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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

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CIRCULATORY SYSTEM DEVICES PANEL

Thursday, March 18, 2004

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P R O C E E D I N G S

**Call to Order**

DR. TRACY: Good morning, everybody. I would like to call to order this meeting of the Circulatory System Devices Panel. The topic today is a discussion of type of data and study required to effectively evaluate performance of aortic anastomotic devices for marketing.

**Conflict of Interest**

MS. WOOD: The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

1           A waiver has been granted for Dr. Clyde  
2 Yancy and a wavier was previously granted for Dr.  
3 Judah Weinberger for their financial interests in  
4 firms at issue that could potentially be affected  
5 by the panel's recommendations. The waivers allow  
6 these individuals to participate fully in today's  
7 deliberations. Copies of these waivers may be  
8 obtained from the agency's Freedom of Information  
9 Office, Room 12A-15 of the Parklawn Building.

10           We would like to note for the record that  
11 the agency took into consideration other matters  
12 regarding Drs. Thomas Ferguson, Mitchell Krucoff,  
13 Cynthia Tracy, Judah Weinberger and Clyde Yancy.  
14 These panelists reported past or current interests  
15 involving firms at issue but in matters that are  
16 not related to today's agenda. The agency has  
17 determined, therefore, that these individuals may  
18 participate fully in the panel's deliberations.

19           In the event that the discussions involve  
20 any other products or firms not already on the  
21 agenda for which an FDA participant has a financial  
22 interest, the participants should excuse him or  
23 herself from such involvement and the exclusion  
24 will be noted for the record.

25           With respect to all other participants, we

1 ask in the interest of fairness that all persons  
2 making statements or presentations disclose any  
3 current or previous financial involvement with any  
4 firm whose products they may wish to comment upon.

5 DR. TRACY: Just before we get started, I  
6 would just like to ask everybody to be sure that  
7 you are speaking directly into the microphone,  
8 including the speakers who will be coming up later  
9 in the open public hearing. A transcript is being  
10 made from these presentations today.

11 At this time I would like to ask the panel  
12 members to introduce themselves.

13 **Introductions**

14 MR. MORTON: I am Michael Morton. I am  
15 the industry representative. I am an employee of  
16 CarboMedics.

17 DR. WEINBERGER: Judah Weinberger,  
18 Director of Interventional Cardiology at Columbia.

19 DR. YANCY: Clyde Yancy, Director of Heart  
20 Failure and Transplantation at UT Southwestern, in  
21 Dallas.

22 DR. WHITE: Chris White. I am the Chief  
23 of Cardiology at Ochsner Clinic Foundation.

24 DR. HIRSHFELD: John Hirshfeld. I am an  
25 interventional cardiologist in the University of

1 Pennsylvania.

2 DR. KATO: Norman Kato, cardiovascular  
3 surgeon, private practice, Encino, California.

4 MS. WOOD: Geretta Wood, Executive  
5 Secretary.

6 DR. TRACY: I am Cindy Tracy,  
7 electrophysiologist, George Washington University.

8 DR. EDMUNDS: I am Hank Edmunds, Professor  
9 of Surgery at the University of Pennsylvania.

10 DR. FERGUSON: Tom Ferguson,  
11 cardiovascular surgeon, Washington University St.  
12 Louis.

13 DR. KRUCOFF: Mitch Krucoff,  
14 interventional cardiologist, Duke University  
15 Medical Center; Director of Devices Trials, Duke  
16 Clinical Research Institute.

17 DR. MAISEL: William Maisel,  
18 electrophysiologist, Brigham & Women's Hospital.

19 DR. BLUMENSTEIN: Brent Blumenstein,  
20 biostatistician, Seattle, Washington.

21 DR. BRIDGES: Charles Bridges, Chief  
22 Cardiovascular Surgery Pennsylvania Hospital,  
23 University of Pennsylvania.

24 MS. WELLS: Chrissy Wells. I am the  
25 consumer representative on the panel.

1 DR. ZUCKERMAN: Bram Zuckerman, Director,  
2 FDA, Division of Cardiovascular Devices.

3 DR. TRACY: Thank you. At this point we  
4 will have the FDA presentation, and Julia Marders,  
5 from the Office of Surveillance, will be the  
6 opening speaker.

7 **FDA Presentation**

8 MS. MARDERS: Good morning.

9 [Slide]

10 My name is Julia Marders, and I am a nurse  
11 analyst in the Division of Postmarket Surveillance,  
12 Office of Surveillance and Biometrics.

13 [Slide]

14 I will present an analysis of adverse  
15 event reports received by the FDA on aortic  
16 anastomotic devices. My presentation will begin  
17 with a brief description of the Medical Device  
18 Reporting System, MDR, which is a system for  
19 adverse events and product problems, and include a  
20 discussion of its limitations.

21 Next, I will describe the database, search  
22 methodology used to obtain the reports of aortic  
23 anastomotic devices and provide a summary of  
24 findings and analysis of conclusions. Then I will  
25 finish the presentation with conclusions,

1 considerations and questions for the panel to  
2 contemplate.

3 [Slide]

4 The Medical Device Reporting System is a  
5 nationwide passive surveillance system which  
6 includes both mandatory and voluntary reporting.  
7 Since 1984 manufacturers and importers have been  
8 required to submit reports to the FDA of  
9 device-related deaths and serious injuries, as well  
10 as events involving device malfunctions that may  
11 cause or contribute to death or serious injury.

12 The Safe Medical Devices Act of 1990  
13 introduced mandatory reporting of device-related  
14 deaths and serious injuries by user facilities,  
15 most notably hospitals and nursing homes.  
16 Voluntary medical device adverse event and problem  
17 product reports, most often submitted by healthcare  
18 practitioners, consumers, patients or family  
19 members, are received through the FDA's MedWatch  
20 program. In general, approximately 95 percent of  
21 the reports received by FDA are from manufacturers,  
22 one percent from importers, and the remainder is  
23 equally split between voluntary and user  
24 facilities.

25 [Slide]

1           The Medical Device System, which is the  
2 MDR system as most people know it, while providing  
3 signals of actual and potential device-related  
4 problems, has some limitations. Under-reporting of  
5 adverse events to hospitals, manufacturers and the  
6 FDA by healthcare practitioners is a well-known and  
7 recognized phenomenon. Thus, events reported  
8 through MDR represent a subset of the total  
9 occurrence of events.

10           In addition, manufacturers are not  
11 required to submit denominator information such as  
12 number of devices manufactured, distributed and  
13 implanted. Thus, due to under-reporting and lack  
14 of denominator data accurate incidence rates are  
15 unable to be determined based on MDR data alone.  
16 Furthermore, reports received may not be  
17 representative and reflective of a variety of  
18 reporting biases. Thus, for example, reporting may  
19 vary by manufacturer or by the presence or absence  
20 of publicity.

21           Although there is a regulatory requirement  
22 for a minimum data set, event narrative  
23 descriptions vary in completeness and complexity.  
24 For example, one aortic anastomotic device report  
25 indicates failure of the connector as the entire

1 event description and no further details are  
2 provided. In addition, many reports do not contain  
3 results of manufacturer failure analyses. Often  
4 devices are not returned to the manufacturer for  
5 evaluation because they are discarded or remain  
6 implanted. Thus, root causes for reported events  
7 are often unable to be determined.

8 [Slide]

9 Now I will describe the search methodology  
10 used to obtain the data set of aortic anastomotic  
11 device reports in this presentation and present the  
12 findings. First I searched the database by product  
13 code. All medical devices approved or cleared for  
14 marketing have a unique three-letter identifier  
15 called the product code. Next, I narrowed the  
16 search by date. This search includes events of  
17 aortic anastomotic devices that were reported from  
18 May 24, 2001, the first marketing clearance date  
19 for these devices, to March 1, 2004. I also  
20 performed additional database queries by brand  
21 names to validated that I had captured all aortic  
22 anastomotic device reports that have been entered  
23 into the database.

24 [Slide]

25 Now the findings, a total of 213 reports

1 are in the database and most reports were received  
2 in 2003. The number of death reports is 23;  
3 injury, 185; and malfunction, 5. The vast majority  
4 of these reports, that is 203, came from  
5 manufacturers, with 2 from user facilities and 8  
6 voluntary.

7 [Slide]

8 Patient age was provided in 129 of the 213  
9 reports and ranged from ages 35 to 83 years, with  
10 most in the 50-65 age range. Slightly over half of  
11 these events are noted in males, a quarter in  
12 females and a quarter were gender unspecified. One  
13 hundred and seventy-three events, or 81 percent,  
14 occurred with patients in the U.S. and 14, which is  
15 7 percent, with patients outside the U.S.; 26 event  
16 reports, 12 percent, did not specify whether the  
17 event is foreign or domestic.

18 [Slide]

19 Of the 23 death reports, 22 were from  
20 manufacturers and one from a user facility. All  
21 patient deaths occurred within 18 days of  
22 implantation and 15 of the deaths occurred within 3  
23 days of implantation. Interestingly, one patient  
24 actually had both a dissection operatively and a  
25 detachment postoperatively and is included in 2 of

1 the problem categories listed on this slide.  
2 Additionally, another patient had both thrombus and  
3 aortic detachment that was discovered on  
4 postoperative day 2 when the patient coded.

5 Twelve reports indicate the problem of  
6 occlusion or thrombus at the connector site. One  
7 report describes the patient was noted to have a  
8 predisposing hypercoagulable state, and 2 reports  
9 indicate that patients had atrial fibrillation.  
10 Aortic dissection associated with deployment or  
11 after the connector is placed was noted in 7  
12 reports. Device detachment, resulting in  
13 hemorrhagic shock, occurred in 6 reports. None of  
14 the devices associated with death were returned to  
15 the manufacturer for evaluation and the  
16 manufacturer has not been able to determine the  
17 root cause of the events.

18 [Slide]

19 Now I will present an actual report to  
20 illustrate these findings in a more clinically  
21 relevant way. A patient was implanted with an  
22 aortic anastomotic device during an off-pump  
23 procedure. No difficulties were encountered with  
24 loading or deployment of the device. Recovery was  
25 good for approximately 40 hours when the patient

1 suddenly lost consciousness after a dramatic drop  
2 in blood pressure. CPR was initiated and blood  
3 appeared in the drains. At re-operation, the  
4 aortic connector was detached from the aorta and  
5 the patient died after 10 minutes. The autopsy  
6 revealed the cause of death was hemorrhagic shock.

7 [Slide]

8 A total of 185 injuries were reported.  
9 Stenosis and occlusion are overwhelmingly noted to  
10 be the first and second most frequently reported  
11 problems respectively. Although infrequently  
12 reported, events involving device detachment have  
13 also resulted in serious injury. Clinically, the  
14 reported outcomes of stenosis and occlusion  
15 resulted in life-threatening conditions resulting  
16 in shortness of breath, chest pain, arrhythmias,  
17 subsequent myocardial infarction and/or hemodynamic  
18 instability requiring either surgical or  
19 interventional treatment including catheterization  
20 for PTCA and stenting.

21 The time from implantation to injury, as  
22 noted in 37 of the 185 reports submitted, of the 30  
23 noting stenosis or occlusion most, or about 60  
24 percent, occurred within 90 days; 4 events occurred  
25 within 4 days. The other 7 are associated with a

1 variety of patient problems other than stenosis or  
2 occlusion. Three reports of device detachment  
3 occurred within one day of surgery, and another  
4 event atypically occurred after 97 days, possibly  
5 due to a fragile aorta and placement of the  
6 connector on a pseudoaneurysm. Of all the  
7 injuries, only 2 devices were returned to the  
8 manufacturer for evaluation, both of which resulted  
9 in manufacture evaluation indicating no device  
10 failure detected.

11 [Slide]

12 Five reports indicated a device  
13 malfunction. One report states the device was not  
14 able to be used because the anchor tip was closed.  
15 Two reports indicate the aortic plug was not seen  
16 by the surgeon upon inspection of the device. Both  
17 of these patients have not experienced any adverse  
18 consequences. The fourth report indicates a device  
19 malfunction resulting in an aortic laceration  
20 requiring repair. It is not clear why the user  
21 facility reported this event as a malfunction  
22 rather than an injury, and no information was  
23 included about the patient's outcome. Follow-up is  
24 ongoing. The fifth report indicates failure of the  
25 connector, with no other details, other than

1 indicating no consequences to the patient.

2 [Slide]

3 Conclusions--the reports of serious  
4 adverse outcomes related to aortic anastomotic  
5 device use raises a signal of a potential public  
6 health problem. Some of these occurrences are  
7 catastrophic, such as aortic dissection or device  
8 detachment, and not expected. Others, for example,  
9 occlusion or stenosis, may be expected depending on  
10 the patient's underlying condition of adequacy of  
11 antiplatelet therapy, or may reflect device-related  
12 events, for example, stenosis at the connection  
13 site or thrombosis potentially related to  
14 bioincompatibility or poor hemodynamics. Lastly,  
15 the reported information to date reflects  
16 short-term experience. Long-term failure  
17 information is also important.

18 [Slide]

19 Considerations--additionally, there are  
20 two other important points to consider, first,  
21 failure analyses of this adverse event data are  
22 lacking or limited. The underlying root cause of  
23 these events, particularly occlusion and stenosis,  
24 is unknown. Multiple factors may be involved which  
25 can make the evaluation of these events difficult.

1 Second, this adverse event data needs to be  
2 factored into the risk/benefit profile for these  
3 devices.

4 [Slide]

5 To conclude my presentation, I have the  
6 following three questions for the panel to consider  
7 that are based on adverse event report findings:

8 First is the question of collection of  
9 long-term failure rate data. Should a longer  
10 period of time for manufacturer collection of  
11 device performance data post implantation be  
12 required to fully understand aortic anastomotic  
13 device failures?

14 Next, should studies comparing short- and  
15 long-term patient outcomes between standard  
16 suturing versus sutureless aortic anastomotic  
17 devices to address risk/benefit issues be  
18 undertaken?

19 Finally, should further study of  
20 device-related events be considered?

21 I encourage the panel to consider these  
22 questions before making final recommendations.  
23 That concludes my part of the presentation and now  
24 I will turn over to Wolf Sapirstein.

25 DR. SAPIRSTEIN: Dr. Tracy, panel members,

1 good morning.

2 [Slide]

3 The people listed up there are members of  
4 the Division of Cardiovascular Devices. My name  
5 is Wolf Sapirstein. We are mandated by statute to  
6 regulate cardiovascular devices, and are hopeful  
7 that this panel will generate guidance for us in  
8 undertaking this activity for these new and unique  
9 devices used in treatment of coronary-artery  
10 disease.

11 [Slide]

12 Vascular suturing was introduced by Carrel  
13 in 1903 and has changed little over the next 100  
14 years, except for the replacement of catgut with  
15 synthetic suture. After about 30 years of attempts  
16 by various investigators internationally, an  
17 automatic device to effect vascular anastomoses,  
18 the Symmetry Aortic Connector, was cleared in 2001  
19 for commercial use by the agency. The drive for  
20 development of these devices has undoubtedly been  
21 coronary arterial bypass graft procedure which also  
22 underscores the clinical importance of assuring  
23 safety and effectiveness for these devices.

24 Incremental modifications to the coronary  
25 arterial bypass graft procedure are seminal to the

1 acceleration in development of these devices. The  
2 surgeons among us will have the forbearance, I  
3 hope, while I undertake a thumbnail sketch of the  
4 changes that have taken place in the performance of  
5 the coronary arterial bypass grafting procedure.

6 [Slide]

7 The CABG procedure was the earliest  
8 surgical therapy validated with a randomized,  
9 controlled trial, the Coronary Arterial Surgery  
10 Study. Autogenous venous conduits remain  
11 extensively employed with anastomosis performed to  
12 the aorta and the coronary artery distal to the  
13 obstructive lesion. Induced ventricular  
14 fibrillation and anoxic cardiac arrest with  
15 hypothermic protection were initially used to  
16 provide the quiet field demanded by the challenge  
17 of suturing vessels 1-2 mm in diameter.  
18 Cardioplegia inducing perfusion of the coronary bed  
19 has since produced cardiac standstill with improved  
20 myocardial preservation during the ischemic period  
21 of conduit anastomosis.

22 Resistance of the internal thoracic  
23 artery, ITA, to the atherosclerotic degeneration  
24 that seemed inexorable with vein conduits has led  
25 to is preferential employment since the late 1980s.

1 This also provides the advantage of eliminating  
2 need for an aortic anastomosis. Patient survival  
3 has since been shown in several studies to be  
4 closely related to the effectiveness of  
5 revascularization achieved for the anterior surface  
6 of the heart and left ventricle. These  
7 developments, patency of the ITA and anterior  
8 cardiac revascularization justified introduction of  
9 the minimal access direct CABG procedure in the  
10 1990s to perform an isolated LIMA-LAD bypass. This  
11 was shortly followed by beating heart and finally  
12 off-pump CABG with elimination of extracorporeal  
13 circulatory support entirely. Thus, were the ill  
14 effects of cardiac arrest, extracorporeal  
15 circulatory perfusion and aortic clamp manipulation  
16 of the aorta obviated.

17 [Slide]

18 These modifications made to the CABG  
19 procedure addressed its changing role in an era of  
20 increasing catheter-mediated coronary treatment.  
21 The MIDCAB is seen as reducing the morbidity of  
22 incisional trauma, particularly in an increasingly  
23 older patient cohort and patients with more  
24 compromised coronary circulation not amenable to  
25 percutaneous coronary interventions, and these

1 patients become candidates for operative  
2 intervention. Dispensing with cardiopulmonary  
3 bypass eliminated a potent activator of both the  
4 systemic inflammatory response and the various  
5 immunological cascades.

6           There is also increasing recognition of  
7 the frequency with which neurocognitive  
8 deterioration, apart from the more overt cerebral  
9 ischemic events, occur with CABG procedures.  
10 Extracorporeal cardiopulmonary bypass and  
11 manipulation of the atherosclerotic aorta for  
12 cardiopulmonary bypass perfusion, as well as  
13 conduit anastomosis, have been indicted as  
14 etiologic factors for these complications.  
15 Anastomotic devices, by facilitating the various  
16 modifications to the CABG that address morbidity,  
17 can certainly play a major role in reducing this  
18 illness.

19           [Slide]

20           Several studies during the development  
21 stage of CABG evaluated the effectiveness of this  
22 revascularization procedure measured as durability  
23 of patency. While this slide presents a generally  
24 accepted distillation of these study findings, it  
25 should be noted that patency of CABG is dependent

1 on multifactorial elements that have likely been  
2 affected by recent changes to the operation itself  
3 that are still being evaluated, and by new measures  
4 to inhibit the progression of coronary-artery  
5 disease. This has to be considered when evaluating  
6 anastomotic devices in a comparison to these  
7 conduit patency rates.

8 [Slide]

9 Failure of the CABG conduit has been  
10 attributed to several causes which are listed here.  
11 They are broadly stratified by the period of their  
12 most prominent effects: the perioperative failures;  
13 6 months o 1 year, failure due to neointimal  
14 hyperplasia; and the continuum from 6 months on are  
15 both coronary-artery disease in the native vessel  
16 and the conduit itself.

17 [Slide]

18 The advent of anastomotic devices carry a  
19 promise for significant benefits in the performance  
20 of the CABG procedure that go beyond simplifying  
21 procedural mechanics for the benefit of the  
22 operator. They have the potential for eliminating  
23 many of the factors contributing to poor patient  
24 outcome. It must be recognized that while the  
25 precise benefit perceived for some of these recent

1 changes to the procedures, such as beating heart  
2 and operations performed without cardiopulmonary  
3 bypass, are as yet unresolved. The use of  
4 non-suture constructed anastomoses will certainly  
5 facilitate and increase the frequency of their use.  
6 These are some of the benefits that seem intuitive  
7 with anastomotic devices.

8 [Slide]

9 Well, Woody Allen has said every silver  
10 lining has a dark cloud, and this is exactly true  
11 with these anastomotic devices. Here are listed  
12 some of the design characteristics that may  
13 contribute to graft failure which do not obtain  
14 with conventional sutured vascular connections.

15 [Slide]

16 In our evaluation of these devices for  
17 clearance with a 510(k) notification, we have  
18 required extensive preclinical data to support  
19 limited clinical studies. The clinical material  
20 was required to substantiate equivalence to  
21 historical data for conduit patency, which was a  
22 surrogate for correcting the deficiency in  
23 myocardial perfusion.

24 We encountered some disagreement regarding  
25 the study design, the duration of follow-up, and

1 the instruments for assessing effectiveness. While  
2 general agreement exists regarding the use of  
3 suture anastomosis as the gold standard to control  
4 for patency, there is considerable advocacy to  
5 employ measures of coronary perfusion for  
6 assessment of patency. This is a reversal of the  
7 original CABG use of patency as a surrogate for  
8 perfusion.

9           With regard to duration of follow-up, the  
10 initial concept was to take into consideration the  
11 multifactorial causes of CABG failure by accepting  
12 a relatively short period, such as 6-9 months, that  
13 focuses on the adequacy of the anastomosis  
14 constructed rather than the other factors in graft  
15 failure. The changes made to the CABG procedure  
16 itself and the introduction of measures aimed at  
17 disease progression were not addressed. It was  
18 also felt that a distinction could be made for  
19 devices used on the proximal aortic or on the  
20 distal coronary artery.

21           [Slide]

22           The problem encountered in designing a  
23 study to evaluate these anastomosis devices goes  
24 beyond the inherent problem of the multifactorial  
25 causes of CABG failure. They involve in general

1 the device-specific variables listed here that may  
2 frustrate attempts at one-design-fits-all study  
3 design for the devices.

4 [Slide]

5 From our initial experience with cleared  
6 devices, we now have the belief that the rigor of a  
7 randomized trials may be required unless there are  
8 very mitigating circumstances to justify otherwise.  
9 To this end, we would like input on an appropriate  
10 template for study design that could be modified to  
11 accommodate some of the variables intrinsic to  
12 their use. This slide lists some of the  
13 considerations we have encountered for designing a  
14 study template and it is just put up for your  
15 consideration as a straw man.

16 [Slide]

17 This slide represents a sample size  
18 estimation for a one-armed study with the endpoint  
19 for effectiveness based on the historical values  
20 listed here for conduits performed with hand  
21 suturing. For instance, a point estimate of 95  
22 percent patency, with a lower confidence level  
23 accepted as 5 percent, would require a sample size  
24 of 150 patients for study. This is just placed  
25 here for your consideration or evaluation for even

1 a one-armed study.

2 This completes my introduction to the  
3 FDA's request for this panel's input in formulating  
4 an appropriate regulatory approach for devices that  
5 present the potential for critically affecting the  
6 treatment of coronary arterial disease, which is  
7 the wound stripe of modern society.

8 Kachi Enyinna, our lead engineer reviewer  
9 for these devices, will now present or crystallize  
10 some of the comments that I have made in the form  
11 of questions that we would like this panel to  
12 address in helping us wrestle with the regulation  
13 of these devices. Thank you very much.

14 MR. ENYINNA: Good morning. My name is  
15 Kachi Enyinna, biomedical engineer and lead  
16 reviewer, Division of Cardiovascular Devices. I  
17 will be presenting the questions we have come up  
18 with and seeking some kind of guidance from panel  
19 on how to evaluate clinical studies of these  
20 devices. I would like to remind the panel members  
21 to keep these questions in mind while I go over the  
22 questions and to keep the questions in mind until  
23 discussion time this afternoon allow members of the  
24 medical community, as well as sponsors and industry  
25 to speak before we discuss the questions.

1 [Slide]

2 Regarding trial design, the first  
3 question, please comment on the choice of control  
4 in the clinical trial required to evaluate vascular  
5 anastomosis devices for CABG. The gold standard of  
6 sutured CABG anastomoses has a well-documented  
7 history of over thirty years.

8 [Slide]

9 Can historical data from sutured CABG  
10 anastomosis device trials be used as the control in  
11 the device studies?

12 [Slide]

13 Alternatively, are concurrently performed  
14 CABG controls necessary given the multifactorial  
15 causes of CABG failure, for example, technical  
16 construction, extent and progression of native  
17 vessel disease, condition of conduit and  
18 progression of intima hyperplastic and atheromatous  
19 degeneration, and the introduction of drugs for  
20 mitigation of atherosclerotic disease?

21 [Slide]

22 If these trial designs are inadequate,  
23 should randomized, controlled clinical trials be  
24 performed?

25 [Slide]

1 With regard to device placement and device  
2 design, please address the following: Given the  
3 considerable differences between the proximal and  
4 distal CABG anastomoses, what, if any, differences  
5 in study criteria should be required?

6 [Slide]

7 Are there certain aspects of the clinical  
8 study design, for example length of follow-up and  
9 endpoints, that should be required for all devices  
10 irrespective of device form and function? For  
11 example, the U-clip performance closely duplicates  
12 that of a suture, whereas the Symmetry has greater  
13 similarity to a stent.

14 It is rarely possible to determine the  
15 cause of conduit failure. Can you suggest criteria  
16 to determine whether failure is device related?

17 [Slide]

18 Number three, do you believe that the  
19 significant differences between an arterial conduit  
20 and a venous conduit warrant distinct study  
21 criteria and assessment for each? If so, please  
22 identify these criteria and analyses.

23 [Slide]

24 Four, should the primary effectiveness  
25 endpoint be graft patency alone, or include both

1 graft patency and myocardial perfusion?

2           Five, with regard to device safety, what  
3 criteria, that is, acceptable adverse event rates  
4 as compared to that for suture should be applied to  
5 the evaluation of device safety as distinguished  
6 from device effectiveness? For example, myocardial  
7 infarction, reoperations, neurologic events,  
8 incidence of aortic complications.

9           [Slide]

10           Regarding endpoint evaluation, number six,  
11 with regard to appropriate patient follow-up, in  
12 view of the possible persisting risk of failure of  
13 some mechanical anastomosis sites, distinct from  
14 the progression of native vessel disease, what  
15 duration of follow-up is advisable for premarket  
16 evaluation?

17           [Slide]

18           Should postmarket follow-up be required to  
19 assess long-term device effectiveness? If so,  
20 please define the appropriate length of follow-up  
21 after primary patency evaluation.

22           [Slide]

23           The last question, can non-invasive  
24 measuring instruments, for example,  
25 echocardiography, ultrafast spiral CT, MRA, EBT,

1 etc., be used for primary assessment of graft  
2 patency or is angiographic follow-up necessary? At  
3 what time points should patency be assessed? Thank  
4 you.

5 DR. TRACY: Does that conclude the FDA  
6 presentation? Does anybody on the panel have a  
7 question for the FDA at this point?

8 [No response]

9 At this point, we will move on to the open  
10 public hearing. Both the Food and Drug  
11 Administration and the public believe in a  
12 transparent process for information gathering and  
13 decision-making. To ensure such transparency at  
14 the open public hearing session of the advisory  
15 committee meeting, FDA believes that it is  
16 important to understand the context of an  
17 individual's presentation. For this reason, FDA  
18 encourages you, the open public hearing speaker, at  
19 the beginning of your written or oral statement to  
20 advise the committee of any financial relationship  
21 that you may have with the sponsor, its product  
22 and, if known, its direct competitors. For  
23 example, this financial information may include the  
24 sponsor's payment of your travel, lodging or other  
25 expenses in connection with your attendance at this

1 meeting. Likewise, FDA encourages you at the  
2 beginning of your statement to advise the committee  
3 if you do not have any such financial  
4 relationships. If you choose not to address this  
5 issue of financial relationships at the beginning  
6 of your statement it will not preclude you from  
7 speaking.

8 MS. WOOD: I have just a couple of  
9 announcements for the open public speakers. We  
10 have asked today, due to the number of speakers  
11 that have requested time, that you limit your  
12 remarks to five minutes each. I would also ask  
13 that you provide me with either an electronic copy  
14 or a hard copy of your presentation for the benefit  
15 of the summary writer and the transcriptionist. If  
16 you could see me at lunchtime, that would be great.  
17 Thank you.

18 DR. TRACY: There are a number of speakers  
19 and I will call them in order. The first is Dr.  
20 Randall Wolfe, from University of Cincinnati.

21 **Open Public Hearing**

22 DR. WOLFE: Members of the panel, ladies  
23 and gentlemen, good morning.

24 [Slide]

25 Thank you for honoring my request to speak

1 before you. My disclosure is that I was the  
2 principal investigator on the multicenter U-clip  
3 distal anastomotic trial. Those results were  
4 presented at AATS two years ago. There is no  
5 financial relationship.

6 I was a past consultant for Ethicon in  
7 laboratory and clinical evaluation of proximal and  
8 distal anastomotic devices, and in the past was a  
9 consultant to Ventrica in helping set up their  
10 clinical distal anastomotic connector trial.

11 I am currently on the steering committee  
12 of the Prevent IV Core Gentech E2F Decoy trial  
13 which uses synthetic DNA to prevent aortic coronary  
14 venous graft atherosclerosis. That study is closed  
15 with over 3,000 patients enrolled. I mention that  
16 because I think we are going to be educated on true  
17 graft patency of the results of that trial which  
18 will be opened first quarter of next year.

19 [Slide]

20 My primary interest is that I have been  
21 presenting summary of anastomotic devices at our  
22 national meetings, both AATS, STS and ISMICS. In  
23 the next five minutes I would like to summarize  
24 some of the things that have been presented at  
25 these meetings.

1 [Slide]

2 Overall, there are a lot of anastomotic  
3 connector devices, and this shows a convenient way  
4 to classify these into proximal and distal and  
5 subsequently into automated versus manual. There  
6 are 13 to 15 different devices in these different  
7 categories but I find this a convenient way to look  
8 at connectors.

9 [Slide]

10 There are different value propositions  
11 with the connectors and they range from traditional  
12 CABG all the way to total endoscopic CABG. I don't  
13 have time to go over this in detail but only to  
14 point out that there is a possibility of  
15 eliminating the heart-lung machine by using certain  
16 connectors and also reducing ischemic time. In the  
17 endoscopic evaluation there is a potential to  
18 reduce patient pain and trauma and to truly enable  
19 endoscopic surgery.

20 [Slide]

21 This is a summary that you will probably  
22 hear more about from other presenters, but vein  
23 graft failures could be a bad vein; the vein could  
24 be too long; it could be too short; there could be  
25 a poor run-off bed; or it could be a distal or

1 proximal anastomotic problem.

2 [Slide]

3 I think this is an important slide. This  
4 is some of the science and this is based on some of  
5 the work of the E2F Decoy trial but there is an  
6 initial wave of inflammation in a venous graft.  
7 There is injury. There is activation of smooth  
8 muscle cells. There is migration proliferation and  
9 intimal soil, if you will, for atherosclerotic  
10 plaque and ultimately accelerated atherosclerosis.  
11 However, this initial wave is in the first two  
12 weeks after the venous graft has been harvested  
13 from the leg and placed on the heart.

14 [Slide]

15 This is a summary of how I look at graft  
16 failure. I divided it into three distinct  
17 categories. The first is immediate, that is a  
18 technical graft failure. These are all venous  
19 grafts, by the way; it could be arterial as well.  
20 Technical failure would be identified in the first  
21 week. In other words, if one obtained a  
22 postoperative coronary angiogram in a patient in  
23 one week technical failures would be disclosed.

24 The next is intermediate, and this is what  
25 I relate to devices. This is usually in the first

1 six to eight weeks. So, a six-month angiographic  
2 evaluation should pick up device failures.

3 The third is chronic and this relates to  
4 accelerated atherosclerosis and this really takes  
5 years. In the E2F Decoy trial we are looking at  
6 one year but, in fact, it probably occurs over five  
7 years. In my opinion, if the St. Jude device had  
8 been evaluated at six months by angiography  
9 stenoses and occlusions would have been discovered  
10 that related to the device. In other words, the  
11 intermediate category.

12 [Slide]

13 We now have second generation anastomotic  
14 devices. They have proven to be more reliable than  
15 hand sewn. There is a consistent orifice size.  
16 They are easier to use. I think, importantly,  
17 another change that has happened with the second  
18 generation is a lack of vein manipulation. So,  
19 these should be evaluated with six-month  
20 angiographic equivalency and we should also look at  
21 performance outcomes.

22 [Slide]

23 In summary, I believe the science supports  
24 six months angiographic data for the intermediate  
25 or device failure area. Proximal stainless steel

1 devices have demonstrated excellent patency, which  
2 will probably be discussed. And, second generation  
3 distal devices demonstrate excellent patency. I  
4 think we have to keep in mind as we think about  
5 this is that unlike stents for coronary-artery  
6 disease, these devices do not rearrange plaque  
7 morphology. Thank you.

8 DR. TRACY: Thank you. Are there any  
9 brief questions for Dr. Wolfe from the panel?

10 DR. EDMUNDS: What data do you have for  
11 that last statement?

12 DR. WOLFE: Which part of it?

13 DR. EDMUNDS: The last statement, how do  
14 you know that the device doesn't rearrange plaque?  
15 I mean I don't know. I would just be interested in  
16 your data.

17 DR. WOLFE: The last statement is  
18 concerning distal devices. This is assuming that  
19 the device is placed to a target site that is  
20 relatively free of atherosclerotic debris. The  
21 second bullet point is for the proximal devices.  
22 The third bullet point is specifically for distal.

23 DR. EDMUNDS: That is what I am talking  
24 about. Are you talking about magnetic coupling?

25 DR. WOLFE: Any type. What I am trying to

1 relate is that stents and anastomotic devices are  
2 not equal in that a stent is supposed to rearrange  
3 plaque to open up a stenosis. For devices that we  
4 are using that is not their purpose. We are not  
5 rearranging the plaque. We are connecting,  
6 hopefully, a fairly normal vein or artery to a  
7 fairly normal coronary distal target.

8 DR. BRIDGES: I have a question about the  
9 second bullet point. Can you also inform us what  
10 data that is based on?

11 DR. WOLFE: I think that will be presented  
12 by others, but I believe that the difference is  
13 that stainless steel is stronger, and in a proximal  
14 position where there is atherosclerotic disease a  
15 stainless steel device can actually hold the aorta  
16 open, whereas a nitinol device may not; it may  
17 buckle and close. So, it is really the strength of  
18 the material. The proximals are different from the  
19 distals. In fact, the people that may need the  
20 proximal devices the most are the ones who have the  
21 worst aortas. They have disease in a situation  
22 where it is maybe not safe to clamp the aorta.

23 DR. AZIZ: With the proximal devices, if  
24 you do get narrowing, how do you propose that be  
25 handled? Let's say in six months you find that you

1 have osteal narrowing, how would you handle that?

2 DR. WOLFE: I don't know the answer to  
3 that.

4 DR. AZIZ: Can they be dilated in the cath  
5 lab?

6 DR. WOLFE: I don't know the answer to  
7 that.

8 DR. AZIZ: And is there intimal  
9 hyperplasia that you are seeing, if you do see it?

10 DR. WOLFE: I believe so with the second  
11 generation devices. With the first generation  
12 devices I think it was a more complicated situation  
13 where the graft could actually embrocate over the  
14 device. But in the second generation devices it  
15 should be more related to disease in the aorta.  
16 However, if a large lumen is maintained then there  
17 shouldn't be significant stenosis. So, let's say  
18 you get neointimal hyperplasia in every graft,  
19 let's say you get a millimeter in every  
20 graft--well, if you get a 1.5 mm opening, that is  
21 significant. If you get a 3 mm opening that is  
22 maintained, it won't be significant.

23 DR. AZIZ: Let me ask you one other thing,  
24 with the proximal anastomotic devices, the angle  
25 that the graft comes off is really at right angles

1 to the aorta. Right?

2 DR. WOLFE: In some of the products, that  
3 is true.

4 DR. AZIZ: You mean there are ones where  
5 you can have it coming off as a cobra head?

6 DR. WOLFE: That is correct.

7 DR. KRUCOFF: Have you actually retrieved  
8 any of these devices and looked at them under a  
9 microscope when they have failed?

10 DR. WOLFE: I have not--well, I have seen  
11 the slides, I certainly have.

12 DR. KRUCOFF: Whose slides are those?

13 DR. WOLFE: St. Jude. I did go over those  
14 at one point and, again, that is a first generation  
15 device and I believe the mode of failure of that is  
16 different from anything you might see in the  
17 future. It is multifactorial but the occlusions  
18 tend to be flush with the aorta. There is  
19 neointimal hyperplasia; there is thrombus. First  
20 of all, the angiogram does not look like a typical  
21 angiogram that you might see with an occluded vein  
22 graft; it is completely different. There is also  
23 the possibility that the vein graft itself has  
24 changed its position on the connector. In  
25 addition, that was a connector that had a high

1 profile. There is also the possibility that there  
2 could be a right angle kink right at the end of the  
3 connector.

4 I think in summary, I give credit to the  
5 pioneers for being the first ones out there. The  
6 first eight patients who received a mitral valve  
7 replacement all died. Fortunately, we still do  
8 mitral valve replacements and maybe with the first  
9 generation connectors we are seeing some of the  
10 same things, some of the mistakes. I think many of  
11 those have been changed by changes in device and  
12 changes in material.

13 DR. YANCY: As you have worked through  
14 your clinical trials with these devices, have there  
15 been concomitant improvements or changes in medical  
16 management because of anticipated problems with  
17 these connectors vis-avis antiplatelet therapy,  
18 anticoagulation, aspirin, etc.?

19 DR. WOLFE: We do have some data from the  
20 E2F Decoy trial. The trial has not opened but we  
21 have some demographic data. It has been shown that  
22 when patients are followed more closely the chances  
23 of them going home on antiplatelet agents are much  
24 higher. Although most surgeons say that they send  
25 their patients home on aspirin or some antiplatelet

1 agent, in fact, many patients do not go home on  
2 that but in a careful study situation they do.  
3 There is a study bias.

4 DR. YANCY: So, those anticipated events  
5 that you thought would be predicted or captured at  
6 six months, do you think they are product failures,  
7 medical management failures or both?

8 DR. WOLFE: I expect they are product  
9 failures and they probably would be in an extreme  
10 environment such as a very atherosclerotic aorta,  
11 but I am not sure. I am not sure.

12 DR. TRACY: I think we are going to have  
13 to move on at this point. There is a number of  
14 other speakers. Thanks very much. Dr. Robert  
15 Emery?

16 DR. EMERY: While we are setting up my  
17 disc here, I am Robert Emery. I am in private  
18 practice in Minneapolis-St. Paul, Minnesota. I am  
19 not being sponsored by any companies but I have had  
20 relationships in terms of research grants by St.  
21 Jude Medical, ATS Medical, AtriCure, Congestive  
22 Heart Failure Solutions. I have been on research  
23 advisory boards for St. Jude Medical, Medtronic,  
24 Myocor, Percardia, CardioGenesis, Inc.; data safety  
25 monitoring boards for Cardioblade and for Myocor,

1 and I have received speaking fees for several of  
2 the aforementioned companies.

3 [Slide]

4 I would like to address our early  
5 experience in the Minneapolis-St. Paul area looking  
6 at why vein grafts fail, the new issues with aortic  
7 connectors. We have been through the etiology of  
8 graft failures so I won't go into that, however,  
9 there are several new issues that are introduced by  
10 the currently used generation of connectors. There  
11 can be overloading of the connector, that is, too  
12 much vein graft placed below the prongs;  
13 double-loading of the connector like putting on  
14 your socks where you can invert the graft and load  
15 that which inhibits flow through the graft. You  
16 can skive the aortic punch and that make take out a  
17 complete circle.

18 There are variations in operative  
19 technique. For instance, performing your proximals  
20 first, as most surgical trainees in the United  
21 States perform distals first you are radically  
22 changing the way we have been trained in our  
23 everyday use in conduct of the operation. Grafts  
24 can move. After the patient is closed the lungs  
25 can push the grafts to various positions and this

1 can cause loss of the 90 degree angle, that has  
2 been mentioned here, that is necessary for the  
3 current generation St. Jude connector.

4 [Slide]

5 Let's look at some of these issues that we  
6 have seen. Here is a surgical technical error at  
7 the distal anastomosis that would lead to graft  
8 failure if not completed. I don't think that could  
9 be blamed on the connector but a connector was  
10 utilized.

11 [Slide]

12 This is the first case I performed in the  
13 United States, the second one done in the United  
14 States after FDA approval. You can see two  
15 technical errors here that I learned over time and  
16 if I had not changed my operative technique one  
17 would have a consistent mode of failure that would  
18 be uncorrected. That is, these grafts are placed  
19 on top of the aorta instead of further down the  
20 side toward the pulmonary artery, therefore,  
21 maintaining a 90 degree angle. The grafts are also  
22 reflected superiorly with some kinking at the  
23 anastomotic site, not maintaining that 90 degree  
24 angle. As I mentioned, these grafts can move. All  
25 grafts should be tacked to keep that important 90

1 degree angle. If you lose that you can predict  
2 some degree of graft failure.

3 [Slide]

4 There can be poor run-off, as shown on  
5 this slide, to a patent vein graft but a poor  
6 distal vessel.

7 [Slide]

8 Another example is shown here. The graft  
9 can be too short, as mentioned. Again, it may be a  
10 variation in operative technique.

11 [Slide]

12 Here a graft is tethered across the  
13 pulmonary artery and you can see the narrowing  
14 several centimeters distant from the connector  
15 device.

16 [Slide]

17 And a similar vein here wrapped around the  
18 pulmonary artery more tightly than one would like  
19 to see.

20 [Slide]

21 Improper placement of the graft is also  
22 important.

23 [Slide]

24 Here is a vein graft that was placed on  
25 the right side of the aorta as we traditionally

1 place our saphenous vein grafts when we suture  
2 them, rather on the anterior surface of the aorta,  
3 riding over the right ventricular outflow tract  
4 maintaining the 90 degree angle. You can see the  
5 acute bend on the right side as this graft reflects  
6 against the patient's pleural surface.

7 [Slide]

8 Aortic disease was mentioned and this can  
9 be important. Here is an occluded connector in a  
10 diffusely diseased aorta and you can see, as Dr.  
11 Wolfe mentioned, the flush occlusion of the aorta.

12 [Slide]

13 A combination of factors--here is a small  
14 vein graft and poor run-off.

15 [Slide]

16 And here is a very small vein graft that  
17 has become atretic over time to a small distal  
18 vessel, still patent through the connector but,  
19 nonetheless, narrowed.

20 [Slide]

21 Then there is the unknown. Here is the  
22 occluded connector again flush at the angiographic  
23 site.

24 [Slide]

25 Here is an occluded vein graft marked by

1 the stainless steel ring in the same patient. You  
2 can see the connector graft slightly to the left  
3 and one or two centimeters down in this example.  
4 There are connector related issues that are key.

5 [Slide]

6 This is what was addressed a little bit in  
7 the prior question, proximal anastomotic problems  
8 in the face of appropriate graft and appropriate  
9 distal connectors that need to be investigated.

10 [Slide]

11 Yet, there are technical issues. Here is  
12 another proximal connector with a very good vein  
13 graft and a large distal run-off system.

14 [Slide]

15 Improved and more extensive training may  
16 obviate several of the modes of failure that we  
17 have seen. We need to develop indications and  
18 contraindications for the use of these devices,  
19 particularly as they come out not just general,  
20 overall approval. There are technical  
21 considerations that need to be mentioned. Many  
22 modes of failure are unstudied or unconfirmed.  
23 Thus, prospective studies are warranted including  
24 operative technical detail, both visual, such as  
25 the photograph I showed you and verbal operative

1 reports, and improved mentoring may be necessary  
2 even for devices that seem intuitively simple.

3 [Slide]

4 There are tips for success that I have  
5 developed in my own practice based on my  
6 experience.

7 [Slide]

8 What we do not want to do is throw the  
9 baby out with the bath water because these  
10 connecting devices offer us a great opportunity to  
11 improve our service to our patients. Thank you.

12 DR. TRACY: Thank you. Are there any  
13 brief questions from the panel members? I do want  
14 to remind you that there are a lot of people who  
15 want to present today.

16 DR. KRUCOFF: Just one question. The  
17 angiograms you showed us, were they part of a study  
18 protocol that required angiography or were these  
19 clinical presentations of people who came back  
20 sick?

21 DR. EMERY: These were clinical  
22 presentations in approximately our first eight  
23 months of use, from May, 2001 through the first  
24 eight months, and we have seen very few since we  
25 have modified our surgical techniques.

1 DR. KRUCOFF: And the denominator for  
2 these eight months?

3 DR. EMERY: It was about 160, and these  
4 are not all of them. These are representative  
5 samples of technical errors that are correctable  
6 with proper training and changing of your  
7 techniques as you learn the process.

8 DR. AZIZ: When you say you tack the  
9 grafts, are you putting many anchoring stitches or  
10 what do you do?

11 DR. EMERY: Three or four generally on the  
12 left side. I put one on the pulmonary artery and,  
13 again, depending on the length of the graft,  
14 because you are doing proximals first with this  
15 device, I will connect it so that it won't move  
16 with respiration. On the right side I connect it  
17 down the body of the right ventricle as the graft  
18 goes directly up from the aorta over the right  
19 ventricle and down to the right coronary artery,  
20 the posterior descending artery, just some 6-0  
21 prolene suture tacking.

22 DR. AZIZ: We normally do the regular  
23 suturing technique; usually you don't have to do  
24 that?

25 DR. EMERY: No, I don't.

1 DR. AZIZ: So, why do you think you need  
2 to do it here?

3 DR. EMERY: Because I learned doing this  
4 distal first and I think my measurement of the  
5 length of the vein graft to the aorta is better on  
6 a distal first process in my hands. So, sometimes  
7 I would rather make my grafts too long than too  
8 short because the shortness of the graft may be one  
9 reason for disconnection of these connectors from  
10 the aorta. As the pulmonary artery fills, if the  
11 graft is too short you can pull these off. I have  
12 pulled them off myself in the operating room by  
13 tugging a little bit too hard and I had to put my  
14 finger over the hole. So, a short graft can lead  
15 to connector displacement from the aorta,  
16 particularly as the patient moves or the heart  
17 fills in the postoperative period.

18 DR. TRACY: Dr. Hirshfeld?

19 DR. HIRSHFELD: I would just like to say  
20 as an angiographer who has probably taken pictures  
21 of thousands of bypass grafts, I have heard a lot  
22 about considerations that I was never aware of  
23 before from your brief presentation, and I think it  
24 calls for a sharing of information between  
25 angiographers and surgeons about many of these

1 technical considerations that affect graft  
2 performance. So, I would hope that out of this  
3 will come that kind of sharing of information.

4 DR. EMERY: I have reviewed all the  
5 angiographs of patients that failed in my hands.

6 DR. TRACY: I think we have to move on; we  
7 have a number of speakers. I am sorry to cut this  
8 short; it is very interesting. To remind you,  
9 there will be more time this afternoon to discuss  
10 things in detail. Dr. Schoettle?

11 DR. SCHOETTLE: Good morning. My name is  
12 Dr. Phillip Schoettle. I am a thoracic and  
13 cardiovascular surgeon in practice at Methodist  
14 University Hospital in Memphis, Tennessee.

15 I am here this morning to discuss my  
16 experience with the Symmetry proximal anastomotic  
17 device. I would like to disclose at the outset  
18 that I have no financial interest in this matter.  
19 I paid my own way to Washington, and I am not  
20 employed by anyone, nor intend to be employed by  
21 anybody with a financial stake in this issue.

22 In September of 2001 I was trained in the  
23 use of the Symmetry proximal anastomotic device,  
24 along with two of my scrub assistants, by St. Jude  
25 Medical. I was attracted to the device because of

1 the reasons mentioned previously which would allow  
2 you to do a proximal anastomosis off the aorta  
3 without the use of a partial occluding or  
4 side-biting clamp with its attendant risk of  
5 embolic debris.

6 I rapidly incorporated that device into my  
7 practice and used it almost exclusively for the  
8 next eleven months. Initially I was very pleased  
9 with the results. I had minimal, if any, technical  
10 issues with the device and was not aware of any  
11 acute or subacute saphenous vein closures.  
12 Unfortunately, at approximately ten months we began  
13 to see almost a deluge of patients returning to the  
14 cardiac catheterization laboratory with vein graft  
15 occlusions or high grade stenoses invariably  
16 occurring in the connector site.

17 This occurrence was totally incompatible  
18 with my previous surgical experience. I reported  
19 this to St. Jude Medical and I felt like it  
20 warranted a distribution to the surgical community  
21 and I began a review of my patients, resulting in  
22 the paper that you see here. This paper was  
23 entitled, "Use of an Anastomotic Device in Coronary  
24 Bypass Surgery: A Word of Caution." It was  
25 published in the January edition of the Journal of

1 Thoracic and Cardiovascular Surgery.

2 Without going into great detail, I would  
3 like to summarize the results of that paper. It  
4 was a review of two years of experience. The first  
5 year was the year prior to my beginning to use the  
6 device, while proximal saphenous vein connections  
7 off the aorta were done in the conventional manner,  
8 that is, hand-sewn with a partial occlusion clamp.  
9 Beginning in September of 2001, for the next eleven  
10 months, comprises the next group of patients where  
11 almost exclusively all proximal anastomoses were  
12 done with the St. Jude Symmetry anastomotic device.

13 I divided the group in group A and group  
14 B. Group A was the first group, the prior year  
15 with hand-sewn anastomoses. I reviewed all  
16 patients who required repeated cardiac  
17 catheterization after coronary artery bypass  
18 surgery. What we found was that even though the  
19 patients in group A had had a year longer of  
20 exposure to my cardiology colleagues, less of those  
21 required repeated cardiac catheterization, although  
22 that number was not significant between the groups.

23 The number of grafts studied between group  
24 A and group B was also similar. However, what we  
25 did find was that the group A patients, those with

1 hand-sewn anastomoses, had an 80 percent patency  
2 rate of vein grafts studied. Remember, these were  
3 symptomatic, or at least theoretically symptomatic  
4 patients. So, 80 percent of the grafts were widely  
5 patent in the hand-sewn anastomoses, with no  
6 significant stenoses, and 20 percent were  
7 occluding.

8           Unfortunately, in the group B patients,  
9 those with the Symmetry proximal anastomotic  
10 device, only 20 percent of the grafts studied were  
11 patent. Fully 80 percent of the grafts were either  
12 totally occluded or had high grade stenoses  
13 uniformly occurring at the connector site. The  
14 significance in p value in favor or patency of the  
15 hand-sewn anastomoses was standardly evaluated with  
16 a p value of 0.0001.

17           Based on my experience with the Symmetry  
18 proximal anastomotic device and review of my own  
19 patients, I have several observations and two  
20 conclusions I would like to make. The use of the  
21 Symmetry St. Jude proximal anastomotic device in  
22 its current generation results in a significantly  
23 higher saphenous vein closure and occlusion rate  
24 when compared to hand-sewn anastomoses.

25           I do not believe that technical issues are

1 the major factor. I can show you arteriograms of  
2 what appear to be perfectly laid out saphenous vein  
3 grafts with a 90 degree angle off the aorta, with  
4 no kinking, where the stenosis arises immediately  
5 in the connector site off the aorta.

6 In two patients that I reoperated, I was  
7 able to harvest the segment of aorta with the  
8 connector and the saphenous vein. This was looked  
9 at microscopically by the pathologists in my  
10 hospital who reported basically a foreign body  
11 reaction in the connector site with associated  
12 neointimal hyperplasia.

13 I would also point out that these  
14 connector stenoses and occlusions are not  
15 clinically insignificant. In this group at least  
16 six patients have required early reoperation.  
17 Thirty patients, over a year ago, required PCI  
18 stents and angioplasty. There have been four  
19 sudden deaths in these patients, two of which were  
20 almost certainly related to myocardial infarction.

21 If I can have the liberty of making a  
22 conclusion, I see no clinical indication for the  
23 current generation of the St. Jude proximal  
24 connector. The use of this connector or any other  
25 vascular anastomotic devices must be evaluated by

1 scientifically controlled, prospective clinical  
2 trials.

3 I do not believe that uneducated surgeons  
4 and uninformed patients should be the testing  
5 ground for these devices that have not proven to be  
6 clinically safe or effective. I clearly am not  
7 opposed to technological advances in coronary  
8 bypass surgery. I have been an early proponent of  
9 off-pump surgery and less invasive coronary  
10 surgery. I do not want to throw the baby out with  
11 the bath water. I do not believe, however, that  
12 the cause of less invasive coronary artery bypass  
13 surgery is furthered by the ill-advised use of  
14 these unproven devices. Thank you. I would be  
15 glad to answer questions if there is time.

16 DR. TRACY: Any brief questions? Dr.  
17 White?

18 DR. WHITE: Would you just clarify for me,  
19 in the early part of your statement you said  
20 something about follow-up at ten months. Was there  
21 a ten-month interval that was special to you?

22 DR. SCHOETTLE: No, I believe it just  
23 would have become apparent to me, you know, with  
24 just the overwhelming evidence of patients. All of  
25 a sudden I was getting call after call from these

1 patients.

2 DR. WHITE: Would six months not have  
3 identified these patients? Would a six-month  
4 follow-up, do you think, not have been adequate?

5 DR. SCHOETTLE: I was asked that question  
6 last night. I don't have that answer. My gut  
7 feeling is that six months would probably be  
8 appropriate but I don't know that answer based on  
9 this review.

10 DR. BRIDGES: I have a question. In the  
11 brief study that you gave us I didn't see the  
12 mortality in the two groups. You said that there  
13 were no sudden deaths in the hand-sewn group but  
14 what was the overall mortality in the two groups  
15 and are there any updates since this paper was  
16 submitted?

17 DR. SCHOETTLE: The operative mortality  
18 was less than three percent but the overall  
19 mortality long-term, I don't have that; there have  
20 been no updates at this point although I intend to  
21 do that.

22 DR. BRIDGES: But both groups--

23 DR. SCHOETTLE: They were very similar.

24 DR. BRIDGES: At least for the graft  
25 connector patients, what would be medical therapy

1 for these?

2 DR. SCHOETTLE: It is in the paper, but  
3 all patients were discharged on aspirin and all  
4 patients were discharged on Plavix for two months.

5 DR. AZIZ: But when you had to reoperate  
6 on them did you have to redo the whole anastomosis  
7 or could you immobilize it and rehook it? How did  
8 you do that?

9 DR. SCHOETTLE: In a couple of cases I was  
10 able to continue to use that vein segment. Conduit  
11 length was an issue. Several of the veins were  
12 totally occluded and we just had to sacrifice those  
13 veins.

14 DR. AZIZ: So, the orifice was like the  
15 whole length?

16 DR. SCHOETTLE: That is correct.

17 DR. AZIZ: So, you probably had intimal  
18 hyperplasia proximally and you had full flow and  
19 then thrombus--

20 DR. SCHOETTLE: And then thrombus  
21 distally, correct.

22 DR. AZIZ: Obviously most people don't,  
23 and they probably should use some flow techniques  
24 to measure flows.

25 DR. SCHOETTLE: All patients in both

1 groups had mediastinal transit time flow evaluation  
2 at the time of surgery, and 95 percent of cases  
3 were done off-pump.

4 DR. AZIZ: When you did proximal  
5 anastomoses with the device did you do any  
6 sequential grafts--

7 DR. SCHOETTLE: No, they were sequential  
8 grafts but I don't have that number available to  
9 me.

10 DR. TRACY: Thank you.

11 DR. SCHOETTLE: Thanks.

12 DR. TRACY: Dr. Frater?

13 DR. FRATER: Let me state immediately I am  
14 the Medical Director of St. Jude and, obviously,  
15 have that as a conflict of interest.

16 I have a few points to make. I had  
17 expected ten minutes so I am going to try and make  
18 them quickly. I think we can all agree that the  
19 MDR system is a warning light that tells us nothing  
20 about incidence and, unless we are very lucky,  
21 doesn't give us much information on causality, hard  
22 as we try to look into every single report that  
23 comes in from the field. I shall not elaborate on  
24 that. I suspect the FDA feels the same about the  
25 MDR's utility as we do.

1           The question of comparing anastomotic  
2 devices to historically published data for sutures  
3 is an interesting one. The data that was obtained  
4 in the past has been cardiac surgeons who were  
5 trying to find out what they were doing 30 years  
6 ago when they were making venous anastomoses. The  
7 patients were younger. The vessels were better.  
8 The extra conditions, such as diabetes, were far  
9 less common and it was a different group of  
10 patients. Those patients have long since been  
11 captured by the interventionalists and the cardiac  
12 surgeon today faces a very different patient.

13           We need to know what the patency rates are  
14 today with the current set of patients. We also  
15 need to know what the difference may be between  
16 off-pump and on-pump. There was a paper presented  
17 just a few weeks ago at the ACC, the so-called Prog  
18 IV Trial, a randomized comparison between off-pump  
19 and on-pump surgery with angiography at one year.  
20 The patency rate of the cases performed on-pump at  
21 one year was 59 percent; the patency rate of those  
22 performed off-pump was 49 percent.

23           There is a paper being published in The  
24 New England Journal of Medicine by Kahn. It came  
25 out of Britain. Again, a randomized study of

1 on-pump and off-pump anastomoses studied at three  
2 months by angiography, which was performed in 80  
3 percent of the patients in the trial. The patency  
4 rate of the on-pump cases was exemplary. At three  
5 months they had a 98 percent patency rate but the  
6 off-pump cases had an 88 percent patency rate at  
7 three months.

8 I present this material, which is clearly  
9 important in trying to assess what will be the  
10 target of patency that we will be looking at in  
11 future trials, and a recognition that times have  
12 changed and circumstances are clearly very  
13 different.

14 We have done a meta-analysis of some 7,000  
15 patients in which angiograms were done between 6  
16 and 12 months. We chose that 6- and 12-month  
17 period for the obvious reason that you have already  
18 heard today, that after 12 months atherosclerosis  
19 dominates the failure of vein grafts. The mean  
20 occlusion rate was 16 percent in this meta-analysis  
21 between 6 and 12 months of sewn anastomoses. But  
22 the range was from 9.5 to 26.5. There is an  
23 immense diversity from different institutions and  
24 we can speculate forever, certainly not in five  
25 minutes, as to what the reasons for those

1 differences are. I am sure that the surgeons in  
2 the Prog IV study have not suddenly become  
3 incompetent; there are factors that we need to look  
4 at.

5           The question of the extent to which  
6 clinical utility data is considered to be  
7 necessary, I think we have already begun to deal  
8 with this. Six months seems to be a period of time  
9 that people are reaching, and that is not  
10 unreasonable considering that stents are a Class  
11 III device which may or may not be identical to  
12 anastomotic devices--that is debatable--are being  
13 evaluated with MACE and target vessel interventions  
14 at six months.

15           Certainly, it is reasonable to state that  
16 it should not be more than 12 months for the  
17 obvious reason that by then atherosclerotic disease  
18 dominates. There is intimal damage and technical  
19 factors in the first week, neointimal hyperplasia  
20 for the next few months, blending finally into  
21 atherosclerotic disease.

22           Now, it is essential that the FDA provide  
23 clarity on the type of clearance that we need. If  
24 the clinical data requirement reaches the point  
25 which would normally be required for a PMA, then it

1 should be a PMA. If you are required to produce  
2 the data for a PMA, then the process should be done  
3 under a PMA process. Thank you very much.

4 DR. TRACY: Any questions?

5 DR. WEINBERGER: I have a question for  
6 you. You said that you were concerned that the  
7 follow-up should be at six months because you  
8 thought that atherosclerosis dominates the  
9 subsequent natural history of graft failure. I am  
10 concerned because we have a pretty good idea that  
11 there is distinct biological heterogeneity in  
12 different vascular beds in terms of the kinetics of  
13 responses to manipulation. For instance, we know  
14 that for coronary interventions basically at six to  
15 nine months the process is over. But if you look  
16 in the periphery, like the iliacs, the usual time  
17 is three years. Do you have any data to suggest  
18 that the process to response to injury in vein  
19 grafts is over at nine months?

20 DR. FRATER: Well, if you look at the data  
21 from peripheral vascular intervention where it is  
22 far easier to follow the patients, it seems fairly  
23 definite that while there is an acute phase, which  
24 is partly technical and partly because of the  
25 damage we do to the vein by the various things we

1 do when we take it out and manipulated it, it  
2 starts in the first week. The neointimal  
3 hyperplasia seems to blend at 12 months in these  
4 peripheral vascular studies with the  
5 atherosclerotic process. It would seem reasonable,  
6 if there is an atherosclerotic process taking place  
7 in veins after 12 months, not to attribute that to  
8 how we handled the vein at the time of the initial  
9 anastomosis.

10 DR. WEINBERGER: Just one follow-up, if  
11 there is any kinking in the vein and you have a  
12 jet, that jet wouldn't lead to an accelerated  
13 atherosclerotic process later on as well?

14 DR. FRATER: It would happen far quicker  
15 than that. Usually, if you leave a kink in a vein  
16 there is a consequence that is soon and definite.

17 DR. WEINBERGER: Data?

18 DR. FRATER: Data? Clinical experience.  
19 I am a cardiac surgeon.

20 DR. TRACY: Dr. Bridges?

21 DR. BRIDGES: Yes, there are two points.  
22 One is to echo Dr. Weinberger's point that I don't  
23 think we know exactly. There is nothing to suggest  
24 that there can't be an interaction between  
25 mechanical factors and atherosclerosis that extends

1 beyond one year. To say that you can divide these  
2 into two discrete processes that are technical,  
3 device related and then atherosclerosis I think is  
4 unsubstantiated and you can't really defend that.

5           Furthermore, I am sure we are going to  
6 hear from Dr. Mack but his own data that was  
7 presented at the STS meeting, just in January,  
8 showed, at least in his series which I am sure he  
9 will comment on, that it was not until you got out  
10 beyond one year that you started to see a  
11 difference in MACE, that is, you know,  
12 cardiovascular events. So, that, in and of itself,  
13 also suggests that the idea of only looking at a  
14 one-year or six-month time period is clearly going  
15 to result in us missing failures.

16           DR. FRATER: The obvious issue is how long  
17 would you like it to be? Clearly, it becomes  
18 extraordinarily difficult if you are suggesting  
19 that we should wait five years, or something like  
20 that. Dr. Mack can speak for himself but I believe  
21 that in diabetes there was a difference and there  
22 may well be factors like that that make a  
23 difference.

24           DR. BRIDGES: My point is not to suggest  
25 how long we need to look, I am simply objecting to

1 the concept that we can definitively or  
2 declaratively state at this point, based on what  
3 evidence we have, that we know that six months or  
4 nine months is an acceptable time frame in order to  
5 exclude device-related issues.

6 DR. TRACY: Dr. Yancy, and then if there  
7 is time Dr. Maisel.

8 DR. YANCY: Just a very short yes/no  
9 question. I have not seen the referred to NEJM  
10 article comparing on-pump versus off-pump surgery.  
11 Were connectors used in the off-pump cases?

12 DR. FRATER: This was absolutely a study  
13 of on-pump versus off-pump vein patency.

14 DR. TRACY: Dr. Maisel?

15 DR. MAISEL: You have eloquently stated  
16 that times have changed and that historical  
17 controls are just that, historical, and you stated  
18 data that the patency rates vary greatly from  
19 institution to institution. In many respects that  
20 is a strong argument for randomized trials but you  
21 didn't come out and state that. Are you a  
22 proponent of randomized clinical trials to assess  
23 these devices?

24 DR. FRATER: You know, in the best of all  
25 possible worlds, yes. I am speaking as a cardiac

1 surgeon now.

2 DR. TRACY: Thank you.

3 DR. EDMUNDS: Did I hear you say that the  
4 one-year patency rate for off-pump proximal veins,  
5 the occlusion rate was 9-26 percent?

6 DR. FRATER: In the meta-analysis that we  
7 did between 6 and 12 months, there was a range from  
8 9.5 to 26.5 percent in this meta-analysis of some  
9 7,000 cases. In the Prog IV study--

10 DR. EDMUNDS: For hand-sewn?

11 DR. FRATER: Hand-sewn anastomoses, in the  
12 Prog IV study the patency rate was 59 percent  
13 patent at one year on pump, 49 percent patent  
14 off-pump. It was just presented at the ACC.

15 DR. TRACY: We do have to move on, I am  
16 sorry. Dr. Mack?

17 DR. MACK: My name is Michael Mack and I  
18 am a cardiac surgeon in Dallas. By way of  
19 disclosure, I am not sponsored by anybody today. I  
20 paid my own way here. I have served as a  
21 consultant in the past at St. Jude, also to  
22 Cardica. I have received research grant support  
23 from St. Jude regarding anastomotic devices, and I  
24 am also on the scientific advisory board for  
25 Medtronic and Guidant, both of which have equity

1 interests in anastomotic device companies.

2           The thrust of my presentation was to  
3 discuss saphenous vein graft patency and not our  
4 own St. Jude device paper, which has been  
5 presented, in view of the fact that I only have  
6 five minutes but I will try and get this done in  
7 four and just spend the last minute discussing  
8 that.

9           [Slide]

10           Specifically, what I would like to discuss  
11 is I thought until I looked at all this that I knew  
12 what the gold standard for saphenous vein graft  
13 patency was. Eeverybody throws around numbers but  
14 until I did a meta-analysis of the literature I  
15 really didn't know, and this is specifically to  
16 address the trial design question number one of the  
17 FDA, the gold standard of sutured anastomoses had a  
18 well-documented history of over the past thirty  
19 years, and I would like to go over those thirty  
20 years right now--

21           [Slide]

22           --or the why of saphenous graft failure in  
23 five minutes.

24           [Slide]

25           Since between 1979 and 2001 there have

1 been thirty studies published, analyzing a total of  
2 28,081 grafts.

3 [Slide]

4 Factors impacting the studies are  
5 angiogram survivors. You lose early graft  
6 occlusions resulting in death so, therefore, you  
7 are automatically losing patency in any angiogram  
8 series because you can only angiogram survivors.  
9 Studies are impacted by the completeness of  
10 follow-up, the percent of patients actually  
11 undergoing angiograms, and whether the study was  
12 done as a surveillance study or done for cause.

13 [Slide]

14 If we look at a meta-analysis of all  
15 studies that looked at 30 days or less, there has  
16 been a total of 11,000 grafts looked at. If you  
17 just skip to the number at the bottom right, the  
18 patency rate at 30 days in these 7 studies,  
19 comprising 11,000 grafts, is 87.8 percent.

20 [Slide]

21 If you now look at 3 to 6 months and look  
22 at the 10 studies published here, with a total of  
23 2,290 grafts, at 3 to 6 months 84 percent is the  
24 saphenous vein graft patency.

25 [Slide]

1           If we now go to 12 months and look at the  
2 13 studies comprising almost 12,000 grafts, the  
3 patency rate is 82.7 percent in the literature.

4           [Slide]

5           Lastly, if we look at 2 to 5 years, with a  
6 total of 3,100 grafts in these 3 studies, the  
7 patency rate between 2 and 5 years is 74.3 percent.

8           [Slide]

9           If we summarize all this, there is a  
10 significant attrition in the literature of about 12  
11 percent of vein grafts in the first 30 days.  
12 Between 30 days and 3-6 months another 3 percent of  
13 grafts are lost at that point. If we go between  
14 3-6 months to 12 months another 1.5 percent of  
15 grafts are lost. Then there is a slightly greater  
16 attrition from 2 to 5 years. If you look at  
17 overall graft patency of all 28,000 grafts done at  
18 any time, it is 84 percent.

19           [Slide]

20           Variables known to impact graft patency  
21 include age, gender, diabetes and how well the  
22 diabetes is controlled, obesity, which vessel is  
23 bypassed, the LAD, the circ. or the right, the  
24 target vessel size, the presence of distal disease,  
25 the size of the vein graft, harvest injury, whether

1 an endarterectomy was done, what the graft flow at  
2 time of implant was, individual versus sequential  
3 vein grafts, how much myocardium was supplied, what  
4 the ventricular function of the patient was,  
5 whether lipid management was tightly controlled,  
6 whether antiplatelets were used, surgeon  
7 experience.

8 [Slide]

9 Variables that are not known how they  
10 impact on graft patency has been alluded to.  
11 Whether it is done on a beating heart or an  
12 arrested heart. That recently has been called into  
13 question. And whether anastomotic connectors  
14 impact positively or negatively on the saphenous  
15 vein graft patency.

16 [Slide]

17 I think how you design your study you can  
18 get 100 percent patency at ten years if you do an  
19 LAD, do it as a sequential and a three millimeter  
20 target with no distal disease, use a small vein,  
21 have a large run-off in a thin male that does not  
22 have insulin-dependent diabetes and normal ejection  
23 fraction, does not have a hypercoagulable state, is  
24 on antiplatelet agents and is well controlled with  
25 statins. On the other hand, you can do the

1 converse of all those and you will end up with a 10  
2 percent patency rate in less than 30 days.

3 [Slide]

4 In conclusion, I think that many variables  
5 other than anastomotic connectors impact graft  
6 patency. Angiography is the only reliable method  
7 to determine patency. Meta-analysis reveals an  
8 overall saphenous vein graft patency of 80-85  
9 percent. There is no significant difference from  
10 3-6 months versus 12-16 months or, for that matter,  
11 even between 30 days and the latter two endpoints.  
12 An angiographically normal graft at the earlier  
13 study times is often likely to develop occlusion on  
14 later follow-up and, in my opinion, a 6-month  
15 angiographic endpoint is adequate to evaluate graft  
16 patency with anastomotic devices.

17 Real quickly regarding our experience, it  
18 has been published on the St. Jude device. We did  
19 find that there were events that happened after six  
20 months. These were clinical events. The study  
21 that we performed was very similar to Dr.  
22 Schoettle's. We took a one-year experience with  
23 the St. Jude device and compared it to one-year  
24 previously with a similar cohort of patients and  
25 found that there was a higher incidence of clinical

1 events in the St. Jude patients. However, these  
2 were all limited to diabetics. We looked at the  
3 non-diabetic population and we looked at all  
4 possible variable by logistic regression diabetes  
5 was the only thing that sorted out. The  
6 confounding variable in all this is that all these  
7 procedures were also done on a beating heart.

8 Thank you.

9 DR. TRACY: Thank you. Panel, you have 4  
10 minutes and 36 seconds to ask questions. Any  
11 questions? Dr. Weinberger?

12 DR. WEINBERGER: In surgical literature  
13 everyone seems to focus on patency. Are you  
14 interested at all in morphology, like quantitative  
15 angiography looking at 30 percent stenosis, 40  
16 percent stenosis? Is that information valid to  
17 surgeons?

18 DR. MACK: Absolutely. Because I do think  
19 that that is a precursor of potential total  
20 occlusion.

21 DR. WEINBERGER: And if that is the case,  
22 are your angiographic colleagues who have looked at  
23 these connectors able to assess the morphology  
24 right around the metallic connector adequately?

25 DR. MACK: I think the answer is yes.

1 DR. KRUCOFF: Not being as familiar with  
2 the surgical literature, in this list you sort of  
3 ended with do you think there is sufficient data to  
4 create a real propensity score in planning a trial?

5 DR. MACK: Yes.

6 DR. KRUCOFF: To actually create risk  
7 categories that could be sufficiently evaluated in  
8 new populations?

9 DR. MACK: Yes, I do. I think that  
10 everything I listed there--one study or another has  
11 listed those factors implicating graft patency and,  
12 yes, I think you can develop a propensity score.

13 DR. TRACY: Dr. Edmunds?

14 DR. EDMUNDS: Mike, you said that all of  
15 these were off-pump bypasses.

16 DR. MACK: In our St. Jude experience,  
17 yes.

18 DR. EDMUNDS: Were they mostly right  
19 grafts?

20 DR. MACK: First of all, we did not have  
21 any connectors placed to the LAD so they all went  
22 to diagonal circumflexes or right, and which vessel  
23 it went to, in our experience, did not sort out as  
24 a factor.

25 DR. EDMUNDS: But non-LAD?

1 DR. MACK: All non-LADs.

2 DR. EDMUNDS: And these were surveillance  
3 angiograms, not for symptoms?

4 DR. MACK: No, the surveillance was  
5 clinical events only. The only angiograms--

6 DR. EDMUNDS: So, you have bias towards  
7 symptomatic patients.

8 DR. MACK: The endpoint was not  
9 angiography. The endpoint of our study was  
10 clinical events, major adverse events at now two  
11 years of follow-up. We did not do a specific study  
12 angiogramming the patients. The only angiograms we  
13 had was in patients that were done for cause.

14 DR. EDMUNDS: The 28,000 patients were  
15 from 30 studies, weren't they?

16 DR MACK: Okay, I am mixing up your  
17 question then. Ask again, Hank.

18 DR. EDMUNDS: Well, the cohort of 28,081  
19 angiograms was from 30 papers--

20 DR MACK: Right.

21 DR. EDMUNDS: --and were those  
22 surveillance angiograms or for symptoms?

23 DR. MACK: I am sorry, I thought you were  
24 talking about our own experience with the  
25 connectors.

1 DR. EDMUNDS: No, I am sorry, Mike.

2 DR. EDMUNDS: No, all of those were  
3 surveillance. Any that was done for cause and I  
4 did not include in that. All those were  
5 surveillance studies. Similarly, there were a  
6 couple of other studies that looked at just  
7 saphenous vein graft, the LAD, I did not include  
8 those because those were abnormally high.

9 DR. TRACY: Dr. Bridges, did you have a  
10 question?

11 DR. BRIDGES: My question really is that  
12 given that in the results you presented recently  
13 there was a difference in major adverse  
14 cardiovascular events, I guess in the manuscript  
15 that I have seen a draft of it was limited to  
16 diabetic patients. However, those were non-insulin  
17 dependent diabetics, I believe, and I was wondering  
18 if you had a hypothesis as to why non-insulin  
19 dependent diabetics would be different than insulin  
20 dependent diabetics. Given that, should we be then  
21 separating diabetics from everyone else in terms of  
22 determining the applicability of these devices?

23 DR. MACK: That is an excellent question,  
24 and we were a little bit surprised to find that  
25 that was the case also because from the stent

1 experience you would expect it would be more so in  
2 insulin dependent diabetics but such was not the  
3 case. We have hypothesized that perhaps it was due  
4 to the fact that with non-insulin dependent  
5 diabetic oral agents the blood sugar is not as  
6 tightly controlled, but we have no proof; it is  
7 total hypothesis.

8 I also think that the way that we look at  
9 diabetes now, today, is totally blurring the line  
10 between insulin dependence and non-insulin  
11 dependent diabetics. I think we have a lot of  
12 metabolic syndrome patients who are actually Type 2  
13 diabetics but are insulin dependent and we are  
14 actually categorizing them as insulin dependent  
15 when, in fact, they really should not be.

16 DR. TRACY: Thank you. Dr. Slaughter?

17 DR. SLAUGHTER: Thank you. I was asked to  
18 speak today on behalf of Converge, and I am a U.S.  
19 investigator for their ongoing trial for distal  
20 anastomotic studies and they did pay my travel here  
21 but I have no other financial relationship with  
22 them.

23 [Slide]

24 To date so far we have heard predominantly  
25 about proximal anastomotic devices and what I would

1 like to do is to tell you a little bit about a  
2 current and ongoing look at distal anastomotic  
3 devices.

4 [Slide]

5 Certainly, this comes up in many issues  
6 and I don't think we need to belabor the fact but  
7 perhaps at the end I will comment briefly on some  
8 of the other questions asked, but there is still no  
9 question, and it is really sort of one of the  
10 unspoken issues for any outcome for the patient,  
11 and that is, you know, the quality of anastomosis  
12 and the overall revascularization and long-term  
13 patency. Certainly surgeon skill is very  
14 important. There are also the other issues of the  
15 anatomy, disease state, access and visibility that  
16 would affect these things. But all these things  
17 are very important in determining not only acute  
18 but long-term graft patency and the overall outcome  
19 for the patient.

20 [Slide]

21 This has been brought up now several times  
22 and I think is very important. This is just  
23 another way of presenting it. It is looking at  
24 sort of the time scale injury. That is, as was  
25 brought up by Dr. Weinberger as well, there is no

1 question that there is good information and good  
2 data as to the initiation of the injury,  
3 inflammation and then subsequently intimal  
4 hyperplasia. As a rule of thumb, the idea is that  
5 within, say, six to eight weeks the injury has  
6 stopped. I don't think anybody in their right mind  
7 would argue that there is not heterogeneity and  
8 certainly there are differences within patients.  
9 Certainly that would show up as stenosis and  
10 changes in morphology, as you mentioned.

11           But the idea is there is reasonably good  
12 science and information to suggest that within  
13 about 60 days a vascular anastomosis has healed,  
14 particularly within the coronary-arterial tree.  
15 So, beyond that time, if there are graft failures,  
16 the question is what are they due to, and it is  
17 generally due to ongoing atherosclerosis, intrinsic  
18 patient factors and/or perhaps a lack of medical  
19 therapy such as antiplatelet agents, aspirin and/or  
20 Plavix.

21           So, you know, if hand-sewn anastomosis is  
22 so perfect, why are we here today? The issue is  
23 they are not perfect and there certainly is room  
24 for improvement. Certainly, by hand sewing in a  
25 bad distal vessel it is calcified in a diabetic.

1 They have lateral calcification. By piercing them  
2 with needles--we all had that experience, you end  
3 up with plaque rupture. You have hemorrhage within  
4 the media. The idea is this is a traumatic event.

5 [Slide]

6 The other is reliability. The issue is  
7 how can you do it day to day, 20,000 a year. The  
8 idea is you want to make it as reliable as  
9 possible and it needs to be reproducible between  
10 different surgeons at different institutions.

11 The other is it must be reversible. The  
12 idea is if you don't like it you have to cut the  
13 suture, take it out and redo it. You want to be  
14 able to do the same thing, perhaps in a less  
15 traumatic fashion, with a coupler device.

16 The other is it must be easy to use. The  
17 idea is if anybody walks up to the podium and is  
18 giving you a talk, they basically should all be  
19 able to have the same results without any  
20 significant extensive training.

21 The other is I think we do need to realize  
22 there are differences between proximals and  
23 distals. I don't think we need to spend a lot of  
24 time on this today but the main two differences are  
25 the flow dynamics which clearly are different at

1 the proximal and distal ends, as well as tissue  
2 characteristics. On the tissue characteristics, on  
3 the right it is either going to the aorta or vein  
4 aorta or artery depending on which you conduit you  
5 use. Certainly for distal anastomoses what you are  
6 looking at is vein to coronary artery or an  
7 arterial conduit to an artery but it is a very  
8 different scenario.

9           Also, with flow dynamics there is no  
10 question that the size or the shape of the opening  
11 or the angle of the take-off is very important, the  
12 pressure differential, as well as the vessel  
13 diameter throughout the length.

14           [Slide]

15           I think one other issue which hasn't been  
16 brought up today which does need to be mentioned,  
17 at least just to bring it up, is actually the type  
18 of material. I think this sort of goes into the  
19 heterogeneity or perhaps ongoing injury to intimal  
20 hyperplasia. These are not new materials. They  
21 have all been used before. They have all been used  
22 in intravascular scenarios and the idea is there is  
23 good evidence to suggest, whether it is nitinol,  
24 stainless steel, titanium, that they are  
25 compatible, and I don't think that we can sort of

1 imply or say that they are intrinsically the source  
2 of perhaps later stenoses or some ongoing failures  
3 beyond the eight-week time period. Certainly there  
4 is the heterogeneity of healing in some patients  
5 but it is a relatively small number. It is like a  
6 cheloid. Some patients get cheloids but not all.  
7 The answer is you see it as it progresses. If you  
8 follow them and you look for it you can identify  
9 who those patients are.

10 [Slide]

11 I would like to just show you a histologic  
12 series which I think is interesting in helps people  
13 visualize. Really the sort of best description I  
14 think for the Converge distal anastomotic device is  
15 that of sort of a compression clip. The idea is it  
16 is two frames which are expandable. In the upper  
17 right it sort of gives you the diagrammatic picture  
18 of a graft into the artery. The important thing  
19 here is that you now are able to mechanically  
20 manipulate flow dynamics as well as other  
21 engineering aspects so you get a perfect 30 degree  
22 take-off; you get perfect dynamics. You won't get  
23 turbulence at the site of the anastomosis.

24 The left side shows the bypass graft,  
25 which is CABG going down to the circumflex artery.

1 I think the important thing here is this was done  
2 at 90 days but, once again, the idea is it is  
3 completely endothelialized so the idea is if you  
4 get an angiogram at six months and you have a  
5 normal lumen you have no narrowing. The idea is  
6 are you going to have ongoing intimal hyperplasia  
7 that would be an unexpected finding? I think the  
8 answer is no.

9 DR. TRACY: If you could finish up in the  
10 next few sentences.

11 DR. SLAUGHTER: Sure, I can finish up in  
12 about 30 seconds.

13 [Slide]

14 The idea is you see very clearly that it  
15 is a well healed anastomosis and you have the  
16 advantages.

17 [Slide]

18 This has already been brought up. The  
19 idea is are historical controls acceptable? I  
20 think the answer is yes.

21 [Slide]

22 There is no question there is lots of  
23 existing data. We have also lots of information to  
24 suggest not only at seven days but at years out  
25 that you can evaluate intimal hyperplasia.

1 [Slide]

2 Certainly angiography--we know the causes  
3 of failure, early failure and what we need to do is  
4 differentiate between a device failure and ongoing  
5 atherosclerosis.

6 [Slide]

7 I will just show--

8 DR. TRACY: I am sorry, we are just going  
9 to have to cut this off if we are going to have  
10 time for questions from the panel.

11 DR. SLAUGHTER: I apologize.

12 DR. TRACY: We have three minutes left for  
13 questions from the panel. Anybody? Dr. Hirshfeld?

14 DR. HIRSHFELD: I would just point out  
15 that in the coronary stent experience if we used a  
16 two-month follow-up we never would have discovered  
17 restenosis.

18 DR. TRACY: Dr. Krucoff, did you have a  
19 comment?

20 DR. KRUCOFF: I would just also say that  
21 in the stent experience I think if we started with  
22 historical controls based on lung literature, we  
23 would have left a lot of important information out.

24 DR. SLAUGHTER: I think the one difference  
25 though, and this has come up I think in other

1 discussions with the FDA panel, is that although it  
2 uses a similar material and it is stent-like, it is  
3 not a stent. The idea is it is just the edges that  
4 are present along the edges of the coronary artery.  
5 It is not compressed plaque and the idea is it is  
6 very different. It is really sort of a compression  
7 clip that applies the vein graft to the distal  
8 coronary artery.

9 DR. TRACY: Dr. White?

10 DR. WHITE: I think there is no evidence  
11 for that, and I think everything that we have heard  
12 today sounds like it is a stent, although a stent  
13 in a graft. So, the question would be if you don't  
14 believe it is a stent, then you should show us data  
15 that suggested that intimal hyperplasia within the  
16 tube is not the primary cause of these closures.

17 DR. SLAUGHTER: Sure.

18 DR. YANCY: And because of that, I think  
19 it is even more important to state that historical  
20 controls would be really problematic I think.

21 DR. TRACY: Any other comments from the  
22 panel?

23 [No response]

24 Thank you. Is Mr. Lotti here?

25 [No response]

1 We will move on then to Dr. Martin.

2 DR. MARTIN: Good morning. As so many  
3 members of the panel have already suggested,  
4 including Dr. White, I can make my comments brief.  
5 My name is Dr. Frank Martin. I am Chairman of the  
6 Department of Cardiology at Methodist Care in  
7 Memphis, one of the largest private hospitals in  
8 the country. I have no financial ties with any  
9 anastomotic device companies or, for that matter,  
10 any stent companies.

11 My historical experience, I trained with  
12 John Simpson back in 1985, '86, and have  
13 relationships with many of the members of this  
14 panel. I trained with people who are icons today,  
15 like Paul Yak, Paul Tierstien, Dean Keriakus, Met  
16 Selman, Morris Bookbinder, Rock Califf, Eric Topal  
17 and did interventional cardiology until  
18 approximately four years ago and made a life style  
19 change, and now I do only diagnostic caths and do  
20 my chairmanship. Also as discussed earlier, in the  
21 late 1980s, with Dr. Chris White, we did brachy  
22 therapy because some of the early DCA slides showed  
23 needle intimal hyperproliferation similar to  
24 cancer.

25 That having been said, I, as many of you

1 all, have honed this sixth sense of skill with  
2 cardiology over the last 15 years of practice. Dr.  
3 Phil Schoettle, who has already presented here  
4 today, and I have worked collaboratively for the  
5 last 20 years. We basically make a good team  
6 because he knows what I do and I know what he does.

7 Our group opened one of the first  
8 outpatient cardiac cath labs and it was a labor of  
9 trust on his part. Both of us have a sixth sense  
10 about when patient is dissected and needs to go to  
11 surgery urgently, and have always had that sort of  
12 feel. Obviously, in the early days of intervention  
13 with PRCA lots of patients went to CABG and, of  
14 course, more and more patients went to CABG at that  
15 time than do now.

16 So, imagine my chagrin in September of  
17 2002 when I cath'd an ER nurse friend of mine and  
18 found one occluded and two stented Symmetry aortic  
19 connectors, the first patient I had ever seen.  
20 When Dr. Schoettle referred to September, 2002 that  
21 was the watershed moment. I walked out of that  
22 cath, called him and said, Dr. Schoettle, I don't  
23 know what this device is but it is a stent and it  
24 will act like a stent and it will always be a  
25 stent. I said, what is it? What do we know about

1 it? And, he basically told me his experience over  
2 the last ten months.

3 At that point I found an interventional  
4 colleague of mine and said, what are these devices?  
5 He said he had been stenting them since April; he  
6 didn't know much about them. I did an Internet  
7 search and found out they were made in nitinol, and  
8 realized at that point in time that no  
9 cardiologists were involved in either the research,  
10 the design, the implementation or the roll-out of  
11 this device basically because all the  
12 cardiologists, interventional cardiologists,  
13 especially know the problems associated with that.

14 It took me about 45 days, almost two  
15 months, with multiple interventional colleagues of  
16 mine and surgeons in Memphis to have it withdrawn  
17 from all the shelves of all three hospitals in  
18 Memphis, Tennessee, and that was in the latter part  
19 of fall of 2002.

20 As patients have returned to the clinic,  
21 dozens, and dozens, and dozens have been found to  
22 have virtually total and/or subtotal occlusions of  
23 these devices. The first contact I had with St.  
24 Jude was in December, 2002 after I had gone to TCT,  
25 in September I believe, and HA in November, telling

1 them about the problem with these devices and why  
2 they acted like stents. Finally, they walked in on  
3 me while I was cath'ing a 70 year-old ob/gyn who  
4 had two patently occluded Symmetry aortic  
5 connectors. Basically, I said this is the problem.  
6 You don't understand anginal syndrome because most  
7 of these patients won't come back with chest pain  
8 for multiple reasons--denervation of the heart;  
9 more LV dysfunction problem. You don't understand  
10 the role of clopidogrel or Plavix in these patients  
11 because most of them go to surgery without Plavix  
12 on board, and you don't understand the fact that in  
13 stent pathology, which we obviously cath a lot, you  
14 can have one patent graft, for instance the LIMA  
15 which most of these patients get, and the other two  
16 can subtotally occlude slowly and their only  
17 symptom is LV dysfunction.

18 We, as cardiologists, as members of this  
19 panel, diagnose ischemia. We send these patients  
20 to a surgeon for treatment and continue to reattach  
21 and stent these folks. They will come back for  
22 years with their LIMAs. An anecdotal experience of  
23 one surgeon in Jonesboro, Arkansas, close by  
24 Memphis, asked two of the cardiologists in his  
25 community, "so what's up with this Symmetry aortic

1 connector?" And the cardiologists response was,  
2 "are you having any problems?" And he said, "well,  
3 I don't know." And they said, "well, don't worry  
4 about it."

5 He wasn't satisfied with that, came to  
6 Memphis, we cath'd him and his two connectors were  
7 occluded and his lumen was patent. After  
8 intervention he told me that as an oral surgeon he  
9 uses nitinol every day to induce scar tissue  
10 formation and keep bridge reconstruction in place.  
11 The fact that you auger a hole in the aorta, hold a  
12 finger over it beginning the platelet clotting  
13 cascade, implant a metallic device with hooks  
14 without the benefit of loading doses of Plavix or  
15 predictable absorption is inconceivable.

16 The idea of a connector makes sense for  
17 improvement of stroke risk, however, I feel the  
18 present device should be withdrawn and should have  
19 been withdrawn years ago. Basically, I think the  
20 cardiologists need to be involved in any future  
21 trials or designs and I think to do otherwise is a  
22 violation of our sacred oath to our patients.  
23 Thank you.

24 DR. TRACY: Thank you. Any questions from  
25 the panel? Comments?

1 [No response]

2 Thank you. Dr. Hausen?

3 DR. HAUSEN: By way of introduction, my  
4 name is Bernard Hausen. I am the present CEO of  
5 Cardica. My background, I am a cardiac surgeon by  
6 training. My financial conflicts are inherent with  
7 my position, otherwise I have none other.

8 [Slide]

9 I want to use this opportunity to show you  
10 new generation of products that we are developing  
11 beyond the pioneers in this field that we have been  
12 discussing so far.

13 [Slide]

14 We have two products in the pipeline. One  
15 is a distal anastomosis system.

16 [Slide]

17 It is called C-Port and it is based on the  
18 principle of simulating interrupted stitch distal  
19 anastomosis by applying a set of eight implantable  
20 clips, all simultaneously, and performing  
21 arteriotomy with the push of one button. This type  
22 of a system results in a minimal amount of metal  
23 exposure. It is applied in distal anastomosis  
24 and it is in clinical evaluation as we speak.

25 [Slide]

1           This is just a video showing how it works.  
2 This is a 1.5 mm LAD. You insert the anvil; pull  
3 it out and you are basically done; place one stitch  
4 to close the anvil insertion hole. This is a 1 mm  
5 diagonal cadaver heart and shows how it works.

6           This technology, we believe, will enable  
7 beating heart surgery as it is quick and does not  
8 require any temporary ischemia of the myocardium  
9 during placement.

10           [Slide]

11           We have a second device which is called  
12 PAS-Port. It stands for proximal anastomosis  
13 system, and it is a second generation proximal  
14 system. We have the advantage of being a company  
15 that is going to be able to take advantage of the  
16 knowledge from the predecessors, predicate devices.

17           [Slide]

18           So we were able in our design to spend a  
19 lot of time on key improvements from things we have  
20 learned from the other devices. We have focused on  
21 trying to minimize or completely eliminate  
22 endothelial trauma of the graft during loading. We  
23 wanted to minimize blood-exposed non-endothelial  
24 tissue, i.e., metal exposure. We wanted to  
25 maximize the orifice area and reduce the incidence

1 of kinking by a low profile.

2 [Slide]

3 We did that by basically having nothing  
4 touch the endothelium of the vein during loading or  
5 deployment. This is a cross-section of the  
6 implant.

7 [Slide]

8 We have a minimal amount of metal exposed  
9 with the stainless steel device. It is the same  
10 material as is being used for coronary stents. And  
11 we wanted to maximize the orifice, especially for  
12 small vein grafts, and have a very low profile  
13 height.

14 [Slide]

15 For all this we have done a clinical  
16 trial. We have had a lab cardiologist review our  
17 data by QCA and determine what is the amount of  
18 narrowing of the implant versus the graft body.  
19 They first looked at some hand-sewns that were done  
20 concurrently in those patients and, as you can see,  
21 the average narrowing of a hand-sewn is about 5  
22 percent at discharge and about 18 percent at 6  
23 months. This is in agreement with all the  
24 published literature.

25 [Slide]

1           Then we asked them to look at the PAS-Port  
2 data. What you find, and you can hardly see this,  
3 this is a minus 7 percent narrowing, i.e., the  
4 grafts at the anastomosis are larger than they are  
5 in the graft body and that is by design. That is  
6 how the implant has been designed.

7           Now at 6 months, the most important  
8 figure, the average narrowing is 3 percent compared  
9 to 18 percent in hand-sewns. I propose that if a  
10 device had a problem at discharge or at 6 months  
11 you would be seeing that in this quantitative  
12 analysis. If you don't see it because the  
13 injurious event was at the time of surgery, you are  
14 very unlikely to see it going forward besides the  
15 normal decay of a vein graft, as alluded to by the  
16 previous speakers.

17                   [Slide]

18           So, Cardica's regulatory position is we  
19 are applying for 510(k) clearance based on  
20 prospective multicenter non-randomized trials, and  
21 our primary study endpoint for this distal device  
22 is vessel patency at discharge and 6 months, and  
23 for the proximal device performing a vessel patency  
24 study at 6 months with QCA. Thank you very much  
25 for your attention.

1 DR. TRACY: Thank you. Any questions?  
2 Dr. White?

3 DR. WHITE: I just noticed that on the  
4 last slide you said you were going to do MRI  
5 follow-up on these metal grafts. How are you going  
6 to do that?

7 DR. HAUSEN: We have done that on the  
8 proximal anastomotic device. Basically, with the  
9 gadolinium contrast injection you can see--the only  
10 thing CTs and MRIs allow you to do is determine is  
11 the graft patent or not. You cannot evaluate the  
12 degree of stenosis at the implant. So, a preferred  
13 method is a quantitative angiography.

14 DR. WHITE: Do you have experience with  
15 MRI?

16 DR. HAUSEN: We have done five MRIs in the  
17 patients in this study.

18 DR. WHITE: And also CT?

19 DR. HAUSEN: And CT too and MDCT.

20 DR. WHITE: And there is no difference in  
21 your hands?

22 DR. WHITE: I like the MDCT much better.  
23 I think the image is much clearer. The 3-D  
24 reconstructions are very impressive.

25 DR. AZIZ: And how does that correlate

1 with angiograms?

2 DR. HAUSEN: It depends on what your  
3 outcome variable is. If you want to just know if  
4 the graft is patent or not, there is a very, very  
5 good correlation. That has been shown in the  
6 literature. If you need more than that, if you  
7 need to know is there a degree of narrowing, that  
8 will not suffice.

9 DR. AZIZ: If you do distal anastomosis if  
10 you have bleeding, how can you control that? Can  
11 you put a regular stitch over that?

12 DR. HAUSEN: Yes, you can. It is the same  
13 as a steel device. It is very firm. The pull-out  
14 force of this device is very high because stainless  
15 steel is three times stiffer than nitinol. So,  
16 what you do, you just place the first string around  
17 the anastomosis and slowly tighten it. That brings  
18 the aorta closer to the implant--

19 DR. AZIZ: If you do distal anastomosis if  
20 you have bleeding, can you do regular stitches?

21 DR. HAUSEN: Yes.

22 DR. AZIZ: You have obviously shown a vein  
23 graft. If you had an arterial graft can you use  
24 your same distal anastomotic site for that?

25 DR. HAUSEN: This generation of device,

1 no; the next generation, yes.

2 DR. TRACY: Dr. Bridges?

3 DR. BRIDGES: You showed differences in  
4 percent stenosis of the proximal anastomoses at  
5 discharge and at 6 months.

6 DR. HAUSEN: Yes.

7 DR. BRIDGES: What about occlusion or  
8 patency at the same time points?

9 DR. HAUSEN: We have 87.9 percent patency  
10 rate so we had 6 occlusions in 50 implants, which  
11 is 100 percent in agreement with the historical  
12 data from the meta-analysis you saw and we did too.

13 DR. BRIDGES: So, how would you interpret  
14 the fact that in spite of having a higher orifice  
15 area or diameter you have the same patency at the  
16 6-month time point?

17 DR. HAUSEN: That is wonderful proof that  
18 it has nothing to do with the connector. It is  
19 probably your distal run-off or any of the other  
20 200 factors that Dr. Mack said.

21 DR. AZIZ: If you had a very thick  
22 proximal ascending aorta--

23 DR. HAUSEN: Yes?

24 DR. AZIZ: --sometimes you do a hand-sewn  
25 vein graft that dunks in and obviously you don't

1 want that.

2 DR. HAUSEN: Yes.

3 DR. AZIZ: Does your anastomosis  
4 technique--where would that fit in? Would the vein  
5 also dunk in?

6 DR HAUSEN: It is inverted over the  
7 implant so it is in the lumen but, because it is a  
8 stainless steel implant, it props the anastomosis  
9 open and you will not have lumen reduction, if that  
10 is where you are heading towards. And we have  
11 shown that, minus 7 percent widening of the  
12 anastomosis is evidence that that is exactly what  
13 the implant does and it accommodates the varying  
14 thickness of the aortic wall because it is like a  
15 paper clip. It can adjust to varying thicknesses.

16 DR. AZIZ: And the angle at which it comes  
17 off proximally, is that oblique or head-on?

18 DR. HAUSEN: It is theoretically 90  
19 degrees. We asked our core lab to evaluate that  
20 too. There are hardly any at 90 degrees. They  
21 vary from 10-70 degree take-offs. Because the  
22 hinge point is so small, only 1.5 mm, the vein can  
23 come off almost at any angle it wants to.

24 DR. AZIZ: So, could you take the proximal  
25 along through the transverse sinus and pull it

1 through?

2 DR. HAUSEN: You could, yes.

3 DR. AZIZ: You could?

4 DR. HAUSEN: Yes.

5 DR. EDMUNDS: What is the size of the shoe  
6 inside the vessel?

7 DR. HAUSEN: The shoe inside the vessel?

8 DR. EDMUNDS: Against which you are  
9 putting the clamps down. The part of the device  
10 that goes inside the vessel, what are the  
11 dimensions of that shoe of the device?

12 DR. HAUSEN: There is really nothing  
13 inside the vessel. The vein is pulled through the  
14 implant and inverted so there is no metal inside,  
15 except for the prongs that penetrated the vein and  
16 then go outward. I would be more than happy to sit  
17 down afterwards and show you maybe some work. I am  
18 kind of limited by the time here.

19 DR. AZIZ: Can you do a sequential of this  
20 for the distal anastomosis?

21 DR. HAUSEN: No. Well, you could if you  
22 did your side by side by hand, absolutely.

23 DR. TRACY: Thank you very much. Prof.  
24 Klima?

25 PROF. KLIMA: Ladies and gentlemen,

1 members of the panel, my name is Uwe Klima.

2 [Slide]

3 I am a full professor at Hanover Medical  
4 School for Cardiac Surgery. The financial  
5 disclosure I have to make is that Ventrica paid for  
6 my trip here and my lodging, and Ventrica provided  
7 us with an unrestricted grant for preclinical  
8 testing of an anastomotic device three years ago.

9 [Slide]

10 I expected a talking time of ten minutes  
11 and I will try to cut that down to five minutes.  
12 Basically, what I want to talk about is mechanisms  
13 of how wound healing takes place after an  
14 anastomosis; give you some of our clinical  
15 experience with hand-sewn anastomosis, especially  
16 with our MIDCAB series; more update or experience  
17 with our anastomotic devices; and I will have a  
18 little discussion of appropriate methods and  
19 follow-up time frames for CABG surgery.

20 [Slide]

21 As background, we all know that hand-sewn  
22 anastomoses now are more or less on the market for  
23 more than four decades. Everything is pretty much  
24 well tested and evaluated. We have a pretty clear  
25 understanding of what happens to an anastomosis.

1 What happens is a healing response--at what time  
2 frame this will be stable. So, I will go into  
3 details with my next slide.

4 [Slide]

5 There are several publications out now  
6 which tell us exactly what happens after an  
7 anastomosis has been performed. We know there is a  
8 lot of trauma coming after surgery. Cell  
9 proliferation is coming out. And the most  
10 important message that comes out of this  
11 publication, for example, is that the repair  
12 process is about to be completed two months after  
13 surgery.

14 [Slide]

15 We wanted to know what is happening with  
16 anastomotic devices. Is it the same response? Can  
17 we expect the same thing to happen? Filsoufi  
18 published, from Boston. He tested the Ventrica  
19 device and what is happening after implantation two  
20 months, three months and six months after surgery,  
21 and we could see that there is a single layer of  
22 endothelium covering after two months, three months  
23 and after six months and there was no sign of any  
24 inflammatory response at the site of the  
25 anastomosis.