical study was originally designed as a group sequential clinical trial using the sequential triangular test to investigate noninferiority. Interim analyses were scheduled every 100 patients. The expected sample size was 600 to 900, with a maximum sample size of 2,400. The randomized study was not conducted according to the original group sequential protocol. An alternative protocol seems to have never been developed. FDA was not informed of any change in protocol prior to PMA submission.

Data from the SAPPHIRE randomized trial were used to make the declaration that stenting is noninferior to CEA. However, statistical inferences for designed studies need to be made according to the statistical plan. Therefore, the statistical inference in the current PMA submission is unplanned, because it made reference to a statistical plan that is not in the current protocol (namely, a fixed sample size design based on 334 patients, the number at which the trial was discontinued prematurely). Because the observed MAE rate for stent is lower than that for CEA, the analyses that produce narrower confidence intervals tend to be more favorable to the declaration of noninferiority.

Dr. Li provided a detailed explanation of the planned statistical methodology and the stopping rule it incorporated. In his analysis, the evidence would not have indicated that the trial should have been stopped (and noninferiority declared), if the original protocol had been followed.

The sponsor used a predefined objective performance criterion (OPC) for the stent registry. After realizing that the OPC had not been met, the sponsor made unplanned comparisons between the stent registry and the CEA arm of the randomized study. Because the patient characteristics in the two groups, by definition, are different, a straightforward comparison is not appropriate. To address this issue, the sponsor used a propensity score method

to compare the two groups, attempting to make a post hoc claim of noninferiority of the stent registry to the randomized CEA arm.

Dr. Li reviewed propensity score methodology. The sponsor may not have taken advantage of the methodology's potential to simultaneously balance a large number of covariates. Not all the observed clinically relevant covariates were included, and not all patients were included in the treatment comparison. Moreover, the analysis itself was unplanned, so the sponsor's conclusions are an issue.

In summary, the original group sequential protocol was not followed, and FDA was not informed of any change in the protocol. The study fails to meet the original OPC, so any noninferiority claim based on the sponsor's post hoc propensity score analysis is problematic.

Ronald Weintraub, M.D., FDA Consultant, reviewed the methodology of the SAPPHIRE pivotal study. He noted that the composite MAE rate at 30 days postprocedure includes MI, which was not included in historical randomized trials comparing CEA and medical therapy, unless fatal. Five centers enrolled the majority of patients. With regard to the primary endpoint of 30-day MAE, the data for several types of events approach, but do not reach, statistical significance favoring the stent arm. At 1 year and 2 years, no statistically significant differences between the groups were found. Subgroup analysis of neurologically symptomatic and asymptomatic cohorts, and analysis of 30-day MAE excluding nonfatal MI, also found no significant difference between the randomized arms.

In the stent registry, the reasons for surgical turndown are not enumerated for half of the patients. In addition, approximately 70 percent of the patients in the stent registry were neurologically asymptomatic. In the stent registry, the OPC was set at 12.94 percent. The observed rate in the trial was 15.76 percent. Therefore, the sponsor could not reject the null hypothesis because the criterion for noninferiority was not met. It is not clear that the sponsor thoroughly explored the propensity score method; questions remain about the adequacy of the sponsor's analysis.

The randomized pivotal trial included more than twice as many asymptomatic as symptomatic patients. Again, no significant differences were found between the randomized stent and randomized CEA groups. Results at one year were similar. There were no differences between the randomized CEA and CAS groups, although the superiority of CAS approached significance. At 30 days, MAE in diabetics occurred more frequently in CEA patients, reaching

statistical significance. At 1 year, MAE occurred more frequently in male patients, almost reaching significance. Recurrent stenosis occurred with similar frequency in all groups.

Dr. Weintraub summarized conclusions derived from historical randomized studies that compared CEA with medical therapy. CEA is generally effective, and risk reduction varies with the level of stenosis. Some data, however, caution against the indiscriminate use of CEA. The sponsor's study findings are limited because the prespecified enrollment plan and study analysis was not carried to completion in the SAPPHIRE randomized study. This resulted in a smaller study with small sample sizes in important subsets of carotid populations. The randomized study suggests noninferiority of stent to CEA, but the registry cohort failed to meet the OPC. Comparability of the registry to the control CEA patients has not been optimally defined or conducted.

PANEL REVIEWS

Dr. Weinberger focused on the issue of whether the sponsor had deviated from the study protocol and suggested that because the sponsor had not examined the data before the first analysis, it may not matter that the first analysis was done at 300, not 100, patients. Dr. Weinberger also focused on the outcomes of the trial. He noted the counterintuitive finding that people with high-risk anatomic features seem to do better with surgery than with a percutaneous approach. He noted that it is not clear which patient population would benefit from the device and said that the criteria for surgical intervention in the study were not clear. He also asked for clarification on the nature of the neurological exam use in the SAPPHIRE study, which the sponsor provided.

Dr. Comeroto reviewed the clinical studies on which the PMA was based. He noted that patients who had CAS generally did not have a high degree of stenosis. Symptomatic stent patients had a higher rate of death and stroke at 30 days than symptomatic CEA patients. Angioguard protection seemed to be effective. Dr. Comeroto also discussed the issue of MI as an endpoint. To provide greater comparability with studies including a group receiving medical care, the sponsor included MI as an component of MAE. However, if one uses that endpoint, MI inherently favors percutaneous procedures. The premature termination of the study appears to bias outcome in favor of stenting because it is well established that patients who have had CABG and who have noncardiac surgery have a 50 percent risk reduction of mortality associated with

that operation. Furthermore, 35 percent of stented patients had prior coronary angioplasty—a statistically significant difference from the other group. Eighty percent of stented patients had prior coronary revascularization versus 54 percent of CEA patients. If coronary revascularization was equivalent and stented patients were protected, would a difference in cardiac events have been observed? There is a good chance that it would not have been. The bias of prior coronary procedures deflates the difference in MI outcomes. Finally, aspirin and Plavix were not offered to CEA patients, perhaps for good reason—but there is now a revascularization and pharmaceutical bias in favor of reduction of MI in patients having stenting.

PANEL DISCUSSION

Panel members spent considerable time asking for clarification on and discussing the SAPPHIRE study protocol and data analysis, including the use of MI as part of the MAE endpoint and whether the sponsor appropriately invoked the stopping rule. They noted that asymptomatic patients appeared to fare worse in terms of MAE. They also discussed the relation of the degree of stenosis to outcomes and choice of procedure, the use of angiography and ultrasound to diagnose patients, the impact of intervention for coronary artery disease on patients' ability to undergo CAS, the effectiveness of the Angioguard, the role of the data safety monitoring board in the SAPPHIRE study, the adequacy of data on the 5 mm and tapered stents, the process for determining whether a patient had had a stroke, and restenosis rates. In discussing the sponsor's training program, it was agreed that specific experience in carotid stenting was important and that diagnostic angiography was not a substitute for that experience. Panel members noted that even though outcomes for the stent group were statistically not inferior to those in the CEA group, it is not clear how the results would compare to best medical therapy.

Dr. White recommended the following changes to the patient brochure:

?? Page 7: Edit the general instructions for the patient to say that he or she will likely be asked also to take Plavix or Ticlopidine before the procedure.

?? Page 9: Add some language to prepare the patient that he or she might have a closure device.

?? Page 10: Edit the text in the second paragraph to be more cautious about reassuring patients that MRIs are not contraindicated. Also, under "Lifestyle Changes," edit the text to eliminate the claim that patients who are able to reduce fats and cholesterol in their diets are less likely to redevelop blockages in the stent.

?? On page 6 of the Instructions for Use (IFU), the text should be edited to list the comorbid and the anatomic criteria for the SAPPHIRE trial so that the operator can follow those carefully. At the bottom of that page, the last bullet point says "Stent placement is not recommended for patients with poor renal function who in the physician's opinion may be at risk for an reaction to contrast." Contrast reactions are unpredictable, so the text should be modified to say "high risk," to allow for physician judgment and the fact that everyone is at some risk for renal insufficiency.

?? On page 7 of the IFU, it says, "Aneurysmal dilatation immediately proximal or distal to the lesion is not recommended," but many patients have some element of ectasia, either proximally or distally, to these bifurcation lesions. The text should define what an aneurysm is or delete mention of it. Also, the text needs to clarify whether the procedure can be done with direct carotid puncture rather than through femoral or brachial access. It also should clarify the meaning of "vital side branch." On the same page, the text says "Venous access should be available during carotid stenting in order to manage the bradycardia and hypotension"; it should clarify that it is talking about peripheral venous access.

OPEN PUBLIC HEARING

Ms. Wood noted that a waiver had been granted for Dr. Maisel.

Robert W. Hobson II, M.D., Principal Investigator, CREST, a group studying the efficacy of CEA versus stenting, discussed the impact of clinical trials on the number of CEAs performed each year. The CREST trial is supported by NIH and uses devices supplied by Guidant to examine the same question as in the SAPPHIRE trial on patients at lower risk. The current consensus indications for CAS on Dr. Hobson's own service are as follows: carotid restenosis after prior CEA; high-risk patients; radiation-induced stenosis; and anatomically inaccessible lesion above C2.

The SAPPHIRE investigators did exactly what FDA told them to do. The sample was extraordinarily small. Only 96 patients were symptomatic. The clinical algorithm cannot be changed based on 96 patients. If fewer than five events had swung one way or another, the result would have been different. It is possible that SAPPHIRE has identified patients that should receive neither treatment. It would have been magnificent if the trial had included a medical therapy arm and 5-year survival data.

CREST investigators can live with approval if introduction of CAS into clinical practice is driven by SAPPHIRE-like patients only. Approval of this device might interfere with the purpose of the CREST trial

Andrew Ku, M.D., Allison Park, PA, stated that current data show that the Cordis Precise stent and Angioguard XP distal protection device may be as safe as surgery in high-risk surgical patients. Current data do not show that the stent and guard device are safer than medical therapy for asymptomatic high-risk patients. Adverse events are lower in stent patients who are symptomatic; in asymptomatic patients, the benefits are not clear. Review of CEA outcomes from Medicare data show much worse outcomes in patients treated subsequent to the trials. It is important to be cautious about comparing trials with the "real world" and to be conservative in analysis to allow the needed margin of safety that real-world conditions demand.

The NASCET study showed benefit in symptomatic patients. In asymptomatic patients, 3 of 4 studies showed no positive benefit from CEA; only ACAS was positive. Eighty-one CEAs were needed to prevent one minor stroke, and the procedure offered no significant prevention of major stroke. The Canadian stroke consortium found no indication for CEA for any level of carotid stenosis. Most people with asymptomatic disease benefit from medical therapy. The Cordis device offers much risk for asymptomatic patients with negative benefit. The label should contraindicate use of the device in patients with asymptomatic carotid disease.

Rodney White, Secretary, representing the **Society for Vascular Surgery (SVS),** read a letter from Dr. Green, President of SVS, into the record. The patients in the SAPPHIRE trial represent a small percentage of those in the general population undergoing CEA, and the study is not reflective of current practice. Little data support use of carotid stenting in high-risk patients. If approved, carotid stenting should be performed by operators with expertise not just on technical aspects of stent delivery but also on all the pre- and postprocedure components that CEA requires. Multispecialty coordination is required to achieve the desired outcomes. Anyone who wishes to perform CAS should have skills associated with an advanced interventionalist, regardless of the target lesion. An arbitrary minimum of diagnostic cerebral angiograms is not an appropriate credentialing prerequisite.

Carlo Dall'olmo, a vascular surgeon from Flint, MI, said that carotid stenting is an exciting new therapy that raises many questions. The procedure can be done safely, but its durability is not known. Three years is not enough follow-up. CEA is a durable procedure. Data

on 334 patients are not enough to extrapolate to the entire population on a broad label. The current criteria seem to be loose and apply to too many patients. The definition of high risk needs to be stringently defined. Until these and other questions are more definitively answered, only limited applicability is appropriate.

Executive Secretary Wood read a letter into the record from **Colin Derdeyn, Associate Professor, Washington University School of Medicine,** stating that surgical revascularization for patients with asymptomatic carotid stenosis is of marginal benefit, even in the most healthy of patients. The event rates reported in the SAPPHIRE trial for both surgical and CEA treatment of asymptomatic patients are extremely concerning. Even with the lower MAE rates seen in the CEA group, the most rational conclusion that can be drawn at present is that these patients should be treated medically. The device should not be indicated for patients with asymptomatic carotid stenosis.

PANEL QUESTIONS

Question 1: Can the data from the investigator-sponsor studies be considered in the evaluation of high-risk stenting given the differences in trial conduct for the high-risk investigator-sponsor registries?

The panel concurred that the investigator-sponsor studies are in no way representative of the patient population the panel was being asked to consider. The event rates are low, and the studies lack adjudication of endpoints. The data cannot be used.

Question 2: How does the large enrollment in the registry CAS arm affect interpretation of results?

The panel noted that patients were placed in the registry for various reasons, some identified, some not. The data collection forms describing clinical characteristics have not yet been culled to ascertain differences and similarities. The outcome of propensity score analysis remains in abeyance in part because of the lack of covariates examined. Without answers to those issues, making comparisons is premature and perhaps hazardous. The large exit of patients from the original trials to the registry qualifies the results of the SAPPHIRE trial.

Question 3: How does premature termination of the pivotal randomized study affect conclusions derived from the study?

The panel referenced its earlier discussion. The Agency should continue to discuss the matter with the sponsor. The endpoint was addressed and found to be adequately powered to reject the null hypothesis, and the premature termination was not the result of inappropriate or biased looks at the data.

Question 4: Please discuss how data from previous carotid treatment trials can be used to analyze the current perioperative/30-day data set with regard to safety.

The panel cautioned against using historical controls. Neither the ACAS nor the NASCET trials provide a proper comparison, in part because the SAPPHIRE trial included MI, which is not part of the composite endpoint in ACAS or NASCET. The event rates in earlier studies are not events discussed today. The earlier studies did not seek to enroll patients with high-risk comorbid backgrounds—for that reason alone, outcomes cannot be compared.

Question 5: Please discuss the impact of the various patient subgroups [in the SAPPHIRE trial] on the ability to generalize safety and effectiveness results.

The panel said that the impact of the subgroups is unclear. Comparisons of the asymptomatic and symptomatic subgroups affect safety and effectiveness data. A better trial design would have included a medical control arm. CEA on asymptomatic patients is controversial, as is stenting in those patients; however, panel members noted that the goal was not to determine the most appropriate treatment but to ascertain whether CAS is a reasonable alternative to CEA. The results are ambiguous. It is not clear which patient populations most benefit from CAS.

Question 6: Please discuss whether chronic data presented for the over-the-wire (OTW) configuration in the SAPPHIRE trial provide evidence of sustained effectiveness of CAS in preventing stroke in patients at high risk for CEA.

The panel concurred that no long-term data, only extrapolations, were provided. Data were insufficient to answer the question.

Question 7: Is it appropriate for the sponsor to employ OPCs developed from NASCET and ACAS outcomes to assess outcomes for both symptomatic and asymptomatic patients in the SAPPHIRE trial? Or should the ACAS rates from the asymptomatic trial be used for comparison?

The panel concurred that the conclusions need to be modified for the NASCET data.

Question 8: The SAPPHIRE trial included MI as a component of MAE. Please comment on the sponsor's choice of composite endpoint.

The panel concurred that the composite endpoint may not be appropriate when comparing surgical and nonsurgical outcomes. Early, sustained, and persistent findings indicate that surgical patients fare less well in terms of long-term mortality. Long-term follow-up data will be critical. MI should be routinely included in composite endpoints in future trials.

Question 9: Are outcomes achieved in this registry acceptable?

The panel observed that placement in the registry was weighted toward clinical, not anatomic exclusions. Not all the reasons for exclusion are known. The outcomes seem acceptable, but it is not clear what is being compared.

Question 10: Please comment on whether the incidence of ipsilateral stroke is acceptable.

The panel concurred that stroke incidence is appropriate, but again, it is unclear what is being compared. Compared with CEA patients in the randomized cohort, incidence of stroke is equivalent, but not necessarily acceptable. Registry patients are an appropriate comparator, but the methodology does not permit such comparison.

Question 11: The various studies employed a total of only four size 5 mm stents. Does the panel believe that there are adequate safety and effectiveness information for this size?

The panel concurred that although little data exist, not having a 5 mm stent would put some operators at a disadvantage, and a 5 mm stent would not be inherently troublesome.

Question 12: Has the totality of data presented . . . shown reasonable assurance of safety and effectiveness for the OTW configuration? If not, what niche indications have been shown to be safety and effectiveness for carotid stenting?

The panel did not reach consensus on whether the investigators demonstrated safety and efficacy. Some members felt that approval of the PMA would constitute an inappropriate change in the care paradigm. The comparison data are for much lower risk patients. The evidence does not demonstrate that stenting is the best treatment for the patients studied. The 30-day adverse event rate was troubling to some panel members.

Question 13: Are the indications and contraindications for the OTW configuration clear and supported by the SAPPHIRE study findings? If not, please identify the indication you believe is supported by the sponsor's data.

The panel referenced its earlier discussion. Use without a distal protection device is a relative, not absolute, contraindication, although distal protection appears to improve outcomes, according to the feasibility study data. The label should indicate that patients who are good candidates for CEA are also good candidates for CAS.

Question 14: If there are candidates [for CAS] that are not optimal that should be added [to the labeling], please identify them.

The panel concurred that the PMA adequately sets forth contraindications involving patient anatomic characteristics.

Question 15: Should any other warnings or precautions be stipulated in the labeling for the OTW configuration in addition to those found in the proposed labeling?

The panel suggested including a warning that if it is not possible to position the distal protection device, risk of poor outcome and embolization may increase.

Question 16: Please comment on whether the sponsor's postapproval study is adequate.
The panel concurred that the study is adequate. Members recommended that an independent neurologist evaluate patients, particularly if minor strokes are counted as adverse events. The neurologist should evaluate patients at 30 days and 1 year. The sponsor should place increased attention on areas where data are most lacking: 5 mm stents and cases in which distal protection cannot be deployed. Three-year follow-up with the IDE cohort is sufficient to show durability.

Question 17: Please comment on whether the sponsor's training plan is adequate.
Panel members agreed that the training plan is adequate and should be distinguished from certification, competence, and credentialing. Categorization of patients as surgical candidates should continue to take place in a multidisciplinary mode and be included in training.

Dr. Hughes noted that the panel was in the uncomfortable position of having to recommend approval or nonapproval on the basis of data received late and with apparent shortcomings. Given the limited follow-up, a device retrieval program or autopsy program could be useful. The manufacturer should consider some form of emergency compensation funds if it is determined that something was overlooked in this review.

VOTE

Dr. Wood read the voting options and definition of safety and effectiveness. The panel voted 6-5 that the device was approvable with the following conditions:

1. The device is indicated for use in the treatment of carotid artery disease in patients requiring carotid revascularization who have one of the following high-risk features:
   - ?? Anatomic factors
   - ?? Contralateral carotid occlusion
   - ?? Contralateral laryngeal nerve palsy
   - ?? Radiation therapy to neck
   - ?? Previous CEA with recurrent stenosis
   - ?? Difficult surgical access
   - ?? Severe tandem lesions
   - ?? Medical comorbidities (CHF [class III/IV] or severe LV dysfunction, open heart surgery within 6 weeks, recent MI, angina at low workload or unstable angina [CCS class III/IV], severe pulmonary disease, or age greater than 80).
2. The label should include a warning that if distal protection cannot be deployed, risks to patient may be higher.
3. The patient information booklet should be revised as discussed by the panel in its earlier discussion.

4. An independent, 30-day neurologic consult must be incorporated into the postmarketing approval process.

POLL

Panel members voting to recommend approval indicated that the felt the device was safe and effective. Safe and proper use of these devices is critical to good patient care. Revascularization is indicated for certain asymptomatic patients. Patients and physicians deserve access to CAS, and physicians can take better care of patients if they have access to these devices. It is not the panel's role to set clinical practice guidelines.

Panel members opposing approval felt that the sponsor had not demonstrated efficacy. Patients will suffer neurologic events that they would not have experienced with medical care. Changing paradigm of patient care. CAS is not necessarily the best approach to patient care, particularly for asymptomatic patients.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 7:25 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on April 21, 2004, and that these minutes accurately reflect what transpired.

_____

Geretta Wood
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

_____

Warren K. Laskey, M.D.
Chairperson

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