

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

March 17 and 18, 2004

**Gaithersburg Hilton
Gaithersburg, MD**

**Circulatory System Devices Advisory Panel Meeting
March 17, 2004**

Attendees

Chairperson

Cynthia Tracy, M.D.
George Washington University

Clyde Yancy, M.D.

University of Texas Southwestern Medical
Center

Voting Members

Salim Aziz, M.D.
Capitol Cardiovascular & Thoracic Surgery
Association

Industry Representative

Michael Morton
Sorin-COBE CV, Inc.

Mitchell Krucoff, M.D.
Duke University Medical Center

Consumer Representative

Chrissy Wells
Translational Genomics Research Institute

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

Food and Drug Administration

Bram Zuckerman, M.D.
Director
Division of Cardiovascular Devices

Christopher J. White, M.D.
Ochsner Clinic

Geretta Wood
Executive Secretary

Consultants

Brent Blumenstein, Ph.D.
TriArc Consulting

Eric Chen, M.S.
Office of Device Evaluation

Charles Bridges, M.D.
Pennsylvania Hospital

Julie Swain, M.D.
Office of Device Evaluation

Thomas B. Ferguson, M.D.
Washington University School of Medicine

Lily Yue, Ph.D.
Office of Surveillance and Biometrics

John W. Hirshfeld, M.D.
University of Pennsylvania Medical Center

Normal S. Kato, M.D.
Cardiac Care Medical Group

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

CALL TO ORDER

Panel Chair Cynthia Tracy, M.D., called the meeting to order at 9:04 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted for Clyde Yancy, M.D., and Judah Z. Weinberger, M.D., Ph.D., for their interests in firms that could be affected by the recommendations of the panel. The Agency took into consideration matters concerning Thomas B. Ferguson, M.D., Mitchell Krucoff, M.D., Cynthia Tracy, M.D., and Dr. Weinberger and Yancy, who reported past or current interests involving firms at issue but in matters not related to the day's agenda. Dr. Tracy then asked the panel members to introduce themselves.

Ms. Wood read the appointment to temporary voting status. Panel consultants Yancy, Weinberger, Hirshfeld, Ferguson, Kato, Blumenstein, and Bridges had been appointed voting members for the duration of the meeting.

OPEN PUBLIC HEARING

Dr. Tracy read the Agency's statement on transparency of the device approval process.

Leo Korbet, Phoenix, AZ, stated that he had been placed on the SynCardia artificial heart prior to receiving a heart transplant and urged the panel to approve the device. He and others would have died without the bridge to transplant that the device provides.

SPONSOR PRESENTATION

Marvin J. Slepian, M.D., CEO, SynCardia Systems, Inc., introduced the sponsor presenters and consultants and provided an outline of the sponsor's presentation. The SynCardia CardioWest Total Artificial Heart (TAH) is indicated for use as an in-hospital bridge to

transplantation in cardiac transplant candidates who are at imminent risk of death due to irreversible biventricular failure. Dr. Slepian summarized the device's development history and noted that it evolved from the Jarvik heart. The device received European CE approval in 1998.

Richard Smith, MSEE, Chief Operating Officer, SynCardia Systems, provided an overview of the CardioWest TAH System. The device has three main components: an implantable system that is inserted next to the chest wall, drivelines, and an external console. The implantable system has six components and occupies the space of the diseased heart. The device weighs less than an actual heart. It can be tailored to individual patients in that the ventricles can be oriented as needed; no surgical pocket is required.

In the heart, four diaphragms separate where air comes in and blood flows. The external console incorporates many redundancies to provide good reliability, including a backup controller and backup air and power. The device uses a simple system that mimics the "starling principle" of heart: Increasing venous return automatically increases the stroke volume.

In inserting the TAH into the patient, the natural valves and ventricles are removed. Issues such as arrhythmias, right ventricle (RV) dysfunction, aortic valve dysfunction, thrombus in left ventricle, and septal defects are thus eliminated or minimized, unlike with similar devices (VADs). The device decreases central venous pressure (CVP) and overcomes pulmonary artery pressure (PAP); it maximizes the differential in pressure across organs, creating optimal conditions for organ recovery. The device provides biventricular cardiac flow to 9.5 L/min.

Long-term in vitro testing resulted in no device failures. The TAH has features that enhance safety and facilitate implantation, eliminates limitations related to native heart dysfunction, and is simple and reliable.

Jack G. Copeland, M.D., University of Arizona/University Medical Center (UMC),

principal investigator of the IDE study, emphasized the clinical need for the TAH. Patients who have biventricular failure and impending organ failure usually die without intervention, but the TAH provides hemodynamic stabilization and organ recovery until transplant is possible.

The clinical study examined safety and efficacy of the TAH device. The study hypothesis was that patients with irreversible biventricular failure could be saved using the TAH as a bridge to transplantation. The clinical study was a prospective, nonrandomized, multicenter trial involving critically ill patients who had irreversible end-stage heart failure (New York Heart Association [NYHA] Class IV). Historical controls consisting of patients meeting identical entry criteria were used. The primary efficacy endpoint was treatment success (i.e., at 30 days posttransplant, the patient was alive, in NYHA Class I or II, ambulatory, and not on ventilator or dialysis). Secondary efficacy endpoints were survival, hemodynamics, end-organ function, and ambulation. Key issues in the design of the study were to define a patient population that needs a biventricular bridge to transplant and to define the natural history of untreated patients using historical controls.

The study involved five centers and 12 surgeons. A total of 130 patients were in the study: 35 control and 95 implant (81 core patients and 14 out of protocol). Inclusion criteria consisted of eligibility for transplant, NYHA Class IV, body surface area (BSA) $>1.7\text{ m}^2$, and hemodynamic insufficiency (as demonstrated by a variety of measures). Patients had to be large enough for the TAH to fit. Exclusion criteria consisted of use of any ventricular assist device (VAD); excessive levels of serum creatinine, bilirubin, or cytotoxic antibodies; dialysis in the previous 7 days; and pulmonary vascular resistance ≥ 8 Wood units. Dr. Copeland elaborated on why the study population was chosen for TAH rather than an LVAD.

The control group consisted of 22 historical controls, 3 prospective controls, and 10 patients found by looking at UNOS Status I patients from all centers. All controls had to meet the inclusion criteria. Control and core patients were comparable on most baseline demographic and risk factors. Noncomparable baseline characteristics included ischemia, smoking history, use of anticoagulants, prior cardiac surgery, current intraaortic balloon pump, and cardiopulmonary bypass (CPB); all noncomparable characteristics favored the core patients, except for CPB, which favored the controls. Patients were comparable on numerous hemodynamic factors, except for systolic arterial pressure (which favored the core patients) and PAP and CVP (which favored the controls). After summarizing the hierarchy of drug support at baseline for the two groups, Dr. Copeland noted that the two groups' laboratory values (except for bilirubin) were comparable.

The control group was not for formal statistical comparison. Rather, the controls give an approximation of the natural history of the patients meeting entry criteria without mechanical support. Patients served as their own controls for hemodynamic and general recovery. Comparisons from published VAD studies provide perspective on core patient results.

At 30 days, 69.1 percent of the core patients but only 37.1 percent of controls met the primary endpoint of treatment success. Following transplant, 30-day and 1-year survival compared favorably with published survival data. Core patients had significantly longer time to transplant than controls, but control patients had much lower survival to transplantation.

Dr. Copeland presented Kaplan-Meier curves comparing survival in the two groups. Long-term survival rates were higher among core patients than controls. Posttransplant survival of core patients compared favorably with published UNOS survival data. The mean time on the TAH device was 79.1 days; the longest was 414 days. Sick control patients did not have as good

an early result after the transplant. Secondary efficacy endpoint data on cardiac index, renal and hepatic function, and ambulation demonstrated hemodynamic recovery among TAH patients.

The most common adverse events were infection and bleeding. Of 125 infections in core patients during the implant period, 13 were deemed clinically significant. Seven infections contributed to death and one caused death, but none were device related. Five infections delayed transplantation. No instances of ascending driveline infections occurred. Fifty-five bleeding events occurred, two of which resulted in death. A total of 26 neurological events occurred, including 11 strokes in 10 patients (both core and nonprotocol); only one resulted in delay of transplantation.

Nineteen device malfunctions—primarily driveline kinks and leaks—in 17 patients occurred. Most events were transitory and did not adversely affect the patient. One case of diaphragm tear occurred; the patient refused a second TAH and subsequently died. The manufacturer has adjusted the design to avoid recurrences. Five fit complications occurred, two of which were contributing causes of death. Twenty-one percent (17) of the core patients died before transplantation; four deaths were due to procedural or technical problems (including two cases of coagulopathy after Feiba administration).

The total success rate was 69.1 percent, and the results are generalizable. The TAH provides immediate hemodynamic and end-organ recovery and allows patients to be ambulatory. The device is reliable and offers significant benefit at reasonable risk to patients.

Walter E. Pae, M.D., Pennsylvania State University, presented a clinical perspective. Donor hearts are in short supply, and mortality is high among patients awaiting transplantation. Practical device therapy is needed, not just to avoid death but also to provide medical stabilization before transplantation. Patients with biventricular failure are at high risk of death.

Right ventricle failure (RVF) in patients on LVADs is not well defined. One-third to one-half of patients with RVF require biventricular support devices (BiVADs). Such patients have half the successful bridge rate of those who do not have RVF. Paracorporeal systems are flow limited by design, require competent aortic valve, and are limited by the liability of the native heart pathology. In contrast, TAH provides immediate high flow and is not limited by native heart pathology. The TAH meets a clinical need for patients who need biventricular support due to a variety of conditions in which the native heart presents a liability. A review of the published literature indicates that the SynCardia TAH compares favorably with other mechanical VADs. Definitions of adverse events vary across studies, however, and published reports do not always provide detailed information on those events. In addition, registry data were previously voluntary, and time frames may differ. Recognizing those limitations, the performance of the SynCardia device is within the parameters established by the published literature.

The SynCardia TAH successfully salvaged patients with biventricular failure. Safety and efficacy are clinically similar to available mechanical support devices. The TAH will fill a therapeutic gap and extend the ability to treat cardiovascular disease.

Dr. Slepian presented concluding comments. Safe and effective therapies are needed to save lives and stabilize patients in imminent danger of dying from biventricular failure. The TAH provides hemodynamic normalization leading to end-organ recovery. The device is safe, effective, and reliable and provides a bridge to transplantation. The benefits of the device outweigh the risks. Finally, Dr. Slepian reviewed the indication for use and noted that patients who are ineligible for cardiac transplantation and those with $BSA < 1.7 \text{ m}^2$ are contraindicated for the device. Training will include didactic and hands-on components. Proposed postmarket

surveillance includes 1 year of follow-up on enrolled patients and on 50 new study patients; to demonstrate generalizability, no more than 10 percent of the new patients.

Panel members asked brief questions for clarification, which the sponsor representatives answered.

FDA PRESENTATION

Eric Chen, M.S., Office of Device Evaluation, lead reviewer, provided an overview of the FDA presentation and listed the FDA review team members. He described the device's function and components, reviewed the indication for use, and summarized the history of the U.S. clinical study. He noted that preclinical testing had yielded satisfactory results. The Agency is still working with the sponsor to resolve certain sterilization and manufacturing issues, but those should not hinder progress of the review. The device is safe from an engineering perspective.

Lily Yue, Ph.D., Office of Surveillance and Biometrics, presented the Agency's statistical analysis. She summarized the study design and pointed out that, among other problems, data for most of the control patients were collected in early 1990s, but data on the implanted patients were collected later. The two groups are not comparable because of the imbalances in the periods of data collection and in multiple baseline covariates. Any direct treatment comparisons are inappropriate, and all resulting p values are uninterpretable.

Adjustments for data imbalances can be made using traditional covariate analysis and propensity score analysis. Dr. Yue explained those techniques and noted that patient age cannot be adjusted for because the two groups are too dissimilar in that variable. Propensity score methods can only adjust for observed covariates, not for unobserved covariates. The method is

seriously degraded when important variables influencing treatment selection have not been collected. The technique works better when data on many covariates are available.

The propensity score analysis involved multiple imputations for 19 percent of patients with missing baseline covariate values. Adjustments were made (if possible) for all imbalanced or clinically important baseline covariates as well as for the year of implant. The propensity score model accurately predicted the treatment group membership. However, the two treatment groups did not overlap enough to allow a sensible treatment comparison.

As a result, one must base judgments on the performance of the TAH group alone and treat the sponsor's clinical study as a single-arm study. Because sicker patients may have received transplants sooner, Kaplan-Meier estimates for survival prior to transplant may be biased. Without appropriate controls, it is difficult to statistically evaluate device effectiveness.

Julie Swain, M.D., pointed out that no randomized controlled studies exist for FDA-approved bridge-to-transplant LVADs; no comparable control groups exist in previous BTT studies; and the research on such devices generally has slow enrollment. The 10-year duration of this study is not out of line with previous devices. Dr. Swain noted the paucity of rigorous studies in this area and listed the inclusion criteria culled from the literature. Based on those data, the Agency developed a performance goal for survival to transplant of 65 to 70 percent before it ever saw the SynCardia device. The sponsor's device performs as well as or better than the performance goal.

LVAD implantation with RV failure presents a diagnostic dilemma. When LV devices are implanted, RV failure rate is 10 to 30 percent. Treatment usually consists of inotropes, volume load, or off-label NO use; short-term pumps; or long-term percutaneous pumps. Determining who needs a BiVAD at the time of bridge presents a dilemma.

In approving the CardioWest study, the Agency agreed that clinical equipoise did not exist. The Agency approved the control group, but it is mainly considering the 81 patients who met all criteria. It is difficult to develop a performance goal for adverse events. The definition varies across studies and is a matter of clinical judgment.

A better understanding is needed of the true indications for using this device. RV failure may become evident only after LVAD implantation. When should the device be used, and how should the label reflect the problem? Moreover, 71.6 percent of the patients in the study were at one center, UMC; the study is essentially a single-center design. Success rates are identical for UMC and other two centers, however. The Agency is also concerned about conflicts of interest, because the primary investigators at UMC have an equity interest in the device.

Survival to transplant was similar to other devices reported in the literature. The adverse event profile trends seem similar to those of other devices, but a direct comparison cannot be made due to differences in definitions.

Panel Questions for FDA

Panel members asked for clarification as to why more devices were implanted than initially planned and whether any safety concerns had arisen as a result of the experience with the first few devices implanted. They expressed concern over the lack of a suitable control group. At least one panel member suggested that the term “control” should be replaced with “reference cohort” in the labeling. They discussed the reasons underlying the paucity of randomized controlled trials in this area and suggested that it would have been helpful to have data on other artificial hearts for comparison. Data on posttransplant mortality also would have been useful, because the TAH may play a role in posttransplant recovery. Agency staff answered their questions.

Panel Reviews

Salim Aziz, M.D., noted that this and similar devices have been around since the early 1980s and asked what accounted for the improvement in thromboembolic complications. The sponsor replied that coagulation and platelets are now treated separately; in addition, running such devices at fairly high outputs (7 or 8 L/min.) discourages plaque formation.

Dr. Aziz also raised questions concerning the relation between grafts and bleeding problems; whether hyperperfusion of the right side is an issue with the device; the impact of transfusions on cytotoxic antibody levels and the ability to receive a transplant; how PAP is measured once the device is implanted; how malfunctions related to kinking of tubes might be prevented; ability to determine patients who have a propensity for neurological events; benefits of TAH versus other approaches; treatment of respiratory failure in patients with the device; and the impact of the device on blood pressure problems and how the device might be adjusted to alleviate those problems.

Sponsor representatives answered Dr. Aziz's questions. **Walter Dembitsky, Sharp Memorial Hospital, San Diego**, noted that TAH is an important technology because for some patients, biventricular support does not work. The device has been used in situations of graft rejection on table. It enables the physician to stop immunosuppression and let the patient recover. The retained heart can be a liability to the patient.

Dr. Aziz noted that implantation of the device is not reversible and negates the possibility of recovery. Clear indications are needed to guide appropriate use of the device.

Dr. Copeland clarified the conflict of interest issue of concern to the Agency. The device was initially owned by a private company and was given to UMC. The complete study was carried out under that ownership. None of the presenters or sponsors were financially attached to

device until a year after the study was completed. UMC ended its participation, and the sponsor representatives formed a company to keep it going and seek FDA approval.

Clyde Yancy, M.D., commented on the trial design. He noted the difficulty of randomized controlled trials because of the urgency of these patients' situation. He is comfortable with the sponsor's methodology. The advantage of the TAH is the biventricular support it provides and its utility for unique applications that were not examined in the trial. The demonstrated patient improvement, 30-day survival, and other outcomes of the study demonstrate reasonable efficacy.

It is unclear which patients are ideal for this device. A number of clinical innovations (e.g., beta blockers) have come about to which the reference group was not exposed. The improvement in hepatic function is compelling, and looking at liver and kidney insufficiency may be a better approach than trying to define RV dysfunction. Treatment algorithms can be developed. The indication should probably be heart disease with multisystem organ failure.

Neurologic events are tragic complications. It seems that most infections are not device related but perioperative and procedural. Bleeding rates appear to be high compared with other platforms, however. Specific data on antibiotic sensitization are needed. In addition, a number of instances of hemodynamic insufficiency occurred; more data are needed on patient hemodynamics. Ideally, a model based on hemodynamic parameters that would show who would and would not do well with this device could be developed. Finally, the device requires a bulky console, which could impede patient rehabilitation; a smaller model would be desirable.

Sponsor representatives responded to Dr. Yancy's questions.

PANEL DISCUSSION

Panel members' concerns focused on the lack of clarity of the indications for use. Which patients should receive LVADs, and which should receive BiVADs? They concurred that the sponsor should provide additional data on clinical characteristics of study patients. Panel members also were concerned about clinical trial design for devices of this type and appropriate approaches to randomization. They suggested that the device should be limited to use in centers that currently do transplantation. They also expressed concern that the results of the clinical trial may not be generalizable because so many of the patients were at one center, UMC. Other issues included management of patient expectations, production of smaller TAH sizes so that women could more readily receive the device, use in patients with failed LVADs or BiVADs, diaphragm ruptures, and ensuring appropriate training of the entire care team in use of the device. Panel members suggested that surgeons should have some sort of hands-on or observational training.

FDA QUESTIONS FOR PANEL

Question 1 (generalizability): The panel had concerns about generalizability, in part because the study investigators have a financial interest in the sponsoring company; however, they were reassured by the fact that the study ended before SynCardia became the device sponsor. Because techniques are the same across centers, outcomes should be similar across centers.

Question 2 (safety): Most panel members felt that the level of adverse events was acceptable, given the highly sick population in which the device will be used; however, a minority of the panel felt that the complication rate was unacceptably high and that the data did not provide reasonable assurance of safety. The sponsor should work toward reducing the complication rate.

Question 3 (efficacy): Most panel members agreed that the device is efficacious as a bridge to transplant. A minority felt that the data do not support that conclusion.

Question 4 (indications and labeling): The panel concurred that the indications for use are appropriate, but the labeling does not adequately define TAH patients as opposed to LVAD patients. The sponsor needs to provide more information on the clinical characteristics of the patients who were in the study and state that the participants were people with idiopathic and ischemic cardiomyopathies. The *p* values should be deleted from the labeling because they are misleading and suggest that an actual control group was involved in the study; the term “reference cohort” may be more appropriate. The panel noted that the contraindication regarding device fit needs to be clarified; even though it is currently based on the study inclusion criteria, better ways of describing appropriate device fit may exist. The labeling should emphasize that the data are extrapolated from an observational study, not a randomized controlled trial. It also should state that patients receiving the device require careful antiplatelet and antithrombotic monitoring and that patients who cannot take anticoagulants are not candidates for this device.

Some panel members recommended that the device should be used only at centers with active heart transplant programs, but Dr. Zuckerman noted that the ability to state that on a label may be limited. He noted the panel’s concern that surgeons have appropriate training and use the device at highly experienced centers.

Question 5 (training): Panel members recommended that surgeons’ first cases be proctored and that the labeling specify that all members of the care team should receive training.

Question 6 (postmarket study and follow-up): The panel agreed that postmarket surveillance of patients for 1 year posttransplant was adequate. Several panel members recommended

creating a registry to follow patients. To interpret adverse event reports submitted to the Agency, it is important to have a denominator as well as to capture pre-implant patient characteristics.

OPEN PUBLIC HEARING

Robert Jarvik, M.D., Jarvik Heart, Inc., New York, NY, noted that the device is easy to control and that it could be practical to outfit a home so that the device is safe to use with the existing console. He asked the panel to make a “statement of no objection” to companies working out a program to certify home use with the Agency.

Aly El-Banayosy, M.D., Rhur University, Bad Oeyenhouse, Germany, concurred with Dr. Jarvik and noted the need for smaller consoles. He described the German experience with the device and presented data.

VOTE

Ms. Wood read the voting options. The panel voted 10-1 to recommend that the Agency approve the device with the following conditions:

1. The sponsor should conduct postmarket surveillance as discussed by the panel, including all patients implanted from point of entry to 1 year posttransplant. The study should collect and correlate data on adverse events and patient characteristics.
2. The labeling should include a contraindication that the device should not be used in patients who cannot be anticoagulated.
3. The sponsor should clarify information regarding proper fit of the device and replace the contraindication regarding BSA with something more general (e.g., “Do not use this device if it will not fit in area vacated by existing ventricles”).

4. The warnings should clarify that safe use of the device requires close monitoring of antiplatelet and anticoagulant therapy.
5. The device should be implanted only at centers that are capable of performing cardiac transplantation.
6. Training should involve some form of hands-on training or onsite proctoring.

POLL

Panel members indicated that they voted to approve the device because a particular group of patients have a compelling need for it. They emphasized that the clinical trial did not meet the usual standards of rigor. SynCardia TAH use should be limited until more data are gathered, and the sponsor should make an ongoing effort to hone the indications. Close and careful follow-up is needed.

One panel member voted not to recommend approval because data do not support safety.

One panel member urged that the Agency not require the device to be used only at transplant centers but instead take the panel's condition as a recommendation.

ADJOURNMENT

Dr. Tracy thanked the participants and adjourned the meeting at 5:59 p.m.

**Circulatory System Devices Advisory Panel Meeting
March 18, 2004**

Attendees

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George Washington University

Clyde Yancy, M.D.

University of Texas Southwestern Medical
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Office of Surveillance and Biometrics

Thomas B. Ferguson, M.D.
Washington University School of Medicine

Quynn Hoang
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CALL TO ORDER

Panel Chair Cynthia Tracy, M.D., called the meeting to order at 9:08 a.m. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. Full waivers had been granted for Clyde Yancy, M.D., and Judah Z. Weinberger, M.D., Ph.D., for their interests in firms that could be affected by the deliberations of the panel. The Agency took into consideration matters concerning Thomas B. Ferguson, M.D., Mitchell Krucoff, M.D., Cynthia Tracy, M.D., and Dr. Weinberger and Yancy, who reported past or current interests involving firms at issue but in matters not related to the day's agenda. Dr. Tracy then asked the panel members to introduce themselves.

FDA PRESENTATION

Julie Marders, R.N., M.S., Division of Postmarket Surveillance, Office of Surveillance and Biometrics, presented an analysis of adverse event reports received by the Agency on aortic anastomotic devices. She described the medical device reporting (MDR) system and its limitations. Underreporting of adverse events to FDA by health care practitioners is well known and recognized. Manufacturers are not required to submit denominator information, such as the number of devices manufactured, distributed, or implanted, so accurate adverse event rates cannot be determined. Reports may not be representative, and they reflect a variety of reporting biases. Event narratives vary in completeness and detail and often do not contain results of manufacturer failure analyses. Devices frequently are not returned to manufacturers because they are discarded or remain implanted.

The analysis covers reports received for product codes for anastomotic devices from May 24, 2001, to March 1, 2004. Additional database queries were made using brand names to verify that all reports were captured. A total of 213 reports were received, mostly in 2003. The reports

described 23 deaths, 185 injuries, and 5 malfunctions, primarily in patients age 65 or older. The reports are a signal of a potential public health problem. Some catastrophic events could be device related. The reported events reflect short-term experience; long-term information also is important. Failure analyses are lacking or limited; the root causes for device failures are unknown. Adverse event data need to be factored in to the risk–benefit profile for anastomotic devices.

Wolf Sapirstein, M.D., M.P.H., F.A.C.S., Medical Officer, summarized the history of vascular anastomotic products for CABG. Vascular suturing changed little from 1903 to 2001, when the first sutureless device was cleared. Improvements in the CABG procedure have obviated the ill effects of cardiac arrest, extracorporeal circulatory perfusion, and aortic clamp manipulation. Minimally invasive direct coronary artery bypass (MIDCAB) reduced the morbidity of incisional trauma, and dispensing with cardiopulmonary bypass eliminated an activator of inflammatory and immunologic responses, improving outcomes. Extracorporeal circulation and aortic manipulation have been implicated in neurocognitive complications. Anastomotic devices can play a major role in reducing morbidity. CABG patency is dependent on many factors that most likely have been affected by recent changes to the operation that are still being evaluated and by new measures to inhibit the progression of coronary artery disease.

Dr. Sapirstein listed factors that affect the integrity of conduit patency for coronary revascularization. Anastomotic devices eliminate factors that contribute to poor patient outcomes; however, their benefits with new procedures are unresolved. The devices also may contribute to graft failure for reasons that include compliance mismatch, materials that promote local thrombus and inflammation, vessel trauma caused by device deployment, design of anastomosis prejudicial to laminar flow, and difficulty with revision.

In evaluating anastomosis devices for 510(k) clearance, the Agency required extensive preclinical data to support limited clinical studies. The clinical material was required to substantiate equivalence to historical data for conduit patency, a surrogate for correcting the deficiency in myocardial perfusion. The Agency encountered some disagreement regarding study design, duration of follow-up, and instruments for assessing effectiveness. Although general agreement exists regarding the use of suture anastomosis as the gold standard to control for patency, some researchers advocate using measures of coronary perfusion for assessment of patency, a reversal of the original CABG surrogate use of patency for perfusion.

The initial concept was to take into consideration the multifactorial causes of CABG failure by accepting a relatively short period (i.e., 6 to 9 months) that focuses on the adequacy of the anastomosis constructed. The changes to CABG itself and the introduction of measures aimed at disease progression were not addressed. It was also felt that a distinction could be made for devices used on the proximal aortic or distal coronary artery.

The study design problem goes beyond multifactorial causes of CABG failure; it involves device-specific variables of proximal versus distal anastomosis devices; vein versus arterial conduit; and differences in device design. The rigor of a randomized trial may be required. The Agency would like the input of the panel on a template for a randomized study design that involves beating heart (BH) CAB versus CABG and is stratified by vein conduit, arterial conduit, and aortic versus distal anastomosis. Dr. Sapirstein presented sample size estimates for a trial based on left internal mammary artery–left anterior descending coronary artery (LIMA-LAD) patency of 95 percent (lower confidence limit [LCL] of 90%) and saphenous vein graft (SVG) CABG patency of 85 percent (LCL 80%).

Kachi Enyinna presented the questions for the panel.

OPEN PUBLIC HEARING

Dr. Tracy read the Agency's statement on transparency of the device approval process.

Randall K. Wolf, M.D., F.A.C.S., University of Cincinnati, Ohio, presented a classification of anastomotic devices as automatic or manual and presented background information on the causes of vein graft failure. If the St. Jude device had been evaluated at 6 months by angiography, stenoses and occlusions would have been discovered. Second-generation anastomotic devices are more reliable than handsewn anastomosis. Second-generation distal devices demonstrate excellent patency; unlike stents for CAD, the devices do not rearrange plaque. The science supports use of 6-month angiographic data as a clinical trial endpoint.

Robert W. Emery, M.D., Cardiac Surgery Associates, St. Paul, MN, presented data on why vein grafts fail. New issues introduced by the current generation of connectors include overloading, double loading, skiving of aortic punch, variations in operative technique, graft movement, and loss of 90-degree graft angle. Improved and more extensive training may obviate modes of failure. Many modes of failure are unstudied or unconfirmed, so prospective studies are warranted, including those on operative technical detail.

G. Phillip Schoettle, M.D., Thoracic and Cardiovascular Surgery Associates, Memphis, TN, discussed his own research, which found high rates of occlusions and stenosis in patients in whom the St. Jude Symmetry anastomosis device was used. Based on his experience, the St. Jude device results in higher rates of saphenous vein closures and occlusion than handsewn anastomoses. Technical issues do not seem to be the issue. The devices are not proven to be clinically safe or effective.

Robert Frater, M.D., Medical Director, St. Jude Medical, Cardiac Surgery Division, defended the Symmetry device. The MDR system is a warning light that tells us nothing about adverse event incidence. Data on handsewn anastomoses are 30 years old: Back then, patients were younger, vessels were better, and diabetes was less common. Doctors face different patients today. We need to know today's patency rates, including the rates for off- and on-pump procedures. Six-month follow-up is reasonable for clinical studies; follow-up longer than 12 months is too late because atherosclerosis dominates at that point. FDA needs to provide clarity on the type of clearance needed for these devices; if the clinical data requirements are equivalent to those needed for a PMA, then the Agency should require a PMA process.

Michael Mack, M.D., Cardiac Surgeon, Dallas, TX, representing the Society of Thoracic Surgeons/American Association of Thoracic Surgery Joint Committee on New Technology, presented data on SVG patency. The gold standard (handsewn sutures) has a well-documented history over past 30 years. From 1979 to 2001, 30 studies were published analyzing more than 25,000 grafts. His metaanalysis of SVG patency found that patency at 30 days is 87.9 percent. At 3 to 6 months, it is 84.1 percent, and at 12 months, it is 82.7 percent. Significant attrition occurs in the first 30 days. It is unknown how beating versus arrested heart procedures and anastomotic connectors affect SVG patency. Angiography is the only reliable method to determine patency. A 6-month endpoint is adequate for trials.

Mark Slaughter, Director, Cardiac Surgery, Advocate Christ Hospital, Oak Lawn, IL (also speaking on behalf of **Rich Lotti, President and CEO, Converge Medical, Inc., Sunnyvale, CA**) noted that factors affecting the quality of sutured anastomoses are surgeon skill, patient anatomy, disease state, access, and visibility. Reasonably good science suggests that anastomoses heal at about 60 days; after that point, failures are due to patient factors, ongoing

atherosclerosis, and improper medication. The purpose of anastomotic devices is to provide a vascular connection that is atraumatic, reliable, reproducible, reversible, and easy to use.

Differences between proximal and distal anastomoses involve flow dynamics and tissue characteristics. Implant biocompatibility is important: Nitinol, stainless steel, and Ti-6AL-4V all are compatible and are not sources of late stenoses. Inflammatory response is similar with all anastomosis devices. One can perfectly manipulate flow dynamics with nonsutured devices.

Historical controls and 6-month follow-up are acceptable for clinical trials.

Henry Frank Martin, M.D., University of Tennessee Center for the Health Sciences, Memphis, observed that interventional cardiologists develop a “sixth sense” about when to intervene. Anastomotic devices behave like stents. No cardiologists appear to have been involved in research and development of the Symmetry device because they know about the problems with nitinol stents. Nitinol induces scar formation. Developers did not understand cardiac disease and the role of Plavix in patients. Many patients have problems with these devices, and the Symmetry device should have been withdrawn years ago. Cardiologists need to be involved in trial design and product development.

Bernard Hausen, M.D., CEO, Cardica, described two products that Cardica is developing. The C-Port distal anastomosis system delivers a set of eight implantable clips with the push of one button. The Pas-Port is a second-generation proximal anastomosis system; key improvements over the previous generation include minimized endothelial trauma during loading and a large effective orifice area. Cardica is applying for 510k clearance for the Pas-Port device.

Uwe Klima, Professor, Cardiac Surgery, Hannover Medical School, Germany (also presenting on behalf of **Mark Foley, President and CEO, Ventrica, Fremont, CA**), presented data from an evaluation of coronary anastomosis in CABG surgery at the Hannover Medical

School using the Converge, St. Jude, and Ventrica anastomotic devices. Clinically significant problems were found at 6 months with the St. Jude device, but not with the other devices.

Prospective, multicenter trials should be used in evaluating the performance of anastomotic devices. Retrospective, clinically driven endpoints are not sufficient. Comparison to established, historical controls should be acceptable, and angiography should be used to evaluate device performance. Six-month angiographic follow up is sufficient to address the performance of anastomoses.

OPEN COMMITTEE DISCUSSION

Panel members discussed the best modes for assessing patency and concurred that it is best for patients to undergo as few invasive procedures as possible. Angiography is important but should be kept to a minimum. Noninvasive methods, such as CT and MRI, can be used for intermediate assessments. Invasive procedures negatively affect patient retention.

Training in appropriate use of the devices is vital; technique plays a role in device function and graft patency. It was noted that when drug-eluting stents first came on the market, many adverse events initially occurred.

The Agency has developed a paradigm for analyzing endovascular stents; those studies may be helpful in designing clinical trials for anastomosis devices. Clinical trials should assess functional outcomes as well as anatomic outcomes. The patient population has changed so much in the past 30 years that historical controls may no longer be relevant. Although in some cases, patients can serve as their own controls, randomized controlled trials comparing the devices to handsewn sutures will be inevitable. Graft failure is related to many factors, including site and flow, and proximal and distal anastomoses involve different issues. Proximal stenosis affects patency. The primary endpoint should be patency; secondary and/or surrogate endpoints can

include major adverse cardiac events and neurologic events. Studies should include a data safety monitoring board.

Panel members expressed concern that new guidance from the Agency could negatively affect ongoing studies, but Dr. Zuckerman said that the Agency would work with sponsors of those studies to ensure that their work to date need not be discarded. Panel members also asked what the Agency was doing to address the issues raised concerning safety of the St. Jude Symmetry device. **Quinn Huang, Office of Surveillance of Biometrics**, said that the Agency is working with the company and is looking at the issue.

FDA QUESTIONS FOR PANEL

Question 1: Please comment on the choice of control in the clinical trial required to evaluate vascular anastomosis devices for CABG.

The panel concurred that some sort of control or comparison group is necessary. The type of control—inpatient, matched controls, or historical data—has to be determined on the basis of statistical analysis. Propensity scores may not be appropriate. Dr. Blumenstein developed rough sample size estimates for studies with patients serving as their own controls versus randomized controlled trials; the panel expressed concern over the potential size of trials, but it nevertheless felt the need for scientific rigor should take priority. Study designs may differ for LIMA and SVG trials. Surrogate endpoints are not adequate; patency is the most important variable.

Question 2: With regard to device placement and device design, please address the following: (a) Given the considerable differences between the proximal and distal CABG anastomoses, what, if any, differences should be required? (b) Are there certain aspects of the clinical study design that should be required for all devices, irrespective of device form and function? (c) Can you suggest criteria to determine whether a failure is device related?

The panel concurred that although proximal anastomosis devices involve unique issues that need to be taken into account in study design, the endpoint ultimately should be patency. In either case, 6 months is an appropriate time frame for determining patency. Endpoints for proximal and distal devices would not warrant totally different designs. Although stenosis may be not be

apparent until 12 months, the appropriate endpoint is graft failure, which should be clear by 6 months. Methodologies from stent trials are worth examining. All endpoints must be measured and observed on case report forms. Results should be generalized into acute procedural and chronic procedural success composite variables.

The biomechanics of conduit failure are not well understood. A DSMB and core lab would be useful in determining prospective outcomes and minimizing the impact of investigator biases. Although panel members concurred that angiograms are necessary measures in studies of anastomosis devices, they expressed concern about the impact on patients of multiple angiograms and the impact of angiography requirements on patient recruitment and retention.

Question 3: Do you believe that the significant differences between an arterial conduit and a venous conduit warrant distinct study criteria and assessment for each? If so, please identify these criteria and analyses. The panel concurred that the endpoint of patency is the same, whether the conduit is venous or arterial. Study designs must take into account the biology of tissue and the site of anastomosis; however, patency is the critical outcome that investigators will be looking for angiographically.

Panel members discussed the importance of having multiple endpoints because different devices will have unique complications. Dr. Zuckerman noted that if adverse event rates are unacceptable, the device would not be acceptable, even if patency were good.

Question 4: Should the primary effectiveness endpoint be graft patency alone or include both graft patency and myocardial perfusion?

The panel concurred that myocardial perfusion may be misleading. Primary effectiveness endpoint is angiographic follow-up. Aortic disruption is another issue. CT and MRI may be useful at intermediate time points. Different devices may require specific endpoints. Trials need to be powered at patency because that is what the experimental devices focus on; other endpoints are continuous.

Question 5: What criteria should be applied to the evaluation of device safety, as distinguished from device effectiveness?

The panel concurred that the same safety and efficacy endpoints that pertain to suture should apply to these devices. Acute aortic disruption is a safety issue. Safety and efficacy overlap to some extent.

Question 6: With regard to appropriate patient follow-up: (a) What duration of follow-up is advisable for premarket evaluation? (b) Should postmarket follow-up be required to assess long-term device effectiveness? If so, please define the appropriate length of follow-up after primary patency evaluation.

The panel concurred that a 6-month angiographic endpoint is appropriate and that postmarket follow-up is necessary. Stent trial models could be useful. Patients should have clinical follow-up for a minimum of 1 year; this could take place by phone after patency is determined.

Question 7: Can noninvasive measuring instruments be used for primary assessment of graft patency, or is angiographic follow-up necessary? At what time points should patency be assessed?

The panel concurred that noninvasive imaging (CT or MRI) can be used acutely and intermediately, at 3 to 6 months, to assess patency. Late follow-up should be angiographic, at a minimum of 6 months. One panel member suggested extending follow-up to 7 or 8 months to avoid unnecessary stenting. A core lab could play a critical role. In addition, panel members noted that patency standards may differ for different vessels.

Panel members observed that with 350,000 bypass procedures taking place each year, accruing several hundred patients to clinical trials should not present an insurmountable hurdle. Panel members concurred that it was probably not appropriate for patients to serve as their own controls.

OPEN PUBLIC HEARING

No comments were made.

ADJOURNMENT

Dr. Tracy thanked the participants and adjourned the meeting at 4:08 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on March 17 and 18, 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.

Cynthia Tracy, M.D.
Chairperson

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