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CIRCULATORY SYSTEM DEVICES PANEL

Volume I

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P R O C E E D I N G S

DR. CURTIS: The first order of business is that we have a conflict of interest statement, to be read by Dr. Stuhlmuller.

DR. STUHLMULLER: The following announcement addresses conflict of interest issues associated with this meeting, and is made 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 potential conflict of interest involved, is in the best interest of the government.

We would like to note for the record that the Agency took into consideration certain matters regarding Dr. Anne Curtis, Jeffrey Brinker and George Vetovec. Each of these panelists reported interest in firms at issue on matters not related to what is being discussed today. Since these matters are not related to the specific matters before the Panel, the Agency has determined that they may

participate fully in today's discussions.

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

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firms or products they may wish to comment on.

Appointment to temporary voting status: pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 20, 1995, I appoint the following people voting members of the Circulatory system Devices Panel for this meeting of September 15 and 16, 1997: Dr. Anne B. Curtis, Dr. Salim Aziz, Dr. Michael D. Crittendon, Dr. Michael J. Domanski, Dr. Renee S. Hartz, Dr. James R. Pluth, Dr. David J. Skorton, Dr. Cynthia M. Tracy, Dr. George W. Vetovec, Dr. Ronald M. Weintraub. For the record, these people are special government employees and are consultants to this Panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and

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have reviewed the material to be considered today, at this meeting. It is signed D. Bruce Burlington, M.D., Director, Center for Devices and Radiological Health, dated September 15, 1997.

Appointment to temporary status as acting chairperson: temporary status as acting chairperson is requested for Anne B. Curtis, M.D. for the Circulatory System Devices Advisory Panel meeting on September 15 and 16, 1997. It is signed D. Bruce Burlington, M.D., Director for the Center of Devices and Radiological Health, dated September 15, 1997.

DR. CURTIS: The first thing I would like to do this morning is have us go around the Panel here and introduce ourselves since there are several new members, in particular.

I am Anne Curtis, cardiac electrophysiologist, University of Florida.

DR. VETROVEC: I am George Vetrovec. I am a clinical cardiologist and interventional cardiologist. I chair the Division of Cardiology at the Medical College of Virginia, Virginia Commonwealth University in Richmond, Virginia.

DR. DOMANSKI: Mike Domanski. I am a cardiologist and I head the clinical trials group at the National Heart,

Lung and Blood Institute.

DR. GILLIAM: I am Roosevelt Gilliam. I am a clinical cardiac electrophysiologist with the Virginia Cardiovascular Specialists and in private practice in Richmond, Virginia.

DR. SIMMONS: I am Tony Simmons. I am a cardiac electrophysiologist at the Bowman-Gray School of Medicine.

DR. HARTZ: Renee Hartz, I am head of the Section of Cardiac Surgery at Tulane University.

DR. CALLAHAN: Tom Callahan, Director of Cardiovascular, Respiratory and Neurology at FDA.

MR. JARVIS: Gary Jarvis. I am the industry representative to the Panel.

DR. TRACY: Cindy Tracy, I am an electrophysiologist at Georgetown University Hospital.

DR. WEINTRAUB: Ronald Weintraub, I am a cardiac surgeon at Beth Israel Deaconess Medical Center in Boston.

DR. SKORTON: I am Dave Skorton and I am a cardiologist, a professor of medicine and electrical engineering and vice president for research at the University of Iowa.

DR. PLUTH: I am Jim Pluth, cardiovascular surgeon, Mayo Clinic.

DR. AZIZ: I am Salim Aziz, Associate Professor of

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Adult Cardiac Surgery at the University of Colorado, in Denver.

DR. CRITTENDON: I am Michael Crittendon and I am a cardiac surgeon at the West Roxbury VA.

DR. STUHLMULLER: I am John Stuhlmuller. I am a cardiologist with the Food and Drug Administration, and executive secretary for the Panel.

DR. CURTIS: I don't believe there is any old business for us to be taking care of today, nor is there any specific new business that I am aware of.

I would like to move directly to the open public hearing. As far as I am aware, no one has previously requested time to address the Panel. Is there anyone in the audience who would like to address the Panel before we get started with the other business?

[No response]

What I would like to do now is move on to an overview of the FDA Product Development Protocol Program, and that is going to be presented by Dorothy Abel.

FDA Product Development Protocol Program

MS. ABEL: Thank you. Good morning. This morning I am going to give you an overview and an introduction to the Product Development Protocols, which I will be referring to as PDPs.

[Slide]

The PDP is an alternative is an alternative to the IDE and PMA process as defined in Section 515[f] of the FD&C Act. It is important to note that the PDP isn't just replacing the PMA process but it actually will be one document to take the place of the pre-IDE, IDE, pre-PMA, PMA and PMA supplement. So it is a comprehensive document that will take the device basically from conception through marketing and postmarketing.

[Slide]

There is to be no reduction in the overall assurance of safety and effectiveness in using this document for this type of approval process. The difference between this process and the current system that you are familiar with is that there is an emphasis on the protocol and criteria versus data evaluation.

[Slide]

The advantages of this process is that it is proactive and not reactive, including the advisory panel input. That is, the advisory panel will be asked to come in on the protocols as opposed to the final data. The process is intended to be an economical approach, and time and money are not spent on testing that does not address all safety and effectiveness issues.

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There should be reduced FDA resources with this process, given that the manufacturer has the responsibility to follow the plan so that there are to be no surprises in the end.

In addition, the review of the PDP data is sequential rather than all at the end, and also there is no duplication as we currently have with the IDE followed by the PMA.

There should be reduced time to market since, once again, if the plan is followed the PDP provides a streamlined marketing clearance route, which I will summarize.

I will be discussing each of these phases in more detail but I thought it would be useful to just provide an overview of the process.

Initially, the manufacturer will submit a pre-submission and there will be a filing review of it. At that time the FDA will determine whether a PDP is an appropriate route for a particular type of device. The full PDP is submitted and there will be an FDA review including the advisory panel review.

Actually, it sounds like they submit the document and we all get together and talk about it, but I see that as being more of an interactive process. We are all going to

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try and figure out the best method for demonstrating the safety and effectiveness of the device.

There is a preclinical phase, of course, followed by a clinical phase, and then a notice of completion is submitted and the FDA determines that the PDP is completed.

[Slide]

As I mentioned, initially there is a pre-submission.

[Slide]

The pre-submission will include information such as the indications for use, the device description, identification of the appropriate guidances and standards, some basic manufacturing information, background information, a summary of the planned testing, and that will include not only a list of the tests but the rationale for why that testing will, again, provide the answers we need in order to determine a determination of the safety and effectiveness of the device. The summary will also include the initial acceptance criteria, the pass/fail criteria that the company thinks that they will be able to demonstrate. There will be a chronology, that is, more of a developmental plan to say, you know, this is the type of information we are going to provide before going on to the next phase, that sort of thing. Naturally, there is some administrative

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information also.

[Slide]

The FDA will review the summary and, in not more than 30 days, determine whether the product appears to be appropriate for the PDP process. Once the PDP is submitted the FDA has 120 days, which may or may not include that initial 30 days, to approve the PDP. As I mentioned, this actually should be an interactive process, and this is the stage where the panel provides their input.

I will talk a little bit more about what will be included in the contents of the PDP. Of course, the contents will be extensive because, again, this one document is intended to take the place of both the IDE and the PMA. The summary that I described just a couple of slides ago will be incorporated with some additional detail as necessary. Comprehensive protocols will be included, which I will talk about a little more in a minute. Quality systems and manufacturing information is provided; and some important administrative information, such as modification plans throughout the development of the device. Finally, plans for reporting are included, specifying both the format and the timing of these reports.

[Slide]

The protocols and methodology not only include how

things are to be done but, again, the justification for why the protocols will be appropriate to demonstrate the safety and effectiveness of the device. Again, the success/failure criteria will be outlined in those protocols. There will be much more specific information on items such as data analysis because, again, the idea is to proactively spell out everything that will be done; how it will be reported; how a determination will be made as far as whether it is appropriate or not. So all that information is included in the protocols which will be reviewed by the panel. Again, we are going to agree to the appropriateness that is to demonstrate safety and effectiveness before they are conducted, and that is assuming that they are conducted as planned.

[Slide]

After the PDP is approved, the manufacturer initiates the preclinical phase of the study. Then they will notify the FDA that they intend to move on to the clinical phase. The clinical data is developed and reported to the FDA as planned.

These reports can include progress reports where data are provided as they become available. Also, before the notice of completion is submitted there is a final report that will basically wrap up all the information that has

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previously been supplied, including a complete table of contents of the entire PDP, all preclinical reports not previously provided, and then the format for the summary of the safety and effectiveness so that we can know exactly what that will look like before the final notice is submitted, and final draft labeling. Also, there will be a notice that the firm is ready for inspection before the notice of completion is submitted.

[Slide]

When all the studies are completed the notice of completion is submitted and, within 90 days, the FDA declares the PDP complete. Then the product can go to market.

The notice of completion includes a declaration by the sponsor that the PDP has been completed as agreed. A final clinical report is provided; summary of safety and effectiveness data and the device label. As long as the protocol is complied with, the results are as anticipated or required, and there is an adequate showing that the device is safe and effective as labeled, the FDA declares the PDP complete and the device goes to market.

[Slide]

Postmarket report requirements are similar to the PMA. There may be some differences in terms of the time

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frame of reporting where there will be a sunset clause--if you stop manufacturing the device you no longer have to report. It may be that you will be able to report on a yearly basis initially, switching to every two years, switching to every four years, as agreed upon on the PDP.

[Slide]

Finally, if you really want to know about the PDP process, look on the Worldwide Web. And there will be some additional information that will appear there this Friday that will include a general outline of what we conceive the PDP may look like.

So if there are any questions about the PDP process, I would be happy to answer them.

DR. SKORTON: I understand that an important part of the process is an agreement with the manufacturer before the fact about how the clinical study will look, and if that is adhered to that will streamline things. What is the role of the Panel and what happens two years later when the Panel convenes if one or more Panel members don't agree with the way the study was originally set up, either statistically or whatever, but the manufacturer has followed the original agreement with the FDA? What is the role of the Panel?

MS. ABEL: Unless there is a safety and effectiveness issue that can be presented, that you could

show that there is a risk to public health if the manufacturer follows the plan as provided, there really isn't a mechanism to go back and say that, you know, there is a differing opinion of the current Panel. Basically, what we agree to up front is what we have to follow through with unless there is a reason to change that.

DR. SKORTON: Just one more quick question, is there a role for the peer review group in agreeing to the original design of the clinical trial, or is that all done by FDA staff?

MS. ABEL: The process, hopefully, will involve more than just FDA staff and the Panel. There is an emphasis on attempting to get professional societies and other types of consulting members involved so that, again, they will present to the Panel actually and will be able to provide a more convincing argument as to why the plan is appropriate.

Are there any other questions?

[No response]

Thank you.

DR. CURTIS: I think we can go ahead and start now with the first company presentation today, the premarket approval application P970002, Alliance Medical Technologies, the Monostrut Cardiac Valve Prosthesis. The company will make their presentations. As each speaker gets up, would you

please identify yourself and your financial interest in the company? Since it is taking them a minute or two to set this up, why don't you go ahead and introduce yourselves now and your financial involvement in the company?

MS. HENDERSON: Charmaine Henderson. I am an employee of Alliance Medical Technologies.

DR. MURPHY: My name is David Murphy. I am a cardiac surgeon at Dalhousie University. I have no financial interest in the company. I am a paid consultant, one time.

DR. ARIS: I am Dr. Alejandro Aris, from Barcelona, Spain, and I have no financial interest in the company either.

DR. CURTIS: Are you a paid consultant?

DR. ARIS: One-time consultant, yes.

MR. OLSON: I am Scott Olson. I am an employee of Alliance Medical Technologies.

DR. CURTIS: I am going to ask Dr. Tom Callahan to make a couple of comments on the whole process of approving heart valves, as we are getting set up here.

DR. CALLAHAN: Thank you. Good morning. I just wanted to take an opportunity to address the Panel and the members of the audience and the industry that are here today on several criteria that we are putting forward today, for the first time, with heart valves, and it does apply to all

three manufacturers so it is probably germane that I say it now before we get started.

These are the first three manufacturers to come through the process with these objective performance criteria. Although there is general agreement that the most scientifically valid clinical data is usually obtained with the conduct of a randomized, controlled trial, discussions with the clinical community over a number of years have found with the heart valve studies a number of difficulties with implementing these kind of studies.

So an alternative study plan was proposed at an FDA workshop at the National Institutes of Health, called Design and Conduct of Clinical Trials with the Evolution of Cardiovascular Devices, and this was in June of 1993. At that time, it was decided that a prospective observational study of the investigational valves, with a comparison of complication rates to pre-established objective performance criteria would be used.

These three companies that you are seeing today are the first three companies to have completed that process. The main advantages of this type of study design are that the sample sizes are much more reasonable. Consenting and eligible patients would receive the investigational valve and, a given advantage, that a limited

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pool of patients at each study site would help the recruitment of patients, and all manufacturers would be held to the same standards. These objective performance criteria really are a literature-based, historical control method which has been first introduced in 1994 subsequent to that NIH panel discussion.

Now, as we went to implement the objective performance criteria, we realized that the data, and there were some 11,000 articles that were looked at in order to perform the database -- that there were some inadequacies in the OPC method. Most noticeable were the absence of several safety controls, that is, death, reoperation, and explant, not in the main objective performance criteria. There was also absence of effectiveness controls and a lack of current updated values. So when these three companies came in we sat down and attempted to bring the database up to the common standards today and use common literature.

These control articles are not intended to act as a statistical comparison to the study valve. Rather, they are provided to inform the Panel of the current state of heart valve technology as expressed by the articles published in quality peer review journals. There is criteria in your sections 512-515, under clinical summaries, which spell out the quality criteria that are involved. For

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interested parties, this material is also available on request.

Because of the long span of data collection of the heart valves, review criteria have, obviously, evolved and that is why they need some consideration with continual updating. And there is always a question in FDA's mind whether the data that is presented by a standard that was promulgated three or four years ago, whether it is germane in today's light.

Much to the credit of the three companies that are involved today, they were very willing participants to try to update the data and they have worked with the FDA staff. Both teams worked very hard in the past year to make these comparisons relevant, and there will be continuing evolution in heart valve evaluation criteria. The FDA is presently working with the HIMA manufacturing association, Health Industries Manufacturing Association, to further evolve some evaluation criteria.

So that is just a little bit of background on the objective performance criteria and the new control articles that we are using.

The second item I would like to mention is that oftentimes when we begin an evaluation of a medical device, it is always a risk-based decision, and there is somewhat

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less data than we might like at the time in front of us in order to make that decision. We are, obviously, interested for mechanical heart valves in long-term freedom from thrombosis and infection, and long-term durability of the device. So even the most vigorous in vitro testing of even the data that you have before you doesn't always speak to the long-term follow-up.

So the question of whether we have enough long-term follow-up available is a central issue you will also have to address today. A recommendation of approval and the Agency's support of that recommendation still doesn't imply we don't need additional data. So your decision may include suggestions or recommendations for postapproval data collection. Tab One of each of your packs includes a discussion of possible postapproval studies.

So we look forward to your comments and discussions, and thank you very much for helping us in this undertaking.

DR. CURTIS: Thank you. Let's go ahead with the presentation by Alliance.

MS. HENDERSON: Good morning, Panel members, representatives of the Food and Drug Administration and guests. I am Charmaine Henderson, Director of Regulatory Affairs, Quality and Compliance, Alliance Medical

Technologies in Irvine, California.

We are here today to present the safety and effectiveness data for the premarket approval of the Monostrut heart valve.

[Slide]

I would like to introduce my colleagues who will be presenting and answering questions today: Dr. David Murphy, a cardiac surgeon from Victoria General Hospital, is one of the principal investigators for the Canadian clinical study. Dr. Murphy will present the results of that study.

Dr. Alejandro Aris, a cardiac surgeon from Hospital de la Santa Creu i Sant Pau, in Barcelona, Spain, provided catheterization data. He will discuss the hemodynamic results.

Dr. Dan Lindblom, a cardiothoracic surgeon from Karolinska Institute, in Stockholm, was a principal investigator for the European clinical study.

Dr. Jeffrey Borer, Professor and Chief, Division of Cardiovascular Pathophysiology, Cornell University Medical College, is a consultant to Alliance Medical Technologies.

Professor Yoganathan, Ph.D., an engineering specialist and bioengineering from Georgia Tech., conducted preclinical testing in the Monostrut heart valve.

In addition, Mr. Scott Olson, our Vice President of Operations at Alliance, and Miss Leslie Willis, our consultant statistician, will also join me.

[Slide]

Patients requiring aortic, mitral, tricuspid or double heart valve replacements were enrolled from 1982 to 1991 at five international centers. The PMA for the Monostrut heart valve was originally filed in 1986, after which an additional clinical study was initiated at three centers in Canada.

The PMA came before the FDA Circulatory System Devices Panel in 1993. The Panel at that time requested more information that was supplied to the Agency in 1994 through the present.

In 1995 FDA approved the Thoratec left ventricular assist device exclusively containing the Monostrut valve. In February of 1997 Alliance Medical Technologies became the sponsor of this PMA.

[Slide]

The Monostrut heart valve is a hingeless, free-floating, tilting disc device, with a 70 degree nominal opening angle that is constructed of a cobalt-base alloy orifice ring with integral struts. The pyrolytic carbon disc occluder has an encapsulated radio-opaque marker. The suture

ring is made of PTFE fabric. The Monostrut valve is available in 17-33 mm diameter sizes, and is intended for use as a replacement for malfunctioning native or prosthetic aortic or mitral heart valves.

[Slide]

It is the sponsor's understanding that all manufacturing and engineering issues have been resolved to the FDA's satisfaction. In vitro and in vivo studies conducted on the Monostrut valve satisfy FDA guidance and indicate acceptable hemodynamic and structural performance. Biocompatibility and toxicological testing results confirm the safety of the valve.

[Slide]

The Monostrut valve has been studied extensively in clinical trials in Canada, which is presented as cohorts 1 and 2 in your Panel pack, and Europe, which is presented as cohort 3. A retrospective study, cohort 4, was conducted in Germany. The overall research experience is shown here, where you can see that we have 569 aortic and 427 mitral valves implanted in 1113 patients, representing a total of 6179 patient years with the Monostrut valve.

In addition, since 1972 over 60 scientific and clinical papers have been published in peer review journals on the hemodynamics, fatigue, strength, biocompatibility and

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clinical performance of the Monostrut heart valve or its components. These studies have supported the safety and effectiveness of the valve.

The Monostrut heart valve has been available in 33 countries, beginning in 1982. Since that time, 120,653 valves in sizes 17-33 mm diameters have been distributed. There have been no reports of structural failures. The Monostrut heart valve has not been withdrawn from any market.

[Slide]

I would now like to present Dr. David Murphy who will present the results of the Canadian clinical trial.

DR. MURPHY: Good morning, Panel members.

[Slide]

The objective of this non-randomized trial was to evaluate in a North American center the hematological and clinical sequelae of single-valve replacements in the aortic and mitral position.

Patients requiring isolated valve replacements were enrolled from 1987-1992 at 3 Canadian centers when the strict inclusion and exclusion criteria were met. Patients were followed postoperatively at 3 months, 1 year and then annually thereafter to 1996.

As you will subsequently see, the valve

performance is compared to the objective performance criteria contained in the 1994 FDA replacement heart valve guide, as well as to FDA historical control literature.

[Slide]

The inclusion criteria for the valve include patients over the age of 18 and signed informed consent prior to surgery.

The exclusion criteria were life expectancy less than 2 years, the presence of endocarditis. There were no double valves or tricuspid, no pulmonary valves. Intolerance to anticoagulant therapy was a contraindication; pregnancy, nursing, alcohol and drug abuse. Additionally, urgent surgery in which no hematological data could be obtained before surgery was also an exclusion criterion.

[Slide]

In the Canadian trial 3 hospitals entered patients, the Toronto General, St. Michael's Hospital in Toronto and the Victoria General Hospital in Halifax. There was a total of 178 aortic valve replacements and 136 mitrals, for a total of 314.

This trial has generated an experience of 820 patient years in the aortic group and 572 in the mitral group, for a total of 1391 patient years. Three quarters of the patients in both group were in New York Heart

Association functional class III and IV.

[Slide]

Of the 314 patients who were enrolled in the Canadian study, 299, or 95 percent of the patients, have follow-up data for the early postop period; 290, or 98 percent, of the available patients have follow-up data for the late postop period, up to 1 year; 102, or 70 percent, for up to 5-6 years.

In the early postoperative period there were 13 deaths, 3 explants and 4 patients selected to drop out of the protocol. At 5-6 years there were 47 deaths, 13 explants and 39 patients were subsequently lost to follow-up.

[Slide]

The clinical trial endpoints are those of the 1994 FDA replacement valve guidance, and they include thromboembolism, valve thrombosis, anti-coagulant bleeds, perivalvular leaks and endocarditis.

[Slide]

Additionally, of course, death, valve-related reops, nonstructural valve dysfunction, hemolysis and other adverse events.

The effectiveness of the insertion of this valve was evaluated by change in New York Heart functional class.

At the request of FDA, all the events were

evaluated by an independent clinical events committee, refereed by Dr. Charles McIntosh and associates, and confirmed and classified all events. In addition, all the deaths were reviewed and classified as valve-related and non-valve-related.

[Slide]

This slide shows the actuarial plots for freedom from all deaths, in blue, and valve-related deaths, in red, over an 84-month period. The vertical axis shows the cumulative freedom from the event presented as a percentage. The horizontal axis shows the months after surgery.

The 30-day mortality was 4.1 percent. Freedom from valve-related death was 97 percent at 12 months and 94 percent at 5 years.

[Slide]

This bar slide summarizes the valve-related complication rates compared to the objective performance criteria, OPC. OPC is shown in red; the Monostrut valve is shown in green. The vertical axis shows the linearized rate and the individual complications, in abbreviations, are listed along the horizontal axis.

The linearized rates for all cases for perivalvular leak appears to exceed the OPC guideline. However, the rate for major PV leaks does not. The rates for

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all other complications with this Monostrut valve appear to be in keeping with the OPC guidelines.

[Slide]

This slide shows the freedom from thromboembolism. At 1 year the probability of absence of thromboembolism is 90 percent, 96 percent and 82 percent at 5 years.

[Slide]

This slide shows the incidence of freedom from all and major perivalvular leaks over an 84-month period. The probability of absence for any PV leak is 98 percent at 1 year, 91 percent at 5 years, and the probability of absence of major perivalvular leak was 97 percent at 12 months, 96 at 5 years.

[Slide]

To arrive at a clinical status of the value of putting this valve in place was assessed by change in New York Heart Association functional class between the preop period and 1-2 years postoperatively. The thickness of each line is proportional to the number of patients. Of the total surviving patients, 86 percent improved. The majority of patients who were in Class III and IV at baseline were near functional Class I at 2 years postoperatively.

[Slide]

The white lies represent those surviving patients

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that did not improve following valve replacement. No patient deteriorated more than 1 New York heart classification.

[Slide]

Dr. Aris will present the hemodynamic data.

DR. ARIS: In compliance with the 1993 request by the FDA, data were obtained from 105 patients from nine centers. Your Panel pack contains a recent article in The American Journal of Cardiology that describes the echo-cardiographic evaluation of 135 patients with 164 Monostrut valves.

[Slide]

This slide shows the demographics and change in New York Heart Association class of the patients who underwent cardiac catheterization as compared with the patients in the Canadian cohorts.

The two groups are similar with regard to sex, mean age, valve position, preoperative functional class and change in functional class.

[Slide]

For patients with aortic valve replacements, this slide presents hemodynamic information for valve sizes 17 to 29. The number of patients with each valve is shown. Cardiac index ranged from 2.8 to 3.5 liters/minute/square meter. The peak-to-peak gradient ranged from 23 to 4 mmHg. The mean

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gradient ranged from 20 mmHg for the 17 mm valve to 4.7 mmHg in patients with large valve sizes.

Using the Gorland formula, the effective orifice area was 1-2.6 cm². The valve index was 0.9-1.4 cm/m². Tables 10 and 11 on pages 552 and 553 of your Panel pack provide the number for each parameter.

[Slide]

For patients with mitral valve replacement, this slide presents hemodynamic information for valve sizes 25-33. Sizes 29, 31 and 33 are combined since the valve orifices are the same size. They are shown separately in your Panel pack on pages 552 and 553.

The cardiac index varied from 3.1 to 2.5 liters/minute/meters squared. The mean gradient ranged from 6.1 to 4.9 mmHg. These results are comparable to the recently published results from our group using the echo Dopplers that are contained in the attachment 6 of your Panel pack.

Using the Gorland formula, the effective orifice area was 1.9 to 2.4 cm² and the valve index was 1.1 to 1.6 cm²/m².

[Slide]

Charmaine?

MS. HENDERSON: We have compared the OPC with the

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linearized complication rates in the three Monostrut studies with the summaries of safety and effectiveness for Carbomedics, St. Jude and Medtronic-Hall.

As you can see, the rates for thromboembolism, anticoagulant bleeding, perivalvular leak, endocarditis and valve thrombosis for all 4 mechanical valves fall within the range of one times the OPC, shown in red, with the exception of perivalvular leak for the Canadian Monostrut study, shown in yellow, thromboembolism for the Medtronic-Hall valve, shown in dark blue, and all anticoagulant bleed and perivalvular leak for the St. Jude valve, shown in light blue.

[Slide]

When the linearized complication rates obtained from the FDA's selected publications are compared to the most recent peer reviewed Monostrut publication, one can note that the Monostrut's complication rates, shown in yellow, are favorable.

[Slide]

The Monostrut heart valve is safe and effective. The safety is supported by comparison with FDA's objective performance criteria for replacement heart valves. The effectiveness is supported by hemodynamic and functional class data.

In addition, Monostrut valve is comparable to other FDA-approved heart valves based on a comparison with FDA-selected literature and summaries of safety and effectiveness.

Thank you.

DR. CURTIS: We will move on now to the FDA presentation.

[Slide]

MS. KENNEL: Good morning, members of the Panel and audience. I would like to present a brief history of this PMA for the benefit of the Panel members who may not be familiar with it since it has a long history with the Agency. First, I would like to acknowledge the efforts of all of my team members who have been involved in the review of this PMA, who are listed in the slide.

[Slide]

Since this PMA has been under consideration for a long time, I plan to go over a history of our FDA heart valve guidance, followed by a history of this PMA, and an overview of the current 1996 data set which is under consideration today.

[Slide]

It is important to point out that there have been a total of four drafts of the FDA heart valve guidance since

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1982. The changes made to this document over the years have not been substantive, and are detailed in the slide displayed. Endpoints have always been pre- and postoperative assessments of New York Heart Association classification, blood parameters for hemolysis and infection, hemodynamic assessment of gradient, effective orifice area and regurgitation, and an assessment of all complications.

[Slide]

The PMA was originally submitted in 1986. It consisted of a study involving 5 centers in Europe and Canada. In response to requests from the FDA for additional blood and catheterization data, the firm submitted a complete re-write of the submission in 1990, adding data from three new Canadian centers. These data were presented to the Circulatory System Devices Panel at a meeting in 1993. The PMA was recommended for non-approval based on lack of data.

[Slide]

The Panel recommended that eight issues be addressed to bring the PMA into approvable status. These eight items will be detailed in the next few slides. Finally, the PMA was again revised in 1996, and that information is before us for consideration today.

[Slide]

The items which the Panel stipulated that needed to be addressed to bring the PMA into approvable status were the following:

Number one, the Panel recommended that the sponsor present the data from the three Canadian centers as the pivotal data, since the follow-up was more rigorous at these centers, and since a different protocol was used in the original cohort as compared to these Canadian centers.

Number two, the previous submission did not include any information on a control group. During the 1993 Panel meeting there were discussions about the need for randomized, controlled trials. As Dr. Callahan mentioned, a workshop was held in June of that same year to discuss the need for randomized trials for heart valves. The outcome was adoption of OPC's, or objective performance criteria. These criteria are limits that have been set for the most frequent complications found in the literature for heart valves, and the OPC approach was incorporated into the most recent, 1994, draft of the FDA guidance document.

Since the articles chosen for the OPC criteria in the 1994 FDA guidance document are now older, a modified approach was used for this PMA. This modified approach was similar to that used in selection of the articles to establish the OPC's in the guidance, but more recent

articles were chosen, and articles relating to effectiveness were also considered as described in the Panel pack. These first two items were adequately addressed in the 1996 revision of the PMA.

[Slide]

The sponsor was instructed to ensure valve implantation in an adequate number of patients in each group, which are representative of the population for which the device is intended. The 1986 guidance, in effect during this study, stipulated a total of 35 patients in each of 3 centers, and for each valve position, aortic and mitral. The current guidance recommends 35 per position per center if a common protocol was used, or 50 per position per center if the protocol differed. The number of patients at one of the three Canadian centers was less than 35 for both aortic and mitral, at which 32 aortic and 16 mitral recipients were enrolled, as depicted in the table on this slide.

[Slide]

The sponsor was asked to obtain a representative number of patients in each size to be marketed. That is item number four. In the 1986 guidance, catheterization data was to be obtained for a total of 7 of the smallest and 7 of the largest for each valve position. Although literature data was not encouraged, FDA realized that obtaining

catheterization data on asymptomatic patients was difficult, and has allowed data from non-cohort center sources as long as it does not overlap the data from the PMA cohort.

In addition, since the sizes 29, 31 and 33 mm all utilize the same occluder and housing, the data may be combined for these sizes. As of the 1990 revision of the FDA guidance, echocardiographic assessments of hemodynamic performance were allowed, and this sponsor was encouraged to obtain such data for their patients. This item was not adequately addressed, and there are still sizes for which the data available are absent or sparse, as detailed in the table in this slide.

[Slide]

Item number five, the sponsor was asked to appoint, with FDA approval, an independent panel of physicians to review the deaths and serious complications to determine if they were related to the valve or not. This item was fully addressed in the 1996 PMA revision.

[Slide]

Item number six, the firm was directed by the Panel to obtain follow-up consistent with the 1986 FDA draft guidance which included four types of data. Number one, catheterizations for 7 largest and 7 smallest or echo for as close to 100 percent of the population as possible; number

two, complete blood data including CBC, reticulocyte count, LDH, and haptoglobin, to be collected preoperatively and twice postoperatively for trend analysis purposes; number three, NYHA and, number four, complication information at each follow-up.

With the exception of the echocardiographic assessment replacing the catheterization, and clarification of the time periods for assessment, there have been no changes to the FDA guidance from the first 1982 issue to the current 1994 issue. This item has not been adequately addressed because there was an inadequate number of patients with hemodynamic data for each size for which marketing clearance is sought. The number of patients with effective orifice area available by each type and size is briefly described in the table on this slide.

[Slide]

Item number seven, the Panel asked the sponsor to restrict marketing approval request to only the Teflon sewing ring. Originally, a carbon-coated ring was also to be offered but the data for this ring were inadequate.

Item number eight, the Panel asked that the full battery of in vitro tests be run on the small "thin occluder" sizes of the valve, since they have a slightly different design than the larger sizes. Also requested by

FDA was a complete discussion of the manufacturing methods. These two items have been adequately addressed with this submission.

[Slide]

In summary, the 1986 version of the FDA guidance was in effect when this PMA was received. With the exception of allowance of echocardiographic data to assess hemodynamic function, the sponsor was asked at the 1993 meeting to meet the criteria in the 1986 draft of the FDA guidance. The 1996 submission from the sponsor is to be considered at this meeting, and is the subject of the next couple of slides.

[Slide]

In the 1996 update, the sponsor included data from three distinct cohorts, identified as cohorts 1, 2 and 3. Cohort 1 included patients implanted with aortic valve sizes 21-27 mm, and mitral valve sizes 27-33 mm. Cohort 2 consisted of patients from two of these same three Canadian centers who received valve sizes larger or smaller than the range covered under cohort 1. The complete range of valve sizes for which the firm seeks approval are aortic sizes 17-33, and mitral sizes 17-33, with the sizes 29, 31 and 33 mm utilizing the same valve with a different sewing ring.

FDA asked that the sponsor combine the data from cohorts 1 and 2 since the two cohorts involve the same

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centers, a common protocol, entrance criteria, complication definitions, and case report forms, and the patient characteristics and outcomes were similar among the three Canadian centers and the two cohorts. Data from these two cohorts is considered the pivotal data for a decision today.

[Slide]

Cohort 3 consisted of patients in the original 1986 PMA data set. Inclusion criteria used in cohort 3 were more relaxed than for the other two cohorts. This study allowed patients implanted with multiple valves, both Monostrut or competitor valve, a carbon-coated or a Teflon sewing ring, tricuspid valve patients, emergency patients, redo's with the Monostrut valve, and graft combination patients. Data from a German center was also presented. The data from cohort 3 and the German center are not considered pivotal and are included as attachments to your Panel pack.

There will be a few slides at the end, which will be detailing FDA questions to the Panel, and they will be displayed after your deliberations today.

Thank you very much.

DR. CURTIS: It is just about 10:30 so we will stop and take a 15-minute break. Then we will come back and have a Panel discussion.

[Brief recess]

DR. CURTIS: One of our Panel members wasn't here when we did the original introductions, and that is David Gooray, the consumer representative.

To continue the discussion of the Monostrut cardiac valve prosthesis, we are going to start with the Panel reviewers. The way we are going to do this is that each of the main Panel reviewers will get 15 minutes to review the information and ask any questions they want. Then we will go around and give each of the Panel members 10 minutes each. At the end of that time, if we still have additional questions we can go back around the room until everybody has been satisfied that their concerns and opinions have been heard.

There is a fax that came in for Anita Womack. It is probably out at the desk.

I think we can start with Dr. Vetovec.

DR. VETROVEC: Thank you. I would like to begin by just asking several questions regarding the data that is included. If one looks at 515, which is entitled Table 2, which is study compliance, I guess I would like a little insight into how rigorous the follow-up was attempted, and how it was actually carried out. I am struck that at five years there is New York Heart Association data only 63 percent of the patients and, yet, that was a significant

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part of your presentation. Could you give me insights on the follow-up?

DR. CURTIS: We need somebody from the company to make a comment on that.

MS. HENDERSON: Dr. Murphy will try to answer the question.

DR. MURPHY: This may be difficult for me to answer but I can perhaps answer on the basis of our particular center, which represents over half of the Canadian group and perhaps reflects on the whole.

Certainly, in our center the follow-up was extremely tight and at 3 months all patients came back, that were alive, of course. At 1 year not all the patients came back, but those that didn't come back, they were seen by their family physician. Blood data, urine analysis and so forth was drawn and data was returned. That is more or less the annual follow-up was carried out.

So I can't answer as to why there was only 63 percent. In our series of 147 patients, 6 were lost to follow-up. Five of those patients we know are alive but they were not included in the data because they didn't want to come back. Five of them had moved away and one refused to come back. One was institutionalized, a deaf-mute. But that is the sort of follow-up that occurred. I hope that answers

your question.

DR. VETROVEC: It does raise a question though that there may be major variability between centers in the follow-up because if the average is 63 and yours was, you are implying, 90-plus, that suggests that there is a very low center in there.

MS. HENDERSON: This is at five years, Dr. Vetovec. The actual number of patients that were reviewed for a change in the New York heart classification was done at the one- to two-year time frame, and there were 252 patients who had preoperative and postoperative data available.

DR. VETROVEC: Okay. Can you turn to 521? I just want to ask a general question about the distribution of the patients between the different centers. The Toronto General Hospital is quite low compared to the other centers, and lower than was anticipated. Is there a reason for this? Is this a center that has a lower valve volume per se, or was there something else ongoing in that?

DR. MURPHY: Perhaps I could answer that as well. Dr. Scully was the principal investigator and essentially the patients that were entered were his private practice patients. So while you would expect a lot more valves to be placed in that center, he was the only person that had

elected to use that valve to be implanted.

DR. VETROVEC: One other question relating to kind of background data is that if one looks at the age distribution of the patients, and particularly considering that at least in the United States the number of patients getting valves over the age of 70 is rising, there were only 8 percent of the patients, as I see it, who were 70 and over. Yet, of the deaths -- and I recognize all the patients are at higher risk -- the deaths of patients undergoing surgery, of the 51 deaths that you list, I calculated that 23 percent of the deaths were in patients over the age of 70. I just want to comment, do you think that was a disproportionate event or was that what you would expect?

DR. MURPHY: Yes, as to the representative population, again I just have to answer for the Halifax portion. The mean age was 53 in both groups. It is true that all centers are putting valves into older patients, but when you look at just single valves, it is surprising that the single valve series in the literature all range around the mean of 53-55 years.

We put in a lot more valves of this type, but these patients elected not to come back in follow-up. In that period of four years, 245 valves were implanted, the Monostrut valve. This is out of 800 valves in total. But of

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those 245, these patients just didn't want to come across country in the winter to be followed. So they were not entered in the study. I would say that is the same reason in Toronto.

DR. VETROVEC: When I read the protocol I couldn't see any directions as to what anticoagulation level was recommended for the patients. Were there guidelines for that?

DR. MURPHY: There were no guidelines. The guidelines that are followed are more or less those that were proposed by the McMaster group in The New England Journal, which is an INR between 2.5 and 3.5. I say that only because it represents what we do in Halifax. I can't speak to the Toronto group. So there were no guidelines in the protocol saying that they had to be anticoagulated.

DR. VETROVEC: Do you have a sense of the values that were obtained in follow-up of these patients? Did they tend to be within those guidelines? Were they outside them? I assume that data is known.

DR. MURPHY: It is known but I don't have it here. Perhaps you do?

MS. HENDERSON: No.

DR. MURPHY: It is available.

DR. VETROVEC: I guess the reason I am asking is

that I wonder if the patients weren't under-anticoagulated since the anticoagulation-related bleeding seems low compared to other studies but the risk of thromboembolism seems high. It might be worth noting that or whether there is some issue related to anticoagulation if one looks forward to what the recommendation should be for how these patients might be managed. Can you give me any insight into the thromboembolism?

DR. MURPHY: Yes.

DR. VETROVEC: Because, as I said, my reading or reviewing of the data suggested that you may have under-anticoagulated. But I would be interested in knowing that.

DR. MURPHY: That was my assumption as well in looking at the results, and it is true, Canadian physicians tend to be conservative in terms of anticoagulation. So while they leave the hospital with the recommendation to their families and physicians to keep the INR above 2.5, in point of fact, when we followed these patients and other patients on warfarin we find that they are all over the map. So I think it is a reflection of Canadian conservatism, that they tend to be under-anticoagulating by American standards. And I think that perhaps explains why we have a low hemorrhagic rate but so-called high thromboembolism.

DR. VETROVEC: I have to ask you about the issue of perivalvular leak, particularly related to the mitral valve. I guess I will begin by asking you for your comments or explanation for that.

DR. MURPHY: Yes, as a surgeon, I guess I would answer it by asking myself, you know, what are the three or four variables that affect the causation of a perivalvular leak. I guess the first one I would ask is, is there anything wrong with this valve prosthesis that would cause a perivalvular leak. My view is that the prosthetic annulus is no more greatly different than any of the other prosthesis we put in -- the biological valves and other metal valves that I have had experience with. So there doesn't appear to be anything special with this valve annulus.

So then how do you explain the incidence? Well, again if you don't mind me using our experience in Halifax, we had 15 reported perivalvular leaks out of 147 valves. When we looked at those, 7 of them were considered minor or trivial and they were picked up as an incidental on echo or on a cardiac cath. But because they were present, the surveillant nurse would mark them as an incident.

Of the other 8 -- I have that data -- I think one of the surprises to me was that there seems to be -- how can I express it? The leaks seem to be associated with the fact

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that if you take out a prosthesis and put a new one in. In other words, of those 15 patients, 8 of them had had a previous valve in and were redo valves; 7 were trivial, mild. Of those patients, 1 was endocarditis and 1 was a tissue impingement, which was a small pannus that had grown over the edge of the valve prosthesis but that was included as a leak on the incident form. The other 4, you would have to point the finger at either the surgeon, which is the other variable, and/or the patient's annulus, which is the other variable. So 4 of those had either something wrong -- their suture had pulled through; 1 of them had a fracture because of a piece of calcium.

DR. VETROVEC: Do you have any insight into the Toronto group? Is this similar?

DR. MURPHY: I would just be suspecting. I couldn't give you that information.

DR. VETROVEC: Other than a redo valve, is there anything about calcification of the annulus that has anything to do with it?

DR. MURPHY: Yes, of course. It would be like with any other valve. If you are not adequately debriding, and sometimes you can't debride all the calcium, it is true; it would predispose to perivalvular leak.

DR. VETROVEC: I guess the question I would ask is

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relative to your other patients who get other valves, would you think that what you saw for this valve was consistent, in your center, with what you see for other valves, or is there something different about it?

DR. MURPHY: I think it is consistent with our experience with the other valves, particularly now that we have transesophageal echo on most every patient that we have a valve in. At that time we didn't but we now suddenly realize we are probably getting a lot more small leaks that we didn't know existed before.

DR. VETROVEC: I guess I will go back to what I asked earlier about the higher percentage of older patients dying, and come back to this with the question I asked about calcification. I am a little bit concerned about whether there is a propensity of this to be more likely in older patients. As I said, the mortality was substantially higher, about three times higher than the proportion of all patients being operated on. It seemed to me that the perivalvular leak might relate to that, and I just want some observations about that.

DR. MURPHY: I don't think I can answer that. I can't answer that.

DR. VETROVEC: I will stop.

DR. CURTIS: Dr. Weintraub?

DR. WEINTRAUB: I just wanted to say a word. I was present at the workshop, back in 1993, so it is interesting to see everything coming full circle or to fruition and these are the valves that, I guess, are being assessed on that basis. So it is personally rather interesting to me.

I am going to try to do something original, I am actually going to try to answer the questions that were put to the Panel by the FDA. I am not sure that has ever been done before. I am going to try it.

[Laughter]

Some of these are just opinion but I will then go on to some of the other things. The first question was, do the data presented permit assessment of the safety and effectiveness of the device? And I am going to defer that one.

The second was, does the indications section adequately define an appropriate population for use based on the data presented? The prosthesis is indicated for the replacement of malfunctioning native or prosthetic aortic or mitral heart valve. So I think that is appropriate.

Is the proposed contraindication section appropriate? Are there any other contraindications? The labeling is to read the Monostrut is contraindicated in patients unable to tolerate anticoagulation therapy.

I am going to expand that a little bit. I am a little concerned about the rather small number of warnings. If you look at the warnings, they really are few. I am trying to find that now. There really are only three warnings: For single use only. Avoid damaging the prosthesis. Do not pass a catheter through the prosthesis as this maneuver may cause valvular insufficiency and may result in dislodgement. It also, sure as heck, can result in entrapment and freezing of the valve.

Now, by comparison, since we are objectively comparing I guess we can objectively compare the labeling with the Carbomedics labeling, which is in the first section I believe. If you look there, there are 19 specific warnings. Now, a lot of these do appear in the labeling in the instructions for use. I understand that. But I think some of these are really important enough that they ought to be underlined and be appropriately warned.

The ones that I think are very important are the use of sizes provided by other manufacturers -- those should not be used. When seating a valve, ensure that sutures or other materials don't entrap the valve. Specifically, the one -- and I am trying to see which one it is, basically don't use any other instrument to turn the valve, to rotate it, except for the holder in which it comes. I think that is

extremely important. I would also mention be sure you use the right size holder. As I recall, with the Bjork-Shiley's, one of the holders may fit two or three different sizes and I assume that is the same here. So I think that really ought to be a warning.

The other thing is, asking those of you who use it, is there a pusher that comes with the valve, a flipper? I call it a pusher.

MR. OLSON: No, we don't have, not yet.

DR. WEINTRAUB: I think there should be instructions about that because there is a tendency to use a metallic, or something, to push the leaflet and it is extremely important to test the valve to make sure that the leaflet swings freely. So either, you know, recommend a Q-tip of something like that or provide, as Carbomedics does, a little plastic pusher. But I think that is important. I think that is it about labeling.

Is patient counseling adequate? I am going to avoid that for now.

Do the data support the approval of all sizes? I would just absolutely flatly say no. The 17, there is no data. I am concerned about the 19 and I will discuss that in a minute. But, certainly, the 17 is just absolutely -- I think there is one implant.

Now, the population question -- the safety and effectiveness of the prosthesis has not been established for the following specific patients, and the only population mentioned is patients implanted for more than ten years. I am not sure you can really claim ten-year follow-up. I won't argue with you how many years you can claim but I think ten years probably -- the data are not there up to ten years. So I would object to that.

Physician training, I think probably there ought to be a section on that. Again, I wouldn't know exactly what to say. The reason I say this, this is basically a form of the old Bjork-Shiley valve and I have certainly put in quite a few of those valves, and there is a real learning curve to it. As in most mechanical valves, each one has little idiosyncrasies and an experienced surgeon who has worked with them learns what to do and not to do, how to have it turned. For instance, with the old Bjork-Shiley the large leaflet, the opening leaflet hangs down a fair piece below the actual sewing ring. You have to be very careful that it doesn't get an obstruction.

That sounds fairly routine but because there are two different sized orifices, the valve can be trapped in two different ways. For those of us who are familiar with the Bjork-Shiley, you know, I would put this valve in pretty

much like I used to put in the Bjork-Shiley's and I know all the tricks. But for the younger surgeons coming along today, they haven't put Bjork-Shiley's in for a long time. How long has it been off the market in North America, the old Bjork's? At least six or seven years I think.

DR. MURPHY: Ten years.

DR. WEINTRAUB: Ten years. So I think that using the experience of older surgeons who put in many, you ought to have a section written about dos and don'ts of this valve. It is a tricky valve. It is mechanically somewhat complex, although, frankly, with the Monostrut it should be less complex but it still has its own idiosyncrasies and I think you could use the experience of surgeons to comment on that.

Now, I have some questions just about the OPC's because, again, this is the first valve that we have had to look at with this. This question is addressed as much to the FDA staff, probably more so than it is to the sponsors. I spent at least an hour and a half going over Gary Grunkmeier's article. It is a tough article and I think I understand it more or less. But I wonder if the statistician would explain to me, or explain to all the Panel, the issue of confidence limits as they relate to the sponsor's data and as compared to the OPC data.

First of all, how are the OPC data obtained? For instance, we will say the linearized periprosthetic leak OPC is 1.2 I think, and two times that, which would be the confidence limits for that, would be 2.4. But how was that number arrived at?

MS. WILLIS: I am Leslie Willis, and I have no financial interest with the company. The linearized rate is basically the number of events divided by the number of patient years and then times 100 to make it a percentage.

DR. WEINTRAUB: No, no, that I understand. But how were the control data arrived at, or the comparative data arrived at?

MS. WILLIS: I can't speak to that.

DR. SAPIRSTEIN: Wolf Sapirstein, and I am with FDA. I was also present at that workshop. These linearized rates were developed on the incidence of these adverse events occurring in a segment of the literature, which was reviewed for a period of ten years prior to 1994. These rates were developed, as was explained, as a percentage of cases occurring in that period of time.

The OPC's were to be compared on the basis of 800 cases to obtain an 80 percent power and 0.5 probability rate compared to these rates. These were to be compared to twice the OPC rates in an equivalence type of evaluation, and we

requested that the upper 95 percent confidence level of the study device OPC should be obtained compared to twice OPC's of the historical.

DR. WEINTRAUB: I guess the question I have is in the comparisons in section 5 of the clinical study, the four manuscripts that are compared with Akins, Copelan, Kahn and Fernandez, I assume that a lot is derived from other data, or is that incorrect? Because of those four papers, some of those are pretty incomplete.

DR. SAPIRSTEIN: Yes.

DR. WEINTRAUB: So there are other sources of those OPC data?

DR. SAPIRSTEIN: The OPC data are what we developed from a review of the literature. In addition to that, we requested some current historical data.

DR. WEINTRAUB: Thank you. Another question that is addressed partly to staff, where are we with respect to hemodynamic evaluation? Clearly, in North America getting postoperative catheterization I would say is virtually impossible, particularly for aortic valves because you would have to do either a direct left ventricular puncture or a transatrial stick, and patients aren't going to stand for it, I don't think, and the insurers aren't going to pay for it. So I just wondered where we are on that now. This is

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sort of falling under the old guidelines but I know we talked about evaluating the patients echocardiographically.

MS. KENNEL: Lisa Kennell. As of the 1990 revision of the guidelines, we were allowing echocardiographic data, and we had suggested to the firm that they capture some of that to supplement the catheterization data that they had in their previous submission. I think the only cath. data that is contained in the file at this time is an attachment to your Panel pack, maybe the last couple of pages. It is an article by Panciabo. That is all that is in as far as echo goes. We certainly would be willing to entertain echo.

DR. WEINTRAUB: So in the future that is acceptable?

MS. KENNEL: Certainly.

DR. WEINTRAUB: Oh, okay. With respect to the data that were submitted, I find it, I must say, somewhat confusing. I have to preface this by saying I don't think that is a make or break issue. But why the mean gradients should be higher than the peak gradients, even though there are individual differences, I still can't figure that out. It doesn't make any sense unless there are some terrible outliers. Can someone explain that to me?

MS. HENDERSON: Yes, Dr. Aris can answer this

question.

DR. ARIS: You are referring to the LT gradients.

DR. WEINTRAUB: Yes.

DR. ARIS: The only thing I can answer, I know that the cardiologists were using hemodynamics and they were very happy to see that the gradients were not very high but they didn't really understand why the mean gradients were as high as they were.

DR. WEINTRAUB: I just have to question the validity. You know, I can't explain that so it is not very real to me.

MS. HENDERSON: Dr. Weintraub, it is my understanding that that data is peak-to-peak ratios, not just peak-to-peak.

DR. DOMANSKI: You know, I may be able to shed some light on that. Say your question again precisely with respect to that because they are using echo data.

DR. WEINTRAUB: Well, no, my understanding is that this is cath. data. It says cath. data.

MS. HENDERSON: That is correct, it is catheterization data.

DR. WEINTRAUB: Again, I don't think it is critical it is just that, you know, I sort of have to wonder about that, about the validity of it.

DR, ARIS: It is my understanding that the mean gradient in the aortic position was calculated by the area of the overlapping between the aortic curve and the left ventricular curve. The peak-to-peak gradient was just what the transducer will record. These were all done in catheterization in partly anticoagulated patients. It was the understanding of the people who were doing this --

DR. WEINTRAUB: The area under the curve of the mean could have been higher --

DR. ARIS: Right. That is the finding as it was reported. However, what was considered as crucial for the hemodynamics was the peak-to-peak gradient, and they were happy that those were rather low.

DR. WEINTRAUB: Now we have to go to the safety issue. I have several problems. The first is periprosthetic leaks. If we go by the criteria that we set out back in 1993 and then revised in 1994 and 1996, the periprosthetic leak rate breaks the ceiling. Let me see if I can refer to it; just a minute -- particularly if you break it down between aortics and mitrals. If you look on page 546, the periprosthetic leak rate is 2 percent, with 95 percent confidence limits as high as 2.9 for aortic valves and 2.83 for mitral valves. Both of those are higher than two times the OPC's. That is worrisome. I wondered if there was any

comment about this, and I presume there was, by the safety panel. I mean, I know they looked at this but I don't have any information about what their conclusions were, aside from a couple of sentences in the booklet. I mean, that is high.

MS. HENDERSON: This category of all perivalvular leaks includes all minor categories as well, and these events were reviewed by the McIntosh group and they were confirmed. Dr. Murphy can address the perivalvular leaks.

DR. MURPHY: I recognize your concern about the incidence of it but, as I mentioned before, as a surgeon I am less concerned about the valve annulus being the cause of this, the valve of the prosthesis being the cause of this. I would look at the Canadian surgeons as perhaps not as gifted as American surgeons. I mean, maybe you guys never have any perivalvular leaks, or maybe your annuli are beautiful as you put these things in. But, I must say, I am not as concerned as you. Maybe the numbers could be perhaps explained further.

DR. WEINTRAUB: Well, I am also thinking in terms of suture technique and what have you --

DR. MURPHY: Yes.

DR. WEINTRAUB: You know, you learn to put in differently different valves. If this is approved, then

there may be some secrets here to which the surgical population needs to be exposed.

DR. MURPHY: Well, that I can answer. The techniques are the standard techniques that are either pledget it from above down, say the mitral for example, or some surgeons prefer to pledget it from below up, some prefer a figure of eight. But, in the main, those are the two clusters of suture techniques that are used. But then you must ask yourself, well listen, is this surgeon putting too big a valve in and it is not seating properly, or is it too small a valve? You know, I don't have to explain that to you, surgeons.

DR. WEINTRAUB: And another question, and this is also true of thromboembolism, particularly in the mitral valve position, the incidence of thromboembolism was 4.4 percent but the confidence limits were over 6 and the OPC's are 6. So, again, this is sort of the upper limit or normal or slightly exceeding it.

Those are the main ones. I was impressed that there was somewhat more hemolysis than with other valves but having been a PI on one of the other valves, I think that probably is to some extent under-reported. I have always been impressed that the LDH's are fairly high on all patients with mechanical valves.

The last thing that I am concerned about is the 19 mm valves. It is interesting to me that there were only 11 19 mm valves implanted out of a total of 178 aortic valves, which is an incidence of somewhere between 6 and 7 percent. Now, in my practice I put a lot more of those in because my practice, as I think most of ours, is turning into a lot of little old ladies. Unless you are doing a lot of enlargement operations, and in 80-year old ladies I tend not to do that, certainly I am putting in more than 7 percent of 19 mm valves. Maybe the Canadians have bigger people. It is possible with all those lumberjacks there in the Rockies. But that seems to be under-represented.

So, number one, there is a question about that, and why do you think that number is low. The second question, which is sort of a corollary, and the reason why I am concerned about it is because the 17 and the 19 are different discs and we have had some experience with that with another similar valve. With only 11 valves assessed, are you really willing to go to market with that in a different leaflet? I really worry about that. I have a major problem with that.

Again as another corollary, talking about the thrombosis and embolization, I was a little concerned -- this is just for ease of reading on all the death summaries,

on many of these the sponsor didn't say whether they were aortic or mitral, and in a lot of these I couldn't tell. There were patient names and I suppose I could have traced that back but I even tried to do that and I couldn't do it.

My question is, on the deaths there were -- you have to excuse me for one moment -- on 525 there is a thrombosis; on 527 -- these are all late, by the way, late thrombosis; on 529 there is a late thrombosis. Do you have any information about what valves they were?

MS. HENDERSON: We have a case history slide that we would like to show you.

DR. MURPHY: While that is going on perhaps I could answer you why so few 19. I guess certainly in our area, unless the patient is a tiny person we would go to route enlargement routinely even in an older person, within reason. And I think that is the reason why.

[Slide]

MS. HENDERSON: What you see on the overhead in front of you is a description of the thromboembolic events.

DR. WEINTRAUB: While you are getting that maybe I can answer another question relating to this. I am reading the reviewer's notes and this is about thromboembolism, and this goes to the linearized embolization rates. The linearized rates for late thromboembolism was 1.8 per

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patient year per AVR and 4.4. And we talked about that a few minutes ago. These were rates are less than 6 per patient year, which is twice that of the mechanicals. However, the upper 95 percent confidence limits is slightly over. This slightly higher rate is due to a total of 6 episodes of thromboembolism in cohort 2, with all episodes occurring in MVR patients and which, analyzed alone, separately from 1, resulted in a linearized rate of 8.12 per year.

In the next paragraph it says, however, the sponsor communicated to the FDA -- oh, I am sorry, 3 of the events occurred in 1 patient in a 2-month time period. Then it says, however, the sponsor communicated to the FDA that these events occurred in patients with either a size 17 or size 19 valve.

Well, that doesn't make sense because no 17's or 19's were put in the mitral position. So, number one, that is incongruous. Secondly, if they were aortics, again that brings up the issue of the 17 mm and 19 mm valves. So I am quite concerned about that.

DR. CURTIS: We are looking for a direct answer to the question about thromboembolism because we are going to need to move on to some other people.

DR. WEINTRAUB: I mean, I really want to know what happened to those 11 patients with the 19. I can't find that

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anywhere in here.

MS. HENDERSON: I don't have that at my fingertips but I will get back to you in a couple of minutes.

DR. WEINTRAUB: I think it is very important because we are talking about some very small numbers, and we need to know whether there is some suggestion whether that valve has a problem.

DR. CURTIS: I think we will have to stop with Dr. Weintraub right now and come back to any further comments later. What we will do is start going around the room. I would like to start with Dr. Hartz.

DR. HARTZ: I have three specific questions. There are almost 6200 patient years in the entire world experience and I believe you said there was no strut fracture?

MS. HENDERSON: That is correct.

DR. HARTZ: How about disc fracture with the 17 or the 19? I don't know if you have all that information but, to me, that would be a crucial issue in deciding on the 17 and 19 valves because it is a different disc and that is really the impetus for redesigning this prosthesis in the first place.

MR. OLSON: I think I can answer that question.

DR. CURTIS: Could we use the microphones a little more, please?

MR. OLSON: I think I can answer that question on size 17 and 19. In all the product complaints that we have had, that have been returned, we have disc fractures that were as a result of disc implantation. None of those were 17 or 19.

DR. HARTZ: How many disc fractures in the 1000 patients? Do you have that information?

MR. OLSON: Yes, I do. There were nine total.

DR. HARTZ: I want to address the other question to Dr. Murphy. I am curious about the issue of "perivalvular leak" with this prosthesis. The bench testing shows that the aortic valve has a 0.8 to 29 percent regurgitant fraction and the mitral 1.3 to 37 percent. Since this prosthesis opens asymmetrically, are you convinced that the leaks that are being seen are periprosthetic or through the prosthesis, and do you have any patients in whom the completion TE echo in the operating room actually changed, or is that perivalvular leak a new finding later on? In other words, are you comparing apples and oranges, or are these just small leaks through the prosthesis that are expected?

DR. MURPHY: I can't answer that. We haven't looked in detail at the 100 echoes that we have with respect to this presentation. All I can report to you is that the leak rate is as they were incidentally picked up in

follow-up. Either a patient came in for cath. The cath. data would come through and it would be "1+" valvular leak. That would be listed as a perivalvular leak whether it was through the disc or around the annulus. Does that answer your question?

DR. HARTZ: Yes, and also did any patient have a small leak with significant hemolytic anemia either through or around the prosthesis?

DR. MURPHY: Yes, as I think I touched on before, there were six patients that required further surgery, and they were significant enough to have the valve explanted.

DR. HARTZ: But not all anemia; some hemodynamic?

DR. MURPHY: In terms of that -- I have to get that, if you don't mind. Yes, what I am referring to here is a manuscript that had been accepted for publication in The Canadian Journal of Surgery. This is in respect to the hemolysis, and at the end of one year of those patients that we were following, five patients were taking iron supplements. Two of these patients had a low hemoglobin; three others had a normal hemoglobin in the presence of a low red cell count and a low hematocrit. Of those five patients, one was known to have a perivalvular leak and another patient had endocarditis. So that answers your question I think.

DR. HARTZ: The final issue relates to every prosthesis I believe that we are going to discuss on the Panel, and it is the labeling information. We have two statements that are emphatically listed: Patients with prosthetic valves who undergo dental or other procedures should be considered for prophylactic antibiotic therapy. Is that what we should say or is this "must" be considered?

The other thing is based around a discussion we have had today. Patients may require anticoagulation and antiplatelet therapy. Yet, one of our contraindications is that patients cannot take anticoagulation therapy. Now, we have heard that the 17's and the 19's are probably the valves that are thrombosing and we don't have an emphatic statement that patients with this prosthesis must require anticoagulation therapy. So I think this is really a hedge on the regulatory commission's part if we don't state what really should be done with those patients. That is just an observation. That is about all my comments.

DR. CURTIS: Dr. Simmons?

DR. SIMMONS: Most of the issues that I would have come up with have already been covered. I guess I would just have two or three. I guess I never realized that, first of all, valves could be resterilized. In your section it says do not sterilize more than ten times. Do you have data to

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substantiate that there is safety in resterilizing valves ten times and that anybody would want to?

MS. HENDERSON: Yes, we do have data to validate that we can sterilize it ten times, but I don't know anyone that has.

DR. SIMMONS: I am sorry? I didn't hear what you said.

DR. WEINTRAUB: She said they have data to validate it but she doesn't know anyone who has done it.

DR. SIMMONS: I just can't imagine that that should be left in there. I don't know. The other issue that I thought about also Dr. Weintraub has already brought up. I don't think there is any data to substantiate the ten years that was asked, and also the valve sizes. But that is all the comments I have.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: Most of what I had concerns about was covered. I think though that since we are asked to look at three valves over the next day and a half, we were discussing sort of in general our belief about valves the night before we started this morning, and the things that brought concerns to me is that we are looking at really 314 patients to make a decision on a valve, and its safety for when we implant it. If we are thinking the average age is 53

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years, we are looking for something that can conceivably be in people for an average of 20 or more years.

Clearly, looking at data with 3-5 year follow-up is truly inadequate for us to really sit back and say absolutely we have convincing evidence for the safety. I guess what I am looking for is that maybe as a Panel we need to consider maybe how we look at these data. Clearly, it is not a reasonable thing to ask companies to give us data that is going to be absolutely convincing for the safety or else we would never have a new device. I mean, that is on the one hand. On the other hand, the real concern is can we truly say anything about the safety of a device where, if there were a failure rate of 1/1000 or 2/1000, with a group of 314 we may not really ever see it. I think that is the dilemma we are in. To get a new valve out we basically have to follow it once it is out there in the public.

One consideration, when we start looking at risk-benefit, and I know this is not the purview of the FDA at this point to say that you must come up with a valve that is in some way better than what is already out there, but I think certainly when I, as a cardiologist, have a patient in my office and I have some input to my surgery colleagues as to what goes in them, maybe what we should be saying is we have to compare this valve with a new valve. As a company,

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should we be looking at a better valve in some way, either to implant a safer valve, a more efficient valve, better hemodynamics or something?

I just say that as a comment and as something that we may want to think about as a Panel to discuss in greater detail.

Looking specifically at your patient counseling information, I do agree with Dr. Hartz that our counseling information is woefully inadequate. I think just stating about dental procedures and you may require anticoagulation -- I think that probably could be a lot more stronger in saying they must, you know, typically be prophylactically treated and must be anticoagulated.

Short of that, I think a lot of the concerns I have -- I think the 17 and 19 valves should be considered as different valves. I think they truly are.

The last thing, you said there were nine cases where it was fractured. Were these fractures with actual separation of the occluder from the strut, or were they just fractures brought in the process of removing the valve?

MR. OLSON: All of those were fractures associated with implantation, and several of those were associated with a particular surgeon in the earlier years of implantation, not using the valve holders as would be indicated in the

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instructions for use, and they were using forceps and that was corrected.

DR. GILLIAM: Because to that end, I think we can truly say that if these were only fractures during the implant time we don't really have a great deal of data, is it fair to say, about whether you can expect a fracture of the actual disc in use?

MR. OLSON: Since 1982 and the 120,000 Monostruts that we have implanted, we have been diligent about keeping track of all the product complaints, and we have no reports of disc fractures or valve breakage of any kind during that time. And that is true in the literature and it is also true in all the clinical studies that we have done. Cohort 3 and cohort 4 also support that conclusion.

DR. GILLIAM: I notice that for many of your deaths there were no autopsies. So I guess my concern with being able to state that absolutely is that there are many people who had sudden death where there was no autopsy. You can't say for sure.

MR. OLSON: That is correct.

DR. GILLIAM: That is all I have for right now.

DR. CURTIS: Dr. Domanski?

DR. DOMANSKI: Well, actually I too had the privilege of being in on some of the early discussions about

valve approval, and I want to amplify a little bit on Dr. Gilliam's point. He makes I think some important points.

One problem with the valves that we have out there is they are really very safe -- that is not a problem I guess, but if you come up with something that is better or come in with an innovation, it would be very difficult in any kind of practical fashion to demonstrate true equivalence because the numbers involved with the low event rate really prohibit that as a practical endeavor. So if we insist on wonderful controlled trials, I mean truly randomized trials, with these things we end up with a situation where we can never introduce an improvement for all practical purposes. And that was intolerable, and was the basis for trying to establish guidelines on the basis of extensive literature and knowledge of these valves that are out there that already exists. So one has to support that.

I think that the issue that is raised is what about the valve that really is just "me too" and really offers very little in terms of the improvement that we are trying to design the process to accept? Then I think the issue of having some reasonable demonstration that it is not obviously worse in terms of safety than the valves that are out there is important. And an issue that I plan to visit in some more detail later in the day is how one puts together a

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reasonable meta-analysis of the literature that is there because, after all, in the end it is reasonable to ask that at least that process is effectively done. So I actually plan to visit that because these are the first valves and I think this Panel needs to be cautious in how they go about using the data that are here, both the data that are collected to generate the OPC's for these valves and also the data that are presented by the company, because it is difficult to completely divorce the two. I think that is actually quite important.

Beyond that, and the fact that I will visit it at some length later, I don't have any questions for this valve.

DR. CURTIS: Dr. Crittendon?

DR. CRITTENDON: I have a couple of questions, but I really would like to echo pretty much what all the other discussants have talked about. I think they have all raised substantive issues.

The first question I have is how many explants do you have from either cohort? Maybe you can just say it in terms of what you have in terms of worldwide, in terms of valves that have been taken out for whatever reason and then sent back to the company to study?

MS. HENDERSON: Can you repeat the question?

DR. CRITTENDON: How many explants have you received worldwide that have been taken out of patients in whom they had been put in?

MS. HENDERSON: I can answer for the cohorts and Scott can answer for the worldwide.

DR. CURTIS: Excuse me, was that included in your PMA?

MS. HENDERSON: Yes. There was a total of 3 explants in the operative time frame, the first 30 days postoperatively, and there was a total of 11 after the 30-day postoperative time frame, for a total of 14.

DR. CRITTENDON: And how were those studied? What types of things did you do to look at these?

MS. HENDERSON: We followed the FDA guidance protocol on reviewing explants.

DR. CRITTENDON: Did you do any metallurgic studies and look for stress fractures?

MR. OLSON: The answer is no since none of them fractured, but we did gross microscopic evaluation, as well as looking at wear.

DR. CRITTENDON: But there must be early sings of that though. There must be some way to look at that to see if there were impending stress fractures. Isn't there a way to look at that?

MR. OLSON: It is a possibility. Those were early on in the study and I don't believe that was done by the prior sponsor.

DR. CRITTENDON: But worldwide, can you address that?

MR. OLSON: Worldwide, the types of returns that we have received were more of a product complaint nature, and we have done evaluations of those much along the same lines as far as the explants go, and we have probably gotten 20 percent back of the product complaints that we do receive.

DR. CRITTENDON: This is a follow-on valve from the original Bjork-Shiley. Was this not originally a Bjork-Shiley valve and the company went bad and Alliance picked it up? Do I understand that correctly.

MS. HENDERSON: This product was developed -- you understand it correctly but I would make the distinction that this valve was manufactured differently and is a different valve compared to the other valves.

DR. CRITTENDON: I know Bjork-Shiley did manufacture a monostrut. Is their design different or is it the same?

MR. OLSON: Answering that, it is essentially the same. It is the Monostrut heart valve.

DR. CRITTENDON: That is what I thought. Inasmuch as this was a very controversial valve, or at least some models of it, I would just wonder if, for the public record, you all could talk about how many years or how much follow-up you had before there were strut fractures encountered, and whether we have any type of similar follow-up now? In other words, if it took six years since the valve was clinically approved before we started noticing fractures, are we anywhere close to that with the Monostrut valve?

DR. MURPHY: I can answer that pretty clearly. We had no structural failures in this valve, and it is not the valve that was involved in stress fractures.

DR. CRITTENDON: That is quite clear but we don't know if that is something that is coming down the pike and we just haven't followed it long enough. Is that a fair statement?

DR. MURPHY: I guess so, sure.

MS. HENDERSON: Can Dr. Lindblom answer this question? Dr. Lindblom is our European clinical investigator.

DR. LINDBLOM: My name is Don Lindblom. I am a cardiac thoracic surgeon in Stockholm. I have no financial connection with the company or with the prosthesis.

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DR. CURTIS: Are you here as a paid consultant?

DR. LINDBLOM: A paid consultant for this meeting, as I traveled from Stockholm yesterday and will go back later today.

I had the unfortunate privilege to write the paper about the strut fracture problem in Stockholm, which was the largest strut fracture problem worldwide regarding older models of the Bjork-Shiley valve, the CC-60 and mainly the CC-70 valve which was not sold in the United States. The Monostrut succeeded these valves and the intention was to eliminate the strut fracture problem.

We implanted a very large number of CC-60 and CC-70 valves and got a very clear picture of the epidemiology regarding the strut fractures. From the beginning, we thought that that was a problem that was appearing during the first years of the implant. After following these patients now for 10 to 20 years postoperatively, we have found that this seems to be a continuing problem with a fairly constant hazard over the years. It certainly doesn't increase over the years but it may decrease over the years. On the other hand, since we started with the Monostrut in Stockholm 15 years ago, we never had one strut fracture or disc fracture, and we have an extremely high incidence of postmortem examinations.

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Virtually all of our patients have had a postmortem examination in the early studies and, although the legislation changed two years ago in Sweden for postmortem examination, for the first cohort and 10-12 years of implants, almost all patients had a postmortem.

DR. CRITTENDON: Thank you. I think it is important just for the public record, that that is stated. What was the rationale for the design change? Was it because of hemodynamics? Was it because of hemolysis? Or was it because of strut fracture?

DR. MORRIS: Good morning. My name is Paul Morris. I am the Director of Research and Development at Alliance. I was director of the cardiovascular with Shiley and it was my group that developed the Monostrut valve.

The Monostrut valve was developed as a result of the strut fractures with the CC valve. Basically, we just increased the thickness of the outer strut and made it one strut so that there was no welding or other manufacturing operations to make the valve.

DR. CRITTENDON: Thank you. I too am concerned about the perivalvular leak and let me just say at the outset, Dr. Murphy, that I am a Canadian trained surgeon. I was at two of the hospitals that were described in the PMA. So I would strongly disagree with your statement about

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Canadian surgeons. I would like to think that all Canadian surgeons are quite excellent.

[Laughter]

Having said that, I want to raise the issue perhaps about the sewing ring of the valve, and I just wonder from your experience whether or not there is an adequate cuff for the aortic one, because I think there are more of the aortics than the mitrals that had a perivalvular leak.

DR. MURPHY: In our experience there were ore mitrals that had a leak and I just have to answer that by saying that the cuff on both of these prostheses, the mitral and the aortic, are pretty much identical to those that you would get. In fact, let me just say that on the aortic one it is more substantial than it is on, say, the pericardial valve. In other words, the surface interface is probably more than in the biological one. Maybe the high incidence has to do with the Maritimes.

DR. CRITTENDON: I just want to reiterate my apprehension about the 17 and 19 mm valves. I agree with all the statements that have been made about that so far. I have a big question mark in my mind about that. Thank you.

DR. CURTIS: We will stop here and take a break and reconvene at 1:00 p.m.

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[Whereupon, at 12:00 noon, the Panel adjourned for
lunch, to reconvene at 1:00 p.m.]

AFTERNOON SESSION

DR. CURTIS: We are going to continue our discussion from this morning. The next member of the Panel will be Dr. Aziz.

DR. AZIZ: I think most of the important questions have been answered. There are just a few that I would like maybe Dr. Murphy to address.

Is there any particular orientation that you would recommend the surgeon place the valve in, either in the aortic or the mitral position, or is any position in terms of the way it rotates suitable?

DR. MURPHY: I guess the recommendation I would make is that the valve should be rotated in its annulus before the stitches are placed because it sort of breaks the inertia of the valve. So if you do place it in whatever way you would like and there is some impediment to its action, then it is easy to rotate. But to answer your question, generally for the mitral the largest orifice we point towards the septum, left ventricular septum. In other words, it falls towards the posterior wall. For the aortic, the larger orifice points towards the right lateral wall, the greater curvature of the ascending aorta. But each time we put it in, as you would do for other valves, you would make sure it works and rotate it appropriately.

DR. AZIZ: Clearly, not very many valves of the 17 and 19 series were placed in either position, particularly the aortic position. Could one of the reasons be that you did a lot of route enlargement?

DR. MURPHY: I think it is fair to say that. With 17's, I think if we had put one in it was in a child, but certainly with the 19's the trend is to try and get as large a valve as possible. So you would go for route enlargement, usually with a piece of Dacron line with a piece of pericardium across the aortic annulus in the usual way.

DR. AZIZ: Clearly, this data pertains to isolated valves in the aortic and mitral position. Maybe the company could answer this, were there any particular tricks or any problems with doing double valves? I am sure the surgeons are going to be using double valve replacements.

MS. HENDERSON: In cohort 3, which addresses double valves and other valves, we did not see any anomalies or any increased linearized rates of that nature.

DR. AZIZ: And just one sort of technical question, going back to the mitral position, you know, with the sort of popularity of living some valvular apparatus or as much of the valve in place, were there any particular, again, tricks that one should know about when one is leaving the valvular apparatus in the mitral position?

DR. ARIS: I can answer the question. With this trend of leaving the posterior leaflet mainly -- now the anterior also but mainly the posterior leaflet, I was surprised to see that all the leakage was referring always to the bi-leaflet valves; it was impossible to do. So I started a crusade to implanting the valves, leaving the posterior leaflet with some tricks that probably will be published shortly. You can do it without any problems, or taking the disc anteriorly, like Dr. Murphy does. With this, I have replaced about 30, 35 valves, leaving the posterior apparatus, with no problem whatsoever as far as movement of the disc.

DR. AZIZ: Okay. And were most of the mitral valves placed through an incision through the left atrial wall or was it by atrial incision, or just a mixture?

DR. MURPHY: In our series it was surgeon's preference -- top of the left atrium, behind the aorta, and probably about half used the traditional, through the AV groove on the right-hand side.

DR. ARIS: May I add a little further? In my experience I have implanted several mitral valves through minimally invasive surgery, through the roof of the left atrium, retracting the aorta.

DR. AZIZ: The dome of the left atrial?

DR. ARIS: The dome, right.

DR. AZIZ: Thank you

DR. CURTIS: Dr. Pluth?

DR. PLUTH: There is one concern I have regarding labeling. I notice that in the Canadian cohort there were 3 deaths related to AV separation, and in reviewing the autopsies on the rest there may have been a fourth. The question in my mind is that this seems to be almost three times the incidence that should be reported or that has been reported in the past, at least 1/100 and perhaps it is even less than that with preserving the posterior cordal structure at the present time. But Bjork at one point, and I am not sure it wasn't even in the labeling of the original Bjork valve, had recommended that we downsize valve size when we measured. The question is, is that going to be included in the labeling or what is the thought on that?

MS. HENDERSON: Yes, we would consider it.

DR. PLUTH: Pardon?

MS. HENDERSON: Yes.

DR. PLUTH: There are a couple of other issues here. I noticed that on page 553 we talk about the postop catheterization data and on the mitral valves size 29 has an incidence of 14/42 patients, and it may be higher because I am not sure now many of the 29 patients actually died

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subsequently, but 14/42 patients in whom a 29 size valve had been implanted had regurgitation to lesser or greater degrees, a much higher incidence than any other valve. And I have a question as to whether or not this particular valve size has some inherent problem with it. I recognize that the 31 and 33 are the same size but, on the other hand, they do have a larger sewing ring. Is there a problem with entrapment of the lens on that particular valve size that causes this incidence?

DR. ARIS: No, that is not the problem. This question, very pertinent question, was already addressed in 1983 when I presented the hemodynamic data in the aortic position, in Phoenix, Arizona, and the same question was asked. There is a problem -- it is not a problem. First of all, this is catheterization data and the degree of regurgitation is very subjective. You would agree about that. You are alluding to number 29, and it is because the larger the number is the greater is the regurgitation because the disc acts as a paddle and it kind of brings back some of the contrast that was injected in the ventricle. In number 23, for example, it was almost nil. In number 29 it was much bigger because of this effect.

DR. PLUTH: In the preclinical and the clinical data, it seems like hemolysis and decreased haptoglobins

appears to be a consistent problem. Do you relate that to the leakage that is around the lens itself, or do you relate it to the high incidence of perivalvular leak that was found in this group of patients?

DR. MURPHY: Would you like me to answer that?

DR. PLUTH: That would be fine, Dr. Murphy.

DR. MURPHY: Let me reiterate, I think perhaps while you say there is a high incidence of perivalvular leak, the overall leak rate is compatible with what the OPC standards are. Certainly in our series the perivalvular leak was judged as trivial or mild.

I too was surprised at the amount of so-called hemolysis. But as your hematologist will tell you, the degree of hemolysis is clinically probably irrelevant because certainly at one year the reticular counts were all normal in our group. And these results are certainly in keeping with those of other mechanical prostheses. So I was assuaged by that finding, for myself anyway, that this valve is no better or no worse than other mechanical prostheses. Okay?

DR. PLUTH: All right. I don't have the systolic ejection times to make my own calculations and I am also concerned about whether those peak-to-peak mean systolic gradients were your calculations. I believe the Gorland

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formula requires that you use the mean systolic pressure gradient. Just roughly approximating it, and since I don't have the mean ejection times I had to use the Hakey formulation, it would appear that the choices that you used as to what gradients you were going to employ for the valve area depended upon the lowest gradient and not necessarily whether it was the mean gradient or the peak-to-peak systolic gradient. Could you explain that for me, please?

DR. ARIS: I am really not prepared to explain all the calculations regarding the Gorland formula.

DR. PLUTH: All right. I have no other questions.

DR. CURTIS: Dr. Skorton?

DR. SKORTON: Thank you. I have nothing to add on the specifics of the company's presentation. So you can stand down and relax. I have a question for the FDA statistical consultant who spoke earlier. I thought there was someone from our gang. Anyway, I have some questions about the comparisons we are doing between the OPC data and the data, but I will only bring them up if there is someone here who could answer them from the FDA's perspective. They are really not a company issue.

DR. SAPIRSTEIN: I am not a statistical consultant. I am a cardiac surgeon but what question could I answer?

DR. SKORTON: Okay, I am not a statistician either. I am just a country boy from Iowa but I just have some questions.

[Laughter]

On page 5-7, 5-8 there is a description of the statistical analysis that I am sure is the party line that we are telling the companies to use and I just have some questions about it. The data from the OPC, the control data, I understand there are linearized event rates, events per 100 patient years.

DR. SAPIRSTEIN: Yes.

DR. SKORTON: I guess that then means that it is assuming a constancy of confidence intervals across time.

DR. SAPIRSTEIN: Yes.

DR. SKORTON: So I guess more of a comment than a question, just for the record, that is going to lump the changes that we all know occur with hazard rates over time.

DR. SAPIRSTEIN: Yes.

DR. SKORTON: It is going to underestimate those events that we know are worse close to the surgery. It is also going to underestimate those events that we know are worse far from surgery. I am just curious whether we have any thought about making an attempt to recalculate the data at other intervals since any differences found would be

washed out by this kind of an approach.

DR. SAPIRSTEIN: Well, this was an attempt to address the problems that are associated with the early sort of perioperative period, the 30-day postoperative period where so many of the events are not related to the device itself but to the patient, the operator technique and the other things. So they were separated, the early events, and they were recorded as incident rates. We assume the constant hazard for the later events, and based on the analysis of the historical literature review and assuming a constant hazard rate, we developed these OPC's, objective performance criteria. I don't know if that addresses it.

DR. SPYKER: My name is Dan Spyker. I am a medical officer but I am a minor in statistics, I guess. Your question was about page 7 and 8, and these are referring to actuarial analysis. These are not the OPC's or linearized rates. I guess I have to put in an engineering plug and say linearized is totally wrong here. What they are is average. If I could change a word, I would change linearized to average and my cardiac surgeon friends can't deal with that.

The linearized rates, as you correctly pointed out, don't make any consideration for when they occur. But the actuarial analysis, which is done usually by Kaplan-Meier in these cases or done by life table, which are

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both simply ways of taking into account the risk at that point in time, and the way they are displayed routinely is precisely attacking or answering the question you ask, i.e. when do they occur? The fancy formula on the next page is just some simple method of putting a confidence interval on these.

The other thing that I have come to love over the last couple of years are confidence intervals. I think simply displaying some method of uncertainty or certainty, depending upon your point of view, with these curves that look at the time domain are a very logical thing to do, whatever else we do. So the OPC's do not deal with those. So this is an important point you brought out, and that is the way we are approaching it.

DR. SKORTON: My second question is just the point you are making, that with the Kaplan-Meier analysis you do calculate the 95 percent confidence limits assuming a certain kind of distribution. But we do not have comparison data from OPC's that are calculated the same way. Is that correct?

DR. SPYKER: That is correct.

DR. SKORTON: So I would point out for the record to my fellow panelists that we don't have any way of knowing what to make of the specific 95 percent confidence limits at

different points in time in the Kaplan-Meier analyses. They are not directly comparable, I believe, to what is lumped average, what is called the linearized rate, across all of the things.

DR. SPYKER: Well said.

DR. SKORTON: So one implication of that is, not in any way to the detriment or benefit of any company, close calls between those rates and the OPC's I don't think we should take seriously because they are not calculated the same way. They are apples and oranges, or maybe Gala apples and Delicious apples, something like that.

DR. SPYKER: Let me respond then briefly. I don't believe we have used actuarial data to make the comparisons. All the comparisons we have at least attempted to make are appropriate, i.e. either linearized or average rates, and vice versa, what we have tried to do is provide you, wherever it is available with either numerical data or the graphical displays from the comparison articles.

DR. SKORTON: I guess what I would say is you can't sort of have it both ways. If you lump hazard or complication rates, they wash out time differences. If you look at the Kaplan-Meier analysis, which is time sensitive, you don't have comparison data. So we never have time sensitive comparison data against controls, as far as I can

see, period.

DR. SPYKER: That is correct.

DR. SKORTON: I guess that is it.

MS. KENNEL: I just wanted to add one thing. I think when we wrote all of the various versions of the guidance documents what we had in mind were acute data. We really weren't anticipating a case such as this, where we would have a sponsor coming to bat that had a fairly lengthy follow-up period. So our thinking was that the rates are somewhat constant in the acute period.

DR. SKORTON: Yes, I think that is absolutely true. It is just that the companies should not be penalized for this but clinicians like us are going to have a look at the three, four, five years, especially for events like this that we know get worse over time like thromboembolism. So that in no way contradicts what you said about acute things but we are also interested in distant things and I think, as a suggestion for refining this over time and not penalizing people today who are trying to play by the rules, we should just recognize that after that acute period we don't know what to make of these bars and so on, whether they are really different or not. They are just sort of interesting to look at, and probably many of us are just calculating them compared to what we think ought to happen but we don't

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really have a statistical person. I am done.

DR. CURTIS: Dr. Tracy?

DR. TRACY: Thank you. I think most of the issues that I had have been addressed by the other members, but I just a couple of questions. Going over the historic follow-up on the valves around page 536 and so on, it looks like about six and seven things start happening. The curves are dropping off. The perivalvular leaks are increasing. The thrombosis is increasing. The hemolysis is increasing. Do you have any long-term data, because it looks like the last point that we have on all of the curves is getting significantly worse? I think we need to continue following these valves' performance. Do you have any estimate of what the longevity of these valves is?

DR. ARIS: Well, we have been implanting these valves since 1983. Last year was published which encompassed 8,599 valves for a period of ten years, with a total follow-up of 27,000 patients. In these, I can confirm that there were no structural failures reported as a complication, and the hazard ratio, as a matter of fact, that was calculated and we found that except for the perivalvular leaks, endocarditis over the first year, the rest of the hazards were completely constant during the first eight years. So your conclusion looking at the data

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that you have in the Panel pack with our larger and longer follow-up is not -- I mean, the rates are constant. They are fairly clinically acceptable.

DR. TRACY: Do you have any idea if the rate of fatal thromboembolism is higher with this particular valve as compared to other types of mechanical valves?

DR. ARIS: In our series, in this particular Spanish series, there were no fatal thromboembolisms.

DR. TRACY: I think that there were several autopsies that reported --

DR. ARIS: I am sorry, I am talking about the Spanish series.

DR. TRACY: Oh, I am sorry. Go ahead.

DR. MURPHY: The question is whether there is an increased incidence of thromboembolism with this prosthesis?

DR. TRACY: No, the question is if a thromboembolism occurs, is it more likely to be likely to be fatal with this particular valvular structure as opposed to another structure or valve?

DR. MURPHY: Gosh, I don't think you can answer that. I couldn't, as a surgeon, tell you whether one thromboembolism is going to be more lethal than another despite what valve is in place. I think they are all potentially lethal. I can't answer that accurately.

MR. OLSON: I don't believe that we have done the analysis.

DR. TRACY: I think that is something that could be done. I am not sure that it needs to be done, but I think it could be done. There seems to be a theoretic concern that with a single leaflet, that if a clot forms it is more likely to be fatal as opposed to a bi-leaflet valve. But that may be a simplistic idea.

I am curious, there was initially a carbon-coated and then a Teflon ring. Why was the change made? I know somebody asked that before but I am not sure I understood the answer.

MR. OLSON: The Monostrut valve is offered in different types of sewing rings, both Teflon and carbon-coated Dacron. Back in 1993, when we were before the Panel, there was some question on the carbon-coated data. It has just been excluded. It was only done in Europe. It is a very small percentage of the Monostruts implanted.

DR. TRACY: So none of the data presented here in cohorts 1 and 2 are carbon-coated valves?

MR. OLSON: That is correct.

DR. TRACY: Just a point of curiosity, if I am understanding the history right, at some point during the development of your product there was a switch to allow

echocardiographic hemodynamic data to be used. There is precious few hemodynamic data. We have already discussed the 17 and 19 in the aortic valve position. There is virtually nothing of hemodynamic data presented for the size 25 mitral valve. I am just curious why you didn't get echocardiographic hemodynamic data.

MS. HENDERSON: The previous sponsor did not proceed to collect that and, as we are a young sponsor -- we are seven months old -- we would want to get that.

DR. TRACY: Again for the record, we talked about the 17 and 19 but I have the same concerns about the 25 for the mitral position. I think those are all the issues that I have.

DR. CURTIS: Dr. Gooray, do you have any comments as the consumer representative?

DR. GOORAY: Just a brief comment, an extension on Dr. Weintraub's concern with thrombosis. The number of patients presented who died in terms of the history, there are 51 patients defined as having died; 37 autopsies were not done. If you look through the data that was presented, 11 patients had associated what can be defined as a thrombotic event as either the immediate or close to immediate cause of death. Looking back, are there any warnings you should use on the labeling which, from looking

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back at these data, there is a patient subpopulation that you should not put this valve in? Because there is no separation of which valve it is. We probably might have to make assumptions. People with atrial fib. more than likely have mitral valve prostheses and vice versa. But this is an inordinate amount of people being labeled as having a thrombotic acute event causing their death. Is there any way of looking at these patients prior to them dying that you can tell a subpopulation of patients who are at increased risk for this type of valve?

DR. FLAX: My name is Dr. John Flax. I am a paid consultant to the company. If you look at the incidence rates for thromboembolism, firstly, the overall incidence of thromboembolism does not exceed the OPC guideline. It is actually below when you take aortic and mitral valves and you put them together.

Additionally, if you look at the incidence of thromboembolism with the mitral valves in the Canadian cohorts, which is the study that is presented as the primary efficacy data here, the incidence is 4.4 percent.

If you take the view that thromboembolism was kind of over-reported or at least was reported even if there was any doubt that there was possibly a thromboembolism and you extend that and you look at some of the other PMA data with

other cardiac valves, and you compare the thromboembolism rate with mitral valves you find that there are valves that have been approved that actually have a higher incidence in their PMA of thromboembolism with mitral valves. So we don't believe the incidence of thromboembolism for this particular valve is any different than any of the other valves.

In addition, if you look at the incidence of thromboembolism in the literature with this valve, it is comparable with literature reports for thromboembolism with other valves.

DR. GOORAY: Okay, that is all.

DR. CURTIS: And the industry representative, Mr. Jarvis, any comments?

MR. JARVIS: I have no questions.

DR. HARTZ: I wanted to ask a question specifically in response to Dr. Gooray's comment of the FDA. That is, since we know that many of these events occur much more often in the early phase, in the first 30 days, why do we not have -- and I have wondered this since I implanted heart valves -- a temporary card that the patient carries with the warnings until the permanent card is received in the mail from the valve company? That is the time when the patient should be warned the most, and that is the time the patient is carrying nothing.

DR. CURTIS: I guess I am not exactly sure who would answer that right now but it is a good point.

DR. CALLAHAN: Anything like that you want to bring up is certainly -- I mean that is the kind of thing you are here to suggest and we can advocate those things.

DR. CURTIS: All right. I have one minor point I want to make and then maybe try to focus the remaining discussion a little bit. One of the comments that was made about the perivalvular leak rates was that when panel physicians had looked at all the information they suggested that it might have been due to the sewing ring or the suture technique used, or coming up with ideas about why there might have been a problem with that. Were there any conclusions drawn, or is there a way that the suturing ought to be done? Is there some warning that should be in the labeling for this device that would help the physician about how to do this?

Secondly, there were some comments made before about which way the valve ought to be oriented, yet, I don't see that in the labeling either. If it should be oriented so that the large hole is toward the septum, or whatever, I don't see any of that and you would have to be assuming that somebody would know that, which is always the worst thing to do. So if you could address those labeling issues.

MS. HENDERSON: We would put in the labeling, regarding the position of the valve, in fact, we would indeed have a surgical technique manual which would describe the operation and that positioning.

DR. CURTIS: And what about the suturing technique issue?

DR. ARIS: Well, the issue of the perivalvular leak has been addressed this morning as a main concern of a member of the Panel. Let me begin by saying that there is nothing wrong with this suture ring. The suture ring is the same ring that was made in the Bjork-Shiley valve 30 years ago, exactly the same. So there is no new material or anything like that, or a new form. So it worked before and it is working now too.

Now, I feel that the numbers that everyone is concerned about is just a reflection of overrating the data. The OPC guidelines were drawn from 1982-1986 and were not based on echo Doppler studies. If you look at the slide where it shows patient ID, month or the complication, outcome, classification, and you even have the size here for aortic valves, you will see that most of the classifications were classified as minor episodes. Most of them were picked up in the follow-up examination. The echo Doppler number shows 1+ or 2+, which is equal to trivial. There is even one

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patient here, 3042, that has a minor leak reported. The patient comes back 20 months later and is reported as a second event. This is overrating what has been happening to these patients. Incidentally, it is one patient with a 19 mm valve, down at the bottom, with a perivalvular leak which would probably answer the question of this morning about the size and valvular leaks.

DR. CURTIS: I guess that is not quite what I was getting at. I see what you are saying, that a lot of these leaks were minor. I am not a cardiac surgeon myself and if there are suturing techniques or ways of putting these valves in that would help avoid the problem, has that been looked at? Are there recommendations you would make to a surgeon putting it in?

DR. ARIS: Well, I believe that most of the surgeons who know how to put in a cardiac valve would know how to do a Monostrut.

DR. CURTIS: So that comment from your physician panel about suturing techniques, you don't really find it relevant?

DR. ARIS: Yes, I think so.

DR. FLAX: Can I just comment on that as well?

DR. CURTIS: Sure.

DR. FLAX: I think the point that is being made

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here is that we are experiencing a situation where we have a high incidence of minor perivalvular leaks reported in this particular study, most of them based on echo Doppler, which wasn't necessarily available when the OPC guidelines were developed and maybe what we are seeing is a higher incidence based on the fact that we have new techniques and are actually able to pick this up and that is creating a situation where there are more reported. Maybe it isn't a particular problem with this valve, which is what the surgeons are saying.

DR. CURTIS: Sure. I want to shift gears a little bit now. I guess I think it is time for all us to think about or emphasize the part that this is not the first time that this particular product has come before the Panel, and at the last time this was presented recommendations were made that certain factors had to be looked at. There were eight conditions made.

I think it is important for us now to sit and focus on the safety and efficacy issue, and whether or not the eight questions have been satisfied by the sponsors of the PMA. That is in several places in our Panel pack. One place is 4-32 that I happen to have open to right now.

There were certain conditions placed: that the analysis should be limited to the Canadian cohort, and a

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more explicit comparison to a control group, etc. For the most part, and if anybody disagrees with this, I think there seems to be reason to believe that many of these have been satisfied, particularly one, two and three, which I just mentioned; number six about a physician review of the deaths; restricting the PMA application to the Teflon sewing ring; and then the engineering issue, number eight.

So I think the remaining issues really, in terms of whether or not we have the information that was requested, have to do with ensuring an adequate number of implantations at different sites. In this particular case what has been requested was three centers with 35 aortic and 35 mitral implants at each of the centers. The criterion was met at two of the three, and the third one almost made it for the aortic and really didn't for the mitral. It may be nit-picking. It is too bad it couldn't be satisfied. There is a lot of other information there, and I am not sure that saying that while you hit 32 and not 35 is not good enough is really reasonable.

I am not too concerned about that. I am interested in the issue about the cardiac catheterization data in the follow-up. In particular, and it has been alluded to several times here, we simply don't have enough information on certain of the valve sizes, period. I mean, no matter what

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else we want to say about labeling issues and everything else, we are missing information and if we have patients for whom we don't know their outcome, and particularly with the small valves and the issue about thromboembolism, I think it is going to be hard to conclude that we know that these things are safe and efficacious without that information. So I think that is one area I was curious about.

Then in particular, looking at the follow-up, I may have missed it but some of these things, like what you just showed me about perivalvular leaks, a lot of it said it was echo Doppler data and all that, but in looking through the Panel pack I saw catheterization data and not a whole lot else. I guess that is the one thing that was a little bit unsatisfying about this, the follow-up of the patients.

What we have seems to suggest that the complication rates are acceptable compared to other valves that have been on the market, but in terms of just some follow-up issues -- the fact that follow-up was completed in, say, 86 percent of patients at 2 years, 85 percent at 3 years, and then out of those groups smaller numbers actually even had New York Heart Association data obtained. I am a little bit underwhelmed by the follow-up of this. I mean, in some respect saying 85 percent may be pretty good but, on the other hand, that means you have 15 percent of the

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population missing and that always begs the question what happened to those people. Even if they came from far away or somebody else followed them, or whatever, it is not that hard to figure out what their Heart Association class is.

The issue of anticoagulation has been brought up previously here. There were huge numbers of patients for whom there is not even any information on what kind of anticoagulation they were on. We don't know if they were on Coumadin or what. It just seems overall in terms of a clinical study and follow-up of patients that that is really not very rigorous, to say the least.

But the bottom line really in terms of follow-up has to do, I think, with the cath. data, and really the numbers were met. One of the pages I have here is 5-54, and 5-52 also has it on there. It appears that what is being reported is a total of 38 patients in the mitral valve position where we have any kind of cath. data, and 67 in the aortic position. If you look at it, it is really minimal information. Certain sizes are missing altogether, for example the 17 mm aortic valve, and there is one patient with a 19 mm aortic valve, and multiple sizes in the mitral position also have no information at all.

It is difficult to impossible to get catheterization data in people after they have had surgery,

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particularly if they are doing well, but it is not hard to get an echocardiogram. It would be nice I think to get more information on this. Certainly, the fact that there were certain valves missing I think would make it very hard for us to, like I said, make a statement about safety and efficacy when you have missing information.

Do you have this echo data some place and I didn't see it or you didn't include it?

MS. HENDERSON: No, we do not have echo data in our hands at this time to provide to you, but we do know of Dr. Aris' study and that he has done echocardiographic data on, and we also know that Dr. Murphy has additional echocardiographic data that he can provide to us as well.

But I want to draw your attention to the fact that the catheterization data was collected not in a particular time frame. It was not required to be collected in a certain time frame. So that is why you see the difference between the follow-up time frames. If you look at the overall catheterization data in Tables 10 and 11, then you will see that the numbers of patients are met, except for the smaller sizes as you have mentioned.

DR. CURTIS: Right, what it basically comes down to is minimal data, but the number of at least seven per valve size was met for several of the different valve sizes

so it is barely acceptable but it is what was asked for.

As I said, I think it would have been easier and possibly more informative to have larger numbers of patients with echo data but that is also rewriting history I guess. But in the future I think it is going to be an easier way to follow this patients and know what is going on.

Those are the major comments I have. What we can do is go around and see if there are any other issues that anybody wanted to mention. At this point, I think it would be nice if there are little minor issues that we may not necessarily have to address in detail now, I would like us to concentrate on have they shown safety and efficacy and have they answered the questions that were raised at the previous Panel meeting. Dr. Hartz, we can start with you.

DR. HARTZ: We are not voting at this point?

DR. CURTIS: No, no.

DR. HARTZ: I think it is important to point out that with every prosthetic heart valve, either bio or mechanical, the patient leaves the operating room with some degree of leak inherent to the prosthesis.

As far as gradients, I am a little concerned about those two small sizes but I can't really make a whole lot out of the leak data.

DR. CURTIS: Okay. Let me just clarify that this

is the last chance to ask the company any questions. So if anybody has any burning issues, this is the time to raise them. After that we will close the discussion and it will just be among the Panel members. Dr. Simmons?

DR. SIMMONS: I don't have any specific comments, but wasn't the company looking for some data on some issues that Dr. Weintraub brought up? I was interested in hearing about that.

DR. CURTIS: Okay, we will get to that.

DR. SIMMONS: There were a lot of, like you said, minor, little things, like typographical errors that I won't bring up.

DR. GILLIAM: No specific comment, other than I think from the safety issue for the smaller valve sizes, 17 and 19, I have no confidence that that has been demonstrated at all at this point. I will stop there.

DR. DOMANSKI: I think the one comment I would make is that it is awfully hard to get these valves and any of these devices up before a Panel, let alone approved. I do think though that it is important to remember that if we put this thing out, we need to be fair to the people out in the community who are going to get valves, as opposed to just the company that presents it. I think that is how we have to consider the data before us. I would rather precipitate

injustice on the company -- and I think this goes for any of the stuff we are doing but I think it is important to be responsible to the public, not what happens to one of the companies.

DR. CURTIS: Dr. Vetrovec?

DR. VETROVEC: Well, I would just go back to the comment about it is hard to get one of these to the Panel if we get all the information that is real. On the other hand, I am still bothered by the New York Heart Association classification and at five years there is 63 percent data. I mean, that really is a phone call even if somebody doesn't want to participate. I find that hard to believe.

DR. CURTIS: Dr. Crittendon?

DR. CRITTENDON: I don't have anything to add.

DR. CURTIS: Dr. Aziz?

DR. AZIZ: I don't have any further questions.

DR. CURTIS: Dr. Pluth?

DR. PLUTH: I don't have any further questions.

DR. SKORTON: No more questions for the company.

DR. CURTIS: Okay, Dr. Weintraub, you are up.

DR. WEINTRAUB: There were seven patients who had thromboses of their valves. Of these, at least three died. So I am still asking the question which valves. And if you have similar data with the thromboembolism, that would be

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nice too.

MS. HENDERSON: First, I would like to clarify that earlier this morning you said that there were three deaths -- three thromboembolic events that were in the 17 and 19 mm sizes, and I went back to check that --

DR. WEINTRAUB: No, that is what I am asking.

MS. HENDERSON: This is your same question then?

DR. WEINTRAUB: No. Both in the deaths and the thromboembolism section the numbers are cited but I don't know what valves, whether aortic, mitral or what, what size.

MS. HENDERSON: In valve thrombosis there were no cases in the operative period. There were three cases of valve thrombosis in the late period in the aortic valves and there were four in the mitral.

DR. CURTIS: What page are you on in the Panel pack, so everybody can follow?

DR. WEINTRAUB: Well, if you look at 5-44 and you count across, the number of events in the interval is up to seven cases of thrombosis. So they were split about half and half, I gather. But how about the sizes?

MS. HENDERSON: The aortic group included 21, 25 and 23, the mitral group included 27, all size 27's.

DR. WEINTRAUB: Do you have a similar breakdown on thromboembolism?

MS. HENDERSON: Yes. In the operative time frame there were 4 atrial aortic valves, TE's in the aortic valve and 3 in the mitral group, of the total of 7 there were 5 residuals and 2 transient. In the late postoperative time frame there were 10 events in 9 patients that were residual in the aortic group. There were 5 in the group that were transient. In the mitral group there were 11 events in 9 patients that were residual and 14 events in 12 patients that were transient. This totals to 21 patients, 18 events that were residual and 19 events in 17 patients that were transient. These valve sizes include 21's, 25's, 27's, 23's in the aortic, and in the mitral 31, 33, 29, 27, 25, 23, 27, 29. Does that answer your question?

DR. WEINTRAUB: And what happened to 17 and 19? I mean, there were 6 episodes of thromboembolism in cohort 2, all episodes occurring in mitral valve patients. However, the sponsor communicated to the FDA that these events occurred in patients with either a size 17 or size 19 valve. Is there some missing information?

MS. HENDERSON: Yes. I would like to correct that apparent error. That actually occurred in the 25 mitral group. Let me just clarify that in the size 19 there were 11 patients with complications: 1 AC bleed, 2 PV leaks, 1 death and 6 had no complications.

DR. WEINTRAUB: That is in which?

MS. HENDERSON: In 19.

DR. FLAX: In 11 patients.

MS. HENDERSON: In 11 patients with 19's.

DR. WEINTRAUB: Thank you. I read somewhere in the packet, and I can't find it, that there was some estimation or calculation or determination of regurgitant fraction, and I seem to recall 27 percent in one valve. Am I thinking of something else and that is why I can't find it because it is not there? Was it in the preclinical? I looked in there again and I couldn't find it. Is that within the kind of range one sees in preclinical testing or, I should say, bench testing of mechanical valves?

DR. YOGANATHAN: Dr. Yoganathan, from Georgia Tech., paid consultant for the company. Yes, that is no different than what you would see with the St. Jude, Carbomedics or Medtronic-Hall valve.

DR. WEINTRAUB: Thank you. I don't have any other questions.

DR. TRACY: No questions.

DR. GOORAY: No questions.

MR. JARVIS: No questions.

DR. CURTIS: All right, this concludes the Panel member questioning of the company, and you can go ahead and

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step back from the table now. Does anyone have any other further comments right now, just among the Panel members? Any concerns that haven't been raised yet?

DR. SKORTON: I am sorry, Chair, not to beat this to death but maybe we could ask Dr. Yoganathan back. I don't see that data in the engineering section. Engineering and preclinical are two different things.

DR. YOGANATHAN: It is in the preclinical summary.

DR. SKORTON: Oh, it is in preclinical, not in engineering. We should comment then that that is not the same as bench testing.

DR. YOGANATHAN: It is part of the bench testing.

DR. SKORTON: Can you tell us where it is?

DR. YOGANATHAN: It is in section 3, page 3-7, hydrodynamic performance, the second paragraph from the top, all the way to the bottom of that paragraph.

DR. SKORTON: My question for Dr. Yoganathan is, this is a volume calculation, not a velocity calculation?

DR. YOGANATHAN: That is right. It is the total volume. It is the closing volume and the leakage that all these mechanical valves have.

DR. SKORTON: So just to make sure that I understand the answer, your earlier statement, Dr. Yoganathan, was that across valve sizes, across types for

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disc valves, you think this is within the ball park for either mitral or aortic?

DR. YOGANATHAN: Correct. The larger the valve in size, the larger the closing volume, the larger the leakage. So that is why it goes up.

DR. SKORTON: Okay.

DR. FLAX: Can I make one comment before you close the company's comments? The company believes that there is a paucity of data, specifically hemodynamic data, on valve 17 and that perhaps is more applicable to a pediatric type indication anyway. The company does, however, feel that there are enough data on the other valve sizes, specifically on the 19 mm aortic with 11 patients and with hemodynamic data on 5 patients.

So the company would be happy to consider the size 17 perhaps as a separate situation, but would be interested in getting approval for the other sizes.

DR. CURTIS: Thank you. This will just be a discussion among the Panel members now about what we have heard so far and any conclusions we would like to come to.

If I could make a comment, it seems overall that there is a problem with a lack of numbers for certain sizes of these valves, the mitral 17 mm to 23 mm size and the aortic 17 mm.

In addition, I would have to go back through but I don't believe there was enough of the cath. data in the aortic 19 or mitral 25, although we could get echo information on that. So I think that maybe we come out in terms of looking at this, but I would be interested in any other comments.

DR. WEINTRAUB: I think on the 19 there were 3 cath., I believe. I am concerned about the 19. I think the 17, you are right, it is probably going to be pediatric but once it is released, it is released. The problem I have with both the 19 and the 17 is that they are different valves. I am taken back to the original Bjork-Shiley when they went to the convex or concave, it was a different valve. And we would not even be considering a valve, a new valve, with only 11 patients followed for -- I can't remember what the follow-up is. I just don't think we can okay that.

My suggestion is, you know, it means that more valves are going to have to be put in and patients are going to have to be followed a little longer. I am not sure what the statistical frame would be for that but I, personally, can't approve a valve for implantation in human beings with only 11 in that cohort when it is a different kind of valve.

DR. VETROVEC: I don't have the history of some other Panel members that have been through the issue about

valves before and in developing standards. One of the questions that came up was this sudden tail-off around five to six years although the data is becoming small. What is the perceived length of time that a valve -- what would our standard be?

DR. PLUTH: I would think that for most of the tilting disc type valves or bi-leaflet valves that we certainly have stemming back from 1978, and we certainly should be able to say a 15-year valve, at least, should be present at the present time. So if we have fall-off at five to seven years, I would have to be concerned.

DR. CURTIS: Any other questions?

DR. TRACY: Actually, this fall-off, I am not sure I know what the fall-off actually is. I think that part of the problem I had going through the packet is that it has clearly taken a long time to get things this far so there is a little of this and a little of that, so it was kind of hard to follow the whole thing through. But I did notice that around five to seven years things started happening. I don't, but maybe somebody does, have a good sense of how many of these valves really did fall apart at that point and had to be replaced.

DR. WEINTRAUB: It is interesting though, if you look at the comparative valves, the same things happen with

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the other valves too. There are a couple of series that go to ten years and there is a significant fall-off on those. So part of this is probably just patient disease; they die.

DR. GILLIAM: I sort of get the impression it is not necessarily the fall-off of the valve as much as a fall-off of data collection.

DR. CRITTENDON: Right.

DR. CURTIS: That is a good point.

DR. GILLIAM: It is not like at five years all of a sudden there are problems with the valve. It is like patients disappear.

DR. CRITTENDON: Some of that was patient follow-up.

DR. GILLIAM: I agree. I think the 17 and 19 worry me greatly because it is a separate valve and I agree with Dr. Weintraub. I think we can't consider this as the same valve. It is separate. I am worried about the data in general. I think we have a lack of long-term follow-up. Most of the criteria that we did set for the company to achieve, they did achieve but not all of it. I am worrying about setting a precedent. If, you know, we say do this and you come close, is that good enough?

DR. CURTIS: Well, as I said before, some of the follow-up was a little bit underwhelming but they did meet

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the bare minimums for many of the valve sizes. So you can say you are not overwhelmed by it but they were met.

When we come to make recommendations I think we may well want to even have separate recommendations about the mitral and the aortic valve, and be specific about valve sizes here in making a recommendation.

If there are no further comments, before we come to a formal vote here, there were some questions for the Panel in the packet and I think we could go through this just to be sure there are no other issues because if there is anything else in here that we need to add, it could become a condition in the recommendation.

The initial question that was posed was do the data presented permit assessment of the safety and effectiveness of this device? I think we have had discussion about that but I would like to go through the specific questions.

Does the indications section adequately define an appropriate population for use based on the data presented, and the proposed contraindications?

I thought they were both adequate. This is on page 1-3. Does anybody have a specific concern about that?

DR. WEINTRAUB: I think I had suggested that the warnings be expanded.

DR. CURTIS: Okay.

DR. WEINTRAUB: That is not contraindications but it is in the same section.

DR. CURTIS: All right.

DR. GILLIAM: Just a point of clarification, earlier there was a question brought up as far as the use of these as replacements for another prosthetic valve, perhaps having a greater occurrence of perivalvular leak. Is this something significant? I will defer to our surgical colleagues. Should there be a difference between replacing a valve and replacing a native valve?

DR. PLUTH: I think there always will be. There is more fibrosis and such that occurs in that scarring that has been there in the past. I think a fresh valve will heal in better than will a valve that has been replaced.

DR. GILLIAM: So that is true of any valve?

DR. PLUTH: That is true of any valve, yes.

DR. CURTIS: When we come to making a recommendation, perhaps we can specifically talk about the warnings that you mentioned.

In terms of patient counseling, there was a concern about being more emphatic about the "must" rather than "should be" given prophylactic antibiotics and "may" require anticoagulation. I agree. We don't usually put

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mechanical heart valves if we can't anticoagulate someone. So I think that probably should be strengthened but the two main ideas are probably okay.

Number five, the patient information. There was a question about whether or not additional information should be provided, and I think this is where the temporary wallet card could fit in very nicely, that a patient should have that upon discharge from the hospital and not have to wait to get a card later on. That should be easy enough to accomplish; it is done with devices all the time.

DR. WEINTRAUB: If I could add, when devices are implanted usually a sticker is put in the patient's chart. It is a multiform. One goes to the company, another one goes -- you could make an extra sticker for the patient to carry with him until he gets the card.

DR. HARTZ: And it should have those warnings on it, the same warnings that are here.

DR. TRACY: I think that if the Canadian practice is to under-anticoagulate people, then the onus is on the patient and the patient should be given very strong counseling that it is their responsibility to have their INR checked and to maintain anticoagulation. I think that would be somewhere in there, either as part of the card or something that the patient must understand that.

DR. HARTZ: Can I just elaborate on that a bit?

This is one place where there is kind of a dodge between the surgeon and the referring internist or cardiologist, and no one is willing to stick out their neck to say this is the target INR. I am thinking that, personally, when I send them home with that temporary wallet card I will put on that card what my recommendation is for the target INR. Based on very recent data, 3 is too low an INR for this particular prosthesis in the mitral position. But it will obligate us, as physicians, to be more emphatic about what we want the patient's anticoagulation status to be and that has been missing in the past for all of the heart valve industry.

DR. CURTIS: We will move over to number six. I don't think we have to reiterate this right now. It is the issue about the valve sizes, and I think in the recommendation we make here we are just going to have to state which valve sizes we are talking about and what we are recommending and not recommending. So that has been definitely an issue today.

Seven was brought up before about the specific patient populations, and the issue about more than ten years. I don't think any of us here at this table would be excited about saying we know it works out to ten years, and we may want to modify that. Is there a suggestion or a

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comment anyone wants to make?

DR. WEINTRAUB: The data we have say five years.

DR. CURTIS: Five years, and that may be an appropriate way to go.

Physician training, the issue about dos and don'ts was raised before about putting the valves in. I agree, it should be somewhat more comprehensive but there was a discussion before about an entire physician manual for that.

I think the major concerns probably that were raised over and over again were issues of thromboembolism and perivalvular leak, and I don't think we have to go back over that, but that was one of the things we were concerned about. Possibly in follow-up afterwards and maybe in postmarketing that would be something we would want to keep track of.

In terms of making recommendations here, if we say approvable with conditions or approvable, or however we want to put it, we would want to make recommendations for postapproval studies and we haven't really discussed that at all yet. We are going to have to do that at least to some extent. There were some suggestions about postapproval studies in the Panel pack on 1-7. How many patients, for how many years would we want follow-up? Would we want hemodynamic data?

We should make some recommendations about that and I would be open to any suggestion. I think for sure there is really no reason why we can't get echocardiographic data on some subset of patients. Cath. is too hard but echo is simple. How many patients would we want to follow for ten years? You know, we have some data up to five years. Should there be a cohort of patients followed out to ten years? Is that something we should do? If so, how many patients would that be, 50, 100? What do we want to do?

DR. WEINTRAUB: I think we need to vote first.

DR. CURTIS: Well, apparently that is part of the approval.

DR. STUHLMULLER: One of the issues would be is if you wanted to vote -- I guess what I could do now, I will read the Panel recommendation options for premarket approval applications and that, I think, will in part address your question. If you want to recommend a postmarket approval study and that is going to be a condition, you have to identify that up front before you vote.

DR. SIMMONS: Whoever is going to make the proposal, usually makes the proposal with whatever recommendations have been outlined including postmarketing surveillance, and then we discuss that issue. If it is going to be a negative vote, then why bother spending 20 minutes

here designing postmarketing studies if we are going to reject the proposal?

DR. CURTIS: I think you are making an excellent point there. Maybe we want to do it that way, it is just that it is hard for somebody to make a recommendation for postmarketing studies having no idea how everybody else feels about it.

DR. SKORTON: Yes. John, isn't the whole point of that business of having a motion that it makes it part of the approval that way? I mean, isn't that the point?

DR. STUHLMULLER: Yes. There are four options; approval, approvable with conditions, not approvable, tabling it. If somebody is going to make a motion for approvable with conditions and you have postapproval requirements, it needs to be a part of the conditions for approval.

DR. SIMMONS: So somebody could propose that it be approved with conditions or disapproved and then we could discuss the conditions?

DR. CURTIS: I guess you could make that motion, that there be postmarketing studies or something like that, and then we would have to be specific about it. We would probably have a second vote, I guess.

DR. STUHLMULLER: But part of the process is to

get input from the Panel on what you think should be part of the postapproval requirements.

DR. WEINTRAUB: The postmarket approval has been in effect for at least two or three years. I think we have passed one or two valves then. What kind of numbers have we usually dealt with in terms of cohort close monitoring?

DR. CALLAHAN: I don't think we have had a valve since 1993 so we probably haven't addressed that, and that is probably a good thing to discuss with you all here.

DR. SKORTON: I just have a process suggestion, one of those things you can only say your first time here. I don't think we should get too hung up with the parliamentary procedures. I think that the Chair can ask a sense from the Panel for a thumbs up or thumbs down. I, for one, if we are going to have postmarket studies think that this is the wrong panel to decide what the N ought to be, especially in this, let's say, atypical statistical world that we are living in here. Most of us grew up with nice clinical trials that probably wouldn't have any real serious basis on which to suggest a number. So if I were going to suggest it, I would have to say that that number would have to be established by the FDA statistical branch. I wouldn't be comfortable coming up with a number out of thin air. We have a group here that is not chosen for statistical expertise.

But I would urge the Chair to first get what I think you can call a sense of the Panel as to whether the Panel is in the mood to approve or disprove overall. If the Panel is in the mood to approve anything, we can take it one by one and eventually come up with a motion that would satisfy the executive secretary's need to follow protocol.

DR. TRACY: I kind of echo that sentiment. I am not sure I feel comfortable coming up with a specific number but, just as a general principle, as we start discussing what we are going to do with these things, the hemodynamic data on 5-52 and 5-53 are completely inadequate on several of the valves and very marginal on others. I guess we have to decide whether we are going to accept marginal data and whether that would affect what the market surveillance would be. Is it okay to allow something with marginal data if you say, well, you need, you know, X times 2 number of fall-off echocardiographic data on that particular valve?

DR. CURTIS: I don't think we are going to get an enthusiastic discussion about postmarketing of these until we get some sense here. So why don't you go ahead and read the directions to the Panel?

DR. STUHLMULLER: Okay. Panel options for premarket approval applications: The Medical Device Amendments of the Food, Drug and Cosmetic Act require that

the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The premarket approval application must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application, or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health outweigh any probable risk.

Effectiveness is defined as reasonable assurance that in a significant proportion of the population the use of the device, for its intended uses and conditions of use, will provide clinically significant results.

Your recommendation options for the vote are as follows: Number one, approval. There are no conditions attached.

Number two, approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting all the conditions are discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant's response to the

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conditions of your approval or recommendation you want, for example, FDA or panel. Panel follow-up is usually done through homework assignments of the primary reviewers of the application or through other specified members of the panel. A formal discussion of the application at a future panel meeting is not usually held. If you recommend postapproval requirements to be imposed as a condition of approval, then your recommendation should address the following points: a] the purpose of the requirement, b] the number of subjects to be evaluated and, c] the reports that should be required to be submitted.

Option number three, not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations: a] the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; b] reasonable assurance has not been given that a device is effective under the conditions of use prescribed, recommended or suggested in the labeling; c] based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading. If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify

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the measures that you think are necessary for the application to be placed in an approvable form.

Option number four, tabling. In rare circumstances the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to the FDA or the applicant, thereby creating ambiguity and delay in the progress of the application. Therefore, we discourage tabling of an application.

The panel should consider non-approvable or approvable with conditions recommendations that clearly describe corrective steps. If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

DR. CURTIS: We need one of the lead reviewers to make a specific recommendation, a motion.

DR. VETROVEC: I will move for approval with conditions, and that would be to exclude approval of the 17 and 19 aortics and 25 mitral pending additional data.

That the approval require a cohort -- and you may force me to put in a number, but a cohort of patients that have postop and yearly echocardiograms, particularly for the mitral but for some number of aortics.

Then to the extent of the one-page follow-up describe follow-up for thromboembolic events.

Two other conditions that I think should be included would be continued follow-up of the current cohorts 1 and 2 that are available to the company, with specific information on what is going to happen over the next five years because I think that is a real clear issue.

Lastly, that there be a specific recommendation regarding the degree of anticoagulation.

DR. WEINTRAUB: Is there any discussion allowed or do we have to vote on that?

DR. VETROVEC: I am open to it being discussed.

DR. STUHLMULLER: Do you want to add more conditions?

DR. WEINTRAUB: Well, I have actually some changes. I think the 25 mitral should be included. The reason I am saying that is because there were 17 in this double cohort, that is cohorts 1 and 2, and again the valve is the same valve. It is the same valve as the aortic, which there is a lot of data on, and it is not a different disc; it is not a different valve. I think it is probably acceptable to accept that.

I would also have as conditions, if others agree with me, increase the number of warnings, which we can delineate.

DR. CURTIS: It is going to be a long mouthful to

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reiterate. We have a difference of opinion about that mitral size 25. I know there were 17 implants but we don't have hemodynamic data on them. It was just not provided, period. We are going to have to vote one way or the other. I suggest that we present it as you just stated it.

The motion was to approve with conditions, except for the aortic 17 and 19 mm valve sizes and the mitral 25 mm, with the conditions that were mentioned.

You excluded the 17 and 19 mm aortics and the 25 mitral. You said pending further data. You are going to have to clarify that. In other words, not approve it; if they did X, they would be okay.

DR. VETROVEC: Well, someone maybe needs to explain to me the FDA process. If the 17 and the 19 were excluded, how could they then get those later approved with more data? Is there an easy mechanism or should we put it in this process?

DR. CALLAHAN: Well, I don't know about an easy mechanism but certainly there is a PMA supplement process that once a valve is approved we would look at other sizes, smaller or larger, as part of a supplement. So they just need to augment the data they have here with another supplement.

DR. VETROVEC: Maybe you can advise me. I mean, my

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idea is that we need more data before we say it is okay. Is it better to make that a part of this process, or just to leave it to the supplemental PMA process?

DR. CALLAHAN: I think you would leave it to the supplemental PMA process. Now, you might advise us about the specific data you want and leave it to the process.

DR. VETROVEC: Let's leave it to the process then.

DR. CURTIS: All right.

DR. HARTZ: I feel strongly about not including the specific target INR because rhythm, size of left atrium and age of the patient will affect that choice and we don't know what that is right now. I don't think anybody here could say what it should be, nor even a minimum. I think we should take the responsibility as physicians to decide that nut; put it in the warnings.

DR. CURTIS: Okay.

DR. VETROVEC: I am willing to remove that from the recommendation provided there is something in the warning about appropriate anticoagulation.

DR. CURTIS: Okay. The motion that was presented was to approve the application with conditions, the conditions being that the 17 and 19 mm aortic valves be excluded, as well as the 25 mm mitral valve, with a requirement for postmarket studies, which we have not yet

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come to a conclusion about or qualified but there would be a requirement for that, and expansion of the warning section in the labeling.

That is the motion that was presented. Is there a second?

DR. VETROVEC: There was one other thing, and that was continued follow-up of the current cohorts 1 and 2 for longitudinal data.

DR. CURTIS: Right.

DR. STUHLMULLER: I missed that point.

DR. VETROVEC: Continued follow-up of the current cohort -- I mean, there is five or six years or more on patients. We shouldn't throw that away.

DR. WEINTRAUB: I thought that the staff and the statisticians would work that out.

DR. VETROVEC: But I just think that should be a part of it.

DR. CURTIS: Well, we need to clarify what that is, or at least make some recommendations that there would be some postmarketing studies, whether or the current cohort of something else. Right?

DR. VETROVEC: Well, I wanted both.

DR. AZIZ: Do I understand that we would be allowing the 19 and 17 mitral to go through?

DR. WEINTRAUB: We only eliminated 25, and I would assume that is 25 and under.

DR. CURTIS: Thank you.

DR. WEINTRAUB: Do they make a mitral 17 and 19, 23?

DR. CURTIS: There shouldn't be any more discussion. What the motion is, is to approve aortic valve sizes 21 and larger and mitral valve sizes 27 and larger, for sure. Do we have a second?

DR. TRACY: I will second the motion.

DR. GILLIAM: We can discuss the motion now that it has been seconded. The one question I have is do we want to eliminate the 25? I will defer to Dr. Weintraub.

DR. WEINTRAUB: I have stated my case. I prefer to leave in 25 and not eliminate it.

DR. SIMMONS: There are other surgeons here.

DR. AZIZ: It is fairly infrequently that one puts in that size, to be quite frank. I think one could leave it, actually.

DR. CURTIS: I was just concerned about the data that was presented for that size.

DR. AZIZ: Well, there were 17 patients I think.

DR. CURTIS: There were 17 patients but there wasn't enough follow-up data.

DR. WEINTRAUB: But, you know, it is in line with all the other data. Granted, there are only three patients. I mean, one could ask them to follow-up with some echocardiographic data on some patients, but I honestly don't think that is a make or break thing. I think the difference between the 17 and 19 and the others is that it is a different valve.

DR. CURTIS: Do you want to restate that?

DR. SIMMONS: I mean, would it be out of line to ask them to just fulfill the OPC criteria that were set forward with 35 valves followed for whatever the number is, or 50 per if there is more than one center? Just ask them to fulfill the criteria set out in the document in 1994. I mean, they haven't done that for those valve sizes. That is the minimum you could ask them to do, I would think.

DR. CURTIS: We have had a motion and a second to it. Why don't we go ahead and vote on that, and if we have to have an amendment on that one particular valve size, I suppose we could but could we vote on that motion that was seconded?

DR. GILLIAM: Can we have the amendment first?

DR. CURTIS: I am not a parliamentarian.

DR. GILLIAM: You make the amendments first and then you vote on the amendment and then you backtrack to the

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motion.

DR. PLUTH: I still think there is a very grave concern about the postoperative cath. data on the size 25 mitral valve. If you look at it, you will see that the valve area is calculated and comes out to 2.4, which is way beyond what can be anticipated for that valve. So the data really does not support anything as far as that valve size is concerned. The gradient across that valve is extremely low compared to the cardiac output, and it is totally out of keeping with the 27, 29 and 31 sizes. So I think the data is inadequate and I personally do not think we should include it.

DR. VETROVEC: It is certainly true that all of the hemodynamic data that is available for valve sizes, for the ones where there is a reasonable number of patients followed sequentially are getting larger and this one is a major aberration.

DR. WEINTRAUB: I will withdraw my objection.

DR. SKORTON: That is too bad because I was just going to argue with you.

[Laughter]

So there is nothing to argue about there. The other argument is that before we vote I think we should clarify all of the postapproval things we were talking about

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because I am still a little bit fuzzy on it, and I would ask the maker of the motion if he could repeat, if not numbers, exactly what postmarketing things for both the current cohort and additional cohorts, so we know what we are voting on.

DR. VETROVEC: Yes, I was a little more specific than the way it was restated. I did not put numbers in but I think a cohort of patients, with both mitral and aortic and probably more mitral than aortic because of the perivalvular leak issue, ought to have post-implantation echoes and yearly echoes thereafter, this cohort.

Then the other issue which was raised by the Agency was a follow-up form, and I think that follow-up form has to clearly have information regarding thromboembolic events.

My other condition was that there be continued follow-up of current cohorts 1 and 2 patients for longitudinal data because we already have five years of information; that clearly should be somehow followed.

Then in the warnings I thought there should be a recommendation regarding anticoagulation.

DR. CURTIS: The FDA provided the suggestions for postapproval studies. There was basically a list of five items. There was clinical follow-up, hemodynamic or echo

follow-up that you mentioned, and it is possible that we could, I suppose, recommend that there be clinical and hemodynamic follow-up required on these patients and that the statisticians and the FDA come up with some reasonable numbers there.

DR. VETROVEC: The numbers are reasonable but I just think you need some cohort specifically looked at.

DR. GILLIAM: Can we require also, given the concern about the Bjork-Shiley valve in the past, that if we do explant some evaluation of the struts be performed in a group of patients and that that data be reported back to the FDA, or will it automatically be reported anyway? Is there any general requirement for the company to look at the explanted valves, say, 18 years from now to see if there is any early evidence that there is, you know, strut wear that might predict that this would have a similar problem as occurred in previous valves that are similar to this?

DR. CALLAHAN: I think if you want to have that kind of data you are going to have to make that case now. It is not done automatically.

DR. CURTIS: Hemodynamic follow-up I would say would be echo Doppler on these patients. What kind of clinical information do we want to know in follow-up?

DR. SKORTON: Perivalvular leak.

DR. CURTIS: Perivalvular leak.

DR. VETROVEC: Thromboembolic.

DR. CURTIS: Thromboembolism.

DR. SKORTON: Does that include valve thrombosis
as well?

DR. CURTIS: I would think so.

DR. VETROVEC: Separate

DR. CURTIS: Okay.

DR. SKORTON: Functional class.

DR. CURTIS: Class. I am just trying to be
specific about the kinds of things we are looking for. We
have autopsy information, patients in the follow-up cohort
who died while implanted with the valve. I think we would
love to have autopsy information as much as possible. I
don't think there has been very much but we would like to
see that. Then there was a suggestion for a case report form
for death reports, and I don't think there would be any
problem with that.

DR. SKORTON: Explanted valves.

DR. CURTIS: Explanted valves.

DR. HARTZ: Is there a well-defined call for a
clinical pathologist to return an explanted valve? I think
sometimes they just sit in the morgues.

DR. CURTIS: I doubt there is any standardization

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right now on how that is done.

DR. SKORTON: Well, the recommendation that you have been reading from on page 1-8 suggests involving a cardiac pathologist. Perhaps that is what Dr. Hartz is talking about. I think that would be a good idea. That could be a pathologist of the company's choice. I would like to ask the maker and seconder if they would accept that?

DR. VETROVEC: Yes.

DR. SIMMONS: Just as an issue, I don't know why it bothers me but this resterilization ten times, I just don't want my valve, having been dropped nine times and then implanted after it was sterilized the tenth time.

[Laughter]

Or that the tamper-proof package was somehow mysteriously broken and that this valve is going to be reimplanted after the tenth resterilization.

I am looking at the Carbomedics' consent form. I think it needs to be clarified with the FDA because their consent form for sterilization and resterilization allows one time. Then there are specific guidelines on company acceptance of consequences of the resterilization or not acceptance of consequences of resterilization, and what happens to that valve after it is resterilized. So I think that needs to be clarified. It needs to be made, at least in

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some way, compatible with previous consent forms.

DR. DOMANSKI: Why does that bother you so much? I guess if they laid the thing out and they resterilized it, it just doesn't grab me that that is a major problem.

DR. SIMMONS: Really? If somebody opens a valve for you and it has the tamper-proof package that is broken, and they run it off to the sterilizer so they will use it anyway?

DR. DOMANSKI: Well, I feel guilty. I mean, I am not sure why we are pushing them on that score --

DR. SIMMONS: I think it should be pristine.

DR. DOMANSKI: If there is a reason I think it is important to do it, and I am happy to be educated but I hate to burden people with that unless there is a reason.

DR. SIMMONS: I still think the consent form should be in line with other types of consent forms.

DR. CRITTENDON: You could see a scenario, however, where you put in a 29 and you say, oh my God, this is too small; the poppet is not working. You take it out and as you are taking it out you say I hate the fact that now we have to eat the cost. Then a nurse eats the packet information and says, oh boy, Dr. Crittendon, we can do this ten times. There is no problem.

DR. DOMANSKI: Well, I am not sure I want to do

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that one once.

[Laughter]

DR. CURTIS: I think we are going off on a tangent here that we don't need to be. We have a motion on the table. It has been seconded. It has been amended. If we can have a vote on it, if I can state what the motion was, it was to approve with conditions the valve sizes aortic 21 and larger and mitral 27 and larger, with a requirement for postmarket studies that include follow-up echocardiograms and the clinical data that we mentioned in an appropriate size cohort, to be decided in consultation with the FDA statisticians; and that there be some revisions to the labeling, expanding the warning section that we had discussed previously.

Can I see all those in favor of the motion? Raise your hand, please. We have to go for voice, excuse me. Dr. Hartz, yes or no?

DR. HARTZ: Yes.

DR. CURTIS: Dr. Simmons?

DR. SIMMONS: Yes.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: Yes.

DR. DOMANSKI: Yes.

DR. VETROVEC: Vetrovec, yes.

DR. CRITTENDON: Crittendon, yes.

DR. AZIZ: Aziz, yes.

DR. PLUTH: Pluth, yes.

DR. SKORTON: Skorton, yes.

DR. WEINTRAUB: Weintraub, yes.

DR. TRACY: Tracy, yes.

DR. CURTIS: All right, the motion passes. We are going to adjourn for ten minutes. We will be back here at 2:45 and start with the second application of the day.

[Brief recess]

DR. CURTIS: We will move on now to the premarket approval application P960031, Medtronic Heart Valves, Inc., the Medtronic Freestyle Aortic Root Bioprosthesis, model number 995. First we will have the company presentation and, as we mentioned before, if you could each identify yourselves and mention your financial interest in the company and the product.

[Slide]

MS. CAFFERTY: Good afternoon, Madam Chairperson, distinguished Panel members, ladies and gentlemen. I am Ann Cafferty. I am the Clinical Program Manager for Medtronic Freestyle Aortic Root Bioprosthesis.

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The agenda for the next 25 minutes will be as

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follows: I will present a brief description of the device and also a brief description of the study overview. Prof. Hans Huysmans, from Leiden University Hospital, The Netherlands, will present the study overview and will incorporate the implant techniques, the operative data and the patient demographics. Dr. Colleen Sintek, cardiovascular surgeon from Kaiser Permanente Medical Center in L.A., will be presenting the safety results. Dr. Jean Dumesnil, an echocardiographer from Hopital Laval, Quebec City, will be presenting the effectiveness results which will incorporate the hemodynamics and the New York heart class.

[Slide]

The Freestyle aortic root bioprosthesis is comprised of a porcine aortic root preserved in glutaraldehyde. Minimal cloth covering serves to strengthen and isolate the porcine myocardial tissue. The green suture demarcation line, which goes around the circumference of the proximal edge, indicates the upper limit for implanting the proximal sutures. The surgeon's flags -- I don't know if it shows up that well here -- are 120 degrees apart and they provide at the inflow aspect the facilitation for implanting the sutures.

[Slide]

The aortic root design of the Freestyle

bioprosthesis allows a physician to trim the prosthesis, very similar to allograft replacement, using the full-root, root-inclusion or subcoronary technique.

Root pressure fixation process maintains the natural collagen structure and native root geometry. The Freestyle bioprosthesis is treated with an AOA process, using alpha-amino oleic acid, which has been shown to mitigate calcification in the animal leaflet during the animal studies.

[Slide]

The clinical study is presently a prospective, non-randomized, multicenter clinical trial. The inclusion criteria is an isolated aortic valve replacement, and that is where the other three tissues are native tissue and there is not another prosthesis in the other three positions.

The endpoints of the study evaluate the safety and effectiveness by means of reporting of adverse events, the New York Heart Association classification and the hemodynamics.

[Slide]

The clinical study began in August of 1991. We have 21 centers participating at this time in this study, and they are all following one common protocol. There are 12 centers in the U.S., 5 in Europe, 3 in Canada and 1 in New

Zealand.

[Slide]

At this time I would like to have Prof. Huysmans' present, as I mentioned before, the implant technique, the patient demographics and the operative data.

DR. HUYSMANS: Madam Chairperson, distinguished Panel members, I am Hans Huysmans from The Netherlands. Medtronic reimburses my traveling expenses here and I serve as a member on the European Scientific Advisory Board of Medtronic.

The investigators of this study were appointed on the basis of their experience with homografts because this valve is aimed at something as good as possible as a homograft.

[Slide]

The implant techniques for such a device are the same as you can have with homografts. The device comes as a full aortic root, as you can see here, with the coronary still attached to it. It means that you cannot use the prosthesis as it comes from the jar. You have to do a certain amount of tailoring. The tailoring can be done in sort of a continuum from minimal to maximal, giving an opportunity to adapt it to all sorts of pathology. There are certain distinctions that will make it used for different

implantation techniques.

On the top you see the full-root configuration or, I should say, one of the full-root configurations where the essential thing is that you take out a patient's aorta and replace it by the device. As was stated in the study purpose, it is feasible to do an aortic root replacement as well as a valve replacement.

The second technique is the next step. That is root-inclusion. In that case a patient's root remains in place but the device is inserted in the root and fixed. The essential feature here is that there is a rim of tissue on top of the commissura that preserves the original geometry of the valve at the level of the so-called sinotubular junction.

The third configuration, with several variations of which you see the two most popular, is making the device fit the subcoronary implant. You can see that either all coronary sinuses are scalloped. You can also scallop just the coronary sinuses or sometimes even just one. The feature that is important here is that you have no continuity between the tops of the commissurae, thereby leaving the preservation of the geometry to the surgeon.

[Slide]

The choice of technique is up to the surgeon, the

surgeon's preference, and that is due to the fact that each surgeon, with his homograft experience, develops a special skill for certain methods. However, it is never limited to that one method because it also sometimes is dictated by the pathology of the patient. There are occasions when you cannot use the subcoronary technique and have to go to either root-inclusion or root-replacement, and that sometimes becomes clear only during surgery.

The age of the patients involved in this study was approximately 70 years. As you see, there are no big differences between the three implant techniques. The same is true for the range of ages in the three techniques which is approximately the same.

Gender has a slight preponderance of males, except in the root-inclusion where the males are clearly dominating. This is probably due to the fact that this technique cannot be performed in the very small aortic root, as you often see in women.

[Slide]

Here we see the distribution of the valvular lesions with each of the techniques. The thing to be commented on is, I think, that pure aortic stenosis is rarer in the root replacement technique, and the pure insufficiency is more common in the root technique,

indicating that there is a certain pathology that makes patients fit to receive root replacement rather than subcoronary implant.

[Slide]

The distribution of the prosthesis size of the technique was that the larger sizes are specially present in the root replacement technique and to a lesser extent in the root-inclusion technique where the small sizes are most common in the subcoronary technique and also in the root replacement technique, again reflecting the pathology that asks for a certain method of implantation.

I should comment too that in the full-root technique or root replacement technique the sizes are usually a bit larger due to the fact that you can place the device supra-annular, in contrast to the other two techniques where it has to be intra-annular.

[Slide]

The ascending aorta pathology also is important to the choice of technique. We see here that, again, in the full-root group there is a difference as compared to the other groups. There are fewer normal aortas in that group. There are more calcified aortas and also there are more aneurismal aortas, again reflecting a certain pathology that is especially adapted to receive a root replacement.

[Slide]

The concomitant procedures -- overall there was about 40 percent concomitant, or even more than that. Here are the most frequent operations performed together with the aortic valve or aortic root replacement, coronary artery bypass grafting, as could be expected. The next group is ascending aorta repair, more common in the full-root technique as I explained before. Aortic wall pathology is more common in this group. You might wonder about the group of "others." That contains a whole list of other procedures like some congenital defects and others.

[Slide]

The drawback of implanting a stentless valve is that it takes you more time. I think it is most clearly reflected in the lower line where you see the implantations without concomitant procedures. To perform a root replacement needs, at least in this study, 102 minutes as a mean for the root replacement; 130 minutes for the root-inclusion; and about 86 minutes for the subcoronary technique, demonstrating, I think, that the root-inclusion certainly is the most difficult technique whereas the subcoronary technique is the easiest of the three.

[Slide]

Another thing worthwhile mentioning is the fact

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that anticoagulation is not performed in a considerable number of patients, initially only 40 percent going up to almost 40 percent at one year. Like in the homograft, it has been shown that that is safe and feasible.

Aspirin was given mainly to those patients who also had coronary-artery disease. Warfarin was given as sort of a precaution, maybe also traditionally, 3-12 weeks after surgery and then decreased quickly. The patients still having warfarin after one year were patients with atrial fibrillation and similar diseases. The others are mainly combinations of these two.

[Slide]

Follow-up is available for a number of patients, 189 in the full-root, 139 in root-inclusion, 913 in subcoronary, for a total of 1241 patient years. There are few patients lost to follow-up, 1.3 percent, and of the 11 patients missing, that is, that did not appear at their 3-6 months or 1 year follow-up study, there are several of which we know that are alive and well.

I think this finished the first introduction and Dr. Sintek will follow me.

DR. SINTEK: Madam Chairperson, members of the Panel, I am Colleen Sintek. Medtronic paid my traveling expenses to be here at the meeting today.

I have the privilege of presenting the safety data for the Freestyle valve divided into the three different implant techniques.

[Slide]

For the full-root, this is the mortality data. All deaths. There was a 14 percent operative mortality. When we looked at this group of patients, as shown in the previous slides, they tended to be sicker patients. Less than one third of these patients had normal aortas. In addition, a high percentage of patients undergoing full-root replacement were New York Heart Association Class IV preoperatively, and this group of patients in this series did have a significantly higher operative mortality rate.

In addition, patients undergoing full-root replacement had a 3 times higher incidence of endocarditis as the indication for surgery. As you know, full-root replacement oftentimes is the best way to treat endocarditis, but these patients do have a higher early and late death rate.

[Slide]

Looking to the literature for full-root replacement with homografts or valve conduits, no comparable patient groups are found. Our average age was 70 and, as we can see, in the series in the literature the ages were in

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the 40's and 50's.

All of these series were from very reputable institutions, with operative mortalities ranging from 1.7 percent all the way up to 48 percent.

[Slide]

If we look at the 1-year and 3-year freedom from death rates for the Freestyle prosthesis, they are very acceptable and I want to clarify that these do include the operative deaths. The mortality data for the root-inclusion technique shows there was a 5 percent operative mortality, with 89 percent at 1 year and 87 percent 3-year freedom from death.

[Slide]

When we look to the control literature, there was really only one article that addressed this implant technique, and that was the inclusion cylinder technique reported by Knott-Craig using homografts. As you can see, the average age of his patient group was significantly below ours. However, the 1-year and 3-year freedom from death rates were very comparable.

[Slide]

For the subcoronary technique we had a 4.9 percent operative mortality, with a 92 percent 1-year and 87 percent 3-year freedom from death rate.

[Slide]

When we look at the literature, the article by Dr. Orsuzlak on Carpentier-Edwards stented valves, it really involved a similar age group of patients, age 72 as opposed to the Freestyle age 71. When we look at the 1-year and 3-year freedom from death rates in the 2 groups, they are very comparable.

[Slide]

Moving to adverse events, for the full-root implant technique if we look at the thromboembolism late events percent per patient year, 3.4 percent. However, only one half of those were permanent neurologic events, the other being TIA's. There were no reoperations and no explants in this group of patients.

[Slide]

For the root-inclusion technique, the thromboembolic rate during the late period was 5.3 percent per patient year. Again, however, the permanent neurologic event rate was only 1.5 percent per patient year, with the large majority being TIA's.

If you can recall from the demographic data and the operative procedures, only 18.5 percent of the patients with the root-inclusion underwent concomitant coronary-artery bypass grafting, opposed to 37 percent of

the other 2 techniques receiving concomitant bypass grafts. This probably accounts for the reason why these patients, at least in the early time period, up to 1 year, had a much lesser rate of being place on aspirin and this may account for the higher TIA rate. There was 1.5 percent per patient year incidence of reoperation and 1.5 percent per patient year incidence of explant.

[Slide]

The adverse event rate for the subcoronary technique shows 1.5 percent per patient year late thromboembolism rate, and 0.8 percent per patient year late reoperation rate.

[Slide]

There were a total of 24 valve-related or unexplained deaths. Of these, 8 were in the early period and 16 were in the late period. This slide summarizes the causes of death in these patients.

[Slide]

In summary, we feel the Freestyle valve is a safe valve. The freedom from death for the three implant techniques is as expected for the patient age and pathology. There has been no incidence of structural deterioration, non-structural dysfunction or primary hemolysis. the incidence of all adverse events for all implants and for

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subcoronary implants are within the acceptable bounds of two times the objective performance criteria for the events.

Thank you for your attention. The next speaker will be Dr. Dumesnil.

DR. DUMESNIL: Madam Chairperson, members of the Panel, ladies and gentlemen, I am Jean Dumesnil. Medtronic paid my expenses to come here and I also serve as a consultant from time to time for Medtronic.

It is my pleasure to report on the effectiveness of this prosthesis in terms of the New York Heart Association functional improvement, and also hemodynamic performance as evaluated by Doppler echocardiography.

[Slide]

What we have on this first slide is a comparison of the New York Heart Association functional class before operation and one year after operation. This shows that preoperatively 82 percent of the patients were in Class III or IV of the New York Heart Association, whereas postoperatively 91 percent of the patients were in Class I and 9.2 percent were in Class II. No patients were in Class III or IV.

[Slide]

This is the same data by the root-inclusion technique showing that preoperatively 70 percent of the

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patients were in Class III, whereas postoperatively 91 percent of the patients were in Class I, 93. in Class II, and no patients were in Class III or IV.

[Slide]

This is the same data by the subcoronary technique, showing that before operations 79 percent of the patients were either in Class III or IV, whereas after operation 94 percent of patients were in Class I, 14 percent were in Class II, and 2 percent were in Class III or IV.

[Slide]

I am now going to present the hemodynamic results as evaluated by Doppler echocardiography, and I would like to mention that this is one of the most complete echocardiographic studies to evaluate hemodynamic performance in prosthetic valves.

The echocardiographic data summaries include all patients in which echocardiographic studies were done, corresponding to more than 90 percent of the patients in the cohort.

[Slide]

This shows the mean gradients at one year by implant technique and by prosthesis size. For all sizes the average mean gradient ranged from 5.3 mmHg to 7.2 mmHg. The highest gradient seen in the 19 mm prosthesis implanted with

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the full-root technique was 16.8 mmHg, but we should point out that this is a small number of patients with a large standard deviation, suggesting that there were only a few patients in there that had a high gradient.

More importantly, on an individual basis 79 percent of the patients had gradients lower than 10 mmHg and only 3 percent had gradients greater than 20 mmHg. These results are equivalent to what is found in homografts and far superior to what we usually see in stented bioprostheses.

[Slide]

This is the data for the effective orifice area at one year by implant technique and by prosthesis size. For all sizes, the average effective orifice area ranged from 1.9 cm² to 2.3 cm². Again, the lower effective orifice area was seen in these patients with the 19 mm prosthesis implanted by the full-root technique.

More importantly, only 5 percent of patients had an effective orifice area lower than 1 cm² and this, again, is far superior to what we usually see with stented bioprostheses.

[Slide]

This is the data for the incidence and severity of regurgitation at one year. Freedom from regurgitation ranged

from 65 to 87 percent, depending on technique. Clinically significant regurgitation, that is, more than 2+ regurgitation, was found only in 2 percent of patients who had undergone the subcoronary technique. The rest of the patients had either trivial or mild regurgitation.

I must emphasize that echocardiography is very sensitive to the detection of regurgitation, and trivial regurgitation really represents a very minute amount of regurgitation which we wouldn't expect to see on angiography, which we sometimes see in a normal patient, and which is smaller than normal closing volume seen in mechanical prostheses.

As for mild regurgitation, it corresponds to 1+ regurgitation we usually see in angiography, and it has no clinical or hemodynamic consequence.

[Slide]

This is a comparison with the control articles, showing that in our cohort only 2 percent of the patients implanted by the subcoronary technique had moderate or greater regurgitation, whereas reported values in the literature ranged from 5-18 percent.

[Slide]

So in summary, the Freestyle bioprosthesis has the versatility of an aortic homograft. This bioprosthesis has

acceptable freedom from death and adverse event rates. New York Heart Association improved after implantation of this prosthesis. Forward flow performance was superior to stented bioprostheses. And there is a minimal incidence of clinically significant regurgitation.

[Slide]

In conclusion, the scientific data presented demonstrates that the Medtronic Freestyle Aortic Root Bioprosthesis is a safe, effective and versatile device for replacement of a diseased native aortic valve, prosthetic aortic valve, or aortic root. Thank you.

[Slide]

MS. CAFFERTY: Medtronic recognizes the need for education and training related to this device, and in collaboration with the investigators Medtronic is committed to providing the programs illustrated on this slide. The programs, as you will note, are very similar to those offered for allograft training and they would be the classroom session, interactive surgical observation session, technical materials, wet lab, on site observation sessions wither at the training surgeon's facility or at the implanting center, valve registry and post-training valve distribution.

[Slide]

At this time also I would like to at least acknowledge additional Medtronic personnel that will be available for answering questions during the discussion period: Kathleen Boehm, who is a senior product regulation manager; myself; Carol Eberhardt, program manager; Christine Eickhoff, senior statistician; Vicky Hench, senior statistician; and Francis Kim, quality assurance manager.

[Slide]

In addition to the Medtronic personnel, we also have a wide range of our investigators and consultants present to answer questions as well: Dr. Cartier, Quebec City; Dr. Elkins out of Oklahoma; Drs. Jean-Marie Girardot and Nadia Girardot, medical design out of Georgia; Dr. Gary Grunkemeier, out of Portland; Dr. Neal Kon, out of Bowman Gray; Dr. Al Krause, out of Good Samaritan Hospital in Portland; Dr. Miller, or Mayo; Dr. Schoen, out of Brigham and Women's; Mr. Stephen Westaby, out of Oxford; and Dr. Yoganathan, out of Georgia Tech.

DR. CURTIS: We can move on now to the FDA presentation.

[Slide]

DR. ALLIS: Good afternoon. My name is Steven Allis and I am the lead reviewer for the Freestyle aortic root bioprosthesis PMA submission. I will report FDA's

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findings regarding the Freestyle clinical study presented for your view today.

[Slide]

Let me introduce the members of the Freestyle team as identified on the current slide.

[Slide]

This afternoon I will present the following information. After a brief description of the Freestyle device and the clinical study, I will address device safety and effectiveness. Next I will review the study limitations, and conclude with the issues presented for Panel comment today.

[Slide]

A brief review of the Freestyle valve reveal several design features. The device consists of a porcine aortic root containing the valve mechanism, which is collagen cross-linked with glutaraldehyde and treated with amino oleic acid as an anti-calcificant. The Freestyle is available in five sizes.

During surgery the implanting surgeon trims the aortic root tissue for replacement of the native aortic root or for modified root insertion within the native aorta. The subcoronary style is used for replacement of heart valve mechanism only. The root-inclusion valve is for implantation

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within the native aorta after removal of the diseased valve. the full-root style is used to replace the entire native valve and aortic root.

[Slide]

The FDA heart valve guidance recommends that at least 800 patient years of data be available at the conclusion of a heart valve clinical study. Each of these 3 styles studied in the Freestyle clinical trial are analyzed in separate cohorts. The subcoronary cohort is composed of 913 patient years. The root-inclusion cohort is composed of 139 patient years, and the full-root cohort had 189 patient years of follow-up data.

Three investigational centers followed at least 50 subcoronary patients for more than one year. No study centers have followed at least 50 root-inclusion and full-root patients for more than one year.

The FDA guidance recommends that at least 15 patients with 1 year of follow-up are available for each device size. The Freestyle subcoronary met this criterion. For the root-inclusion the 3 larger sizes had more than 15 patients with 1 year of data. The 2 largest full-root sizes had more than 15 patients at 1 year.

[Slide]

In our safety evaluation the adverse event rates

for the Freestyle device are compared to the FDA objective performance criteria and several FDA-selected literature articles. For most events, comparable performance was observed.

With respect to linearized rates for mortality, the higher rate for the full-root style could not be attributed to pathological findings at operation or to patient demographics. This cohort also exhibited a higher early mortality rate when compared to the other implantation techniques.

With respect to reexamination of implanted bioprostheses, the company states that 31 devices were returned for their evaluation, 19 subcoronary, 6 root-inclusion and 6 full-root. No details regarding these devices have been submitted to the Agency.

The Freestyle valves examined at reoperation were in general removed for subacute bacterial endocarditis, and were replaced with prosthetic heart valves other than the Freestyle. This occurred in 6 subcoronary patients and 4 root-inclusion patients. Autopsy reports are available on 3 subcoronary, 1 root-inclusion and 5 full-root replacements. All devices were reported as microscopically intact. Histological examination was only performed on a single root-inclusion and demonstrated minimal calcification

microscopically. Morbidity was compared between cohorts and matched that reported in FDA-selected literature articles.

[Slide]

In our evaluation of effectiveness the Freestyle device was noted to have improved pressure gradients and effective orifice areas compared to those reported for stented valves in FDA-selected literature articles.

Freestyle pressure gradients demonstrated near physiologic values at 1 year. These hemodynamic values tend to improve during the course of the first year. The evaluation of effective orifice areas emphasizes a low flow impediment.

Valve regurgitation was noted in about a third of the subcoronary patients and approximately 1/10 of the patients receiving the 2 root styles. Valve leak in all cohorts was estimated. It was trivial or mild and did not increase in severity over time.

[Slide]

This slide lists the major limitations we find with the Freestyle study. The first is the failure to derive implantation criteria for selection among the three styles. This is demonstrated by the similarity of operative findings reported between cohorts. The need to establish implantation criteria for the three styles is evidenced by the increased mortality with the full-root implantation style.

Second, the study has limited data for the root-inclusion and full-root styles. The cohorts were smaller than the subcoronary cohort. This was also reflected by the fact that no centers or investigators had experience in implanting more than 50 of these device styles.

Third, the study had limited data for the smallest valve sizes in the root-inclusion and full-root cohorts.

A fourth limitation is that the duration of the study is shorter than the expected life of the Freestyle device, a limitation that is common in heart valve clinical trials. In the Freestyle study device safety and effectiveness data extended to three years. This limitation precluded analysis of calcification, affecting both cost mechanism and aortic valve of the root styles, as well as other causes of long-term valve failure. Ultimately, 8-10 years of follow-up data on a heterograft will be necessary to establish long-term durability.

Lastly, information has not been provided on explanted devices. This can be critical in an assessment of valve function and device durability.

In review, as you discuss the data presented here today, please keep in mind the specific questions presented in section 1 of the Panel pack. These questions generally relate to device labeling, the adequacy of the data

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presented by the sponsor, postapproval study requirements, and the FDA historical control methodologies.

In regard to the control methodologies, I would like to ask for the Panel's comments regarding the historical controls developed for observational studies as presented in the information provided to you prior to this meeting. This new method, which uses a selection of articles tailored to match the Freestyle patient population, relies on a side-by-side display of the Freestyle device and the devices identified in the selected literature.

We are also interested if this new method should supplement or supplant the objective performance criteria. Depending on the Panel's comments, the new method can be refined to improve the presentations provided for future consideration.

We appreciate your careful consideration of these issues. Thank you.

DR. CURTIS: We will go ahead now and start with the Panel. One of our primary reviewers is Dr. Aziz. If you could go ahead?

DR. AZIZ: Thank you. First, I would like to congratulate the FDA staff for putting together a well-organized folder on the subject. It clearly made reviewing the topic much easier and enjoyable. I would also

like to commend Medtronic and its consultants for a very succinct presentation.

I think important strides continue to be made, both in the lab and clinically, that have highlighted the mechanical and biochemical factors that contribute to improved valve function, hemodynamics and durability, and reducing the complications of valve replacements.

The characteristics an ideal valve should possess I think have been defined, and everybody is making efforts to introduce these features into a new valve design and I think this is the way the stentless valves are heading.

Today I will review the data submitted pertaining to the Medtronic stentless porcine valve from the point of view of is the device safe and is the device effective. My comments are directed towards the study design.

This is a prospective observational, unrandomized, multicenter trial conducted according to a common protocol. I still believe that the old-fashioned randomized study design is good but, obviously, we cannot have the luxury of doing that all the time. Clearly, historical controls will be used and data pooling was used to analyze the results.

The objectives of the study were to evaluate safety and effectiveness of the Freestyle prosthesis. Clinical safety was evaluated by postop mortality, by

prosthesis-related morbidity and blood data, and clinical effectiveness was evaluated by improvement in postoperative New York Heart Association classification and hemodynamic data by echocardiography. Sample size was according to the 1994 replacement heart valve guidance.

It seems that only patients who needed an isolated aortic valve replacement, either in the subcoronary position, the full-root replacement or inclusion technique as a primary procedure or replacement of a previously implanted prosthetic valve were eligible for the study.

Just before going on, is the inclusion technique similar to the mini-root technique?

DR. HUYSMANS: It is about the same.

DR. AZIZ: It is? Okay. A vast body of in vitro bench testing was accumulated by the company and was provided. In addition, details from animal experiments, both short- and long-term, were presented.

Looking at the bench test data, biocompatibility, immunologic and toxicology studies were stated to support the biocompatibility of the stentless valves used and that data was not in the booklet but I presume it was shared with the FDA.

The hydrodynamic performance results in all three positions, again in bench testing, were better if not

comparable to the controls. The flow pressure and flow regurgitation were better than seen in controls.

Animal studies, both in the short-term and in the long-term, were reviewed. It seems that in the short-term leaflet calcification was noted. In the long-term, the model that they used was the apical conduit. Just for a point of clarification, was the animal's own valve left in place so the blood flow was going in two directions?

MS. CAFFERTY: Fred Schoen will answer that question.

DR. SCHOEN: I am Fred Schoen, from Brigham and Women's Hospital in Boston. I am a paid consultant to Medtronic. The animal's native aorta was tied off at the time of placement of the apical aortic.

DR. AZIZ: And so the flow to the coronary was retrograde?

DR. SCHOEN: Retrograde.

DR. AZIZ: Okay. Then looking at the clinical results, the majority of patients with the valve implant using the subcoronary technique, most of the patients in were the older than 60 age group, in fact, 91 percent, with only 4 patients, or 0.6, in the less than 40-year age, and a small percentage in the other groups. Is the reason the percentage of younger patients is so small, is that because

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of selection or is it the patients with the pathology were in the old age group?

MS. CAFFERTY: Prof. Huysmans, do you want to answer that?

DR. HUYSMANS: Yes, I think it was mainly because those patients were in the old age group.

DR. AZIZ: Then, again, only a small percentage, I think only 4.3 percent of the patients in the subcoronary location had a 19 mm valve implanted. Again, is this because of the number of patients who had a small annulus, or was it because root enlargement procedures were done if you had a patient who could have a larger valve implanted? In other words, what was the percentage of patients who had a concomitant root enlargement procedure done?

DR. HUYSMANS: I showed the slide that showed the numbers. Root enlargement was a small percentage. I am looking for it. Root enlargement was done in no patient that had the root replacement technique. It was done in 2.5 percent in root-inclusion, and just 0.3 percent in the subcoronary technique.

DR. AZIZ: A topic that I would like to sort of address is anticoagulant need. Dr. Sintek presented the fact that patients with the root-inclusion technique had a fairly high incidence of TIA's, and I believe that a lot of them

weren't on antiplatelet agents. Would you suggest or recommend by looking at this sort of data that they should, for a short period of time in the immediate postoperative period, be on antiplatelet agents?

MS. CAFFERTY: Yes, I think that is something that we definitely would consider, given our results.

DR. AZIZ: Something else that you presented, you mentioned that there was a higher incidence of root replacement in patients with endocarditis. Was there any reason why one would not use a homograft in such cases rather than going to using a stentless porcine valve?

DR. HUYSMANS: The simple reason was that a homograft wasn't available in patients with active endocarditis.

DR. AZIZ: If you had a homograft, you still would recommend that be used in endocarditis?

DR. HUYSMANS: Right. So far the use of the Freestyle as replacement for the homograft was limited to those cases where no homograft was available.

DR. AZIZ: Okay. There was fairly impressive data presented on the lack of incompetence following placement of this Freestyle stentless valve. It seemed that there was really less AI in patients who had a full root versus if they had subcoronary or inclusion technique, and when AI was

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present, it was obviously trivial or mild which, I think, attests to both the surgical skill and I think also the valve used.

The other point that I would like to bring out is placement of the stentless valve is technically much more demanding, I would imagine, for most surgeons. It is like placing a homograft and placing the stentless valves that are currently available. You don't seem to agree with that?

DR. HUYSMANS: Well, if I may, it is more difficult than a stented valve; it is not more difficult than a homograft. I must say that it turns out to be easier than a homograft.

DR. AZIZ: So you basically have to be trained in placing a homograft before, I think, getting into doing these sort --

DR. HUYSMANS: Or at least that has been shown to be a very reliable method of learning how to do these valves.

DR. AZIZ: Okay. I think the extent of bleeding seen in patients who had full-root replacements was, I believe, 12 percent versus 3.5 in the subcoronary position. Do you think that is related to the longer pump runs or more suture lines?

MS. CAFFERTY: Dr. Kon, would you answer that one?

DR. KON: My name is Neal Kon. I have served as a consultant for Medtronic, and Medtronic paid my expenses here. The question of bleeding or operative mortality related to the full-root technique -- the differences you will see across the board are well-described in the literature and the Panel pack. You will see numbers where very difficult cases were done, in Kirkland's series, up to 50 percent. And you will see numbers as small as 1.7 percent when there is not a lot of aortic root pathology, in Mark O'Brien's series.

This series showed some more Class IV patients, more patients with endocarditis and more patients with pathology in the aorta. If you try to break down this data and look at surgeons who did more aortic root replacement and less subcoronary replacement, for instance, if you looked at our series individually, we prefer to use just aortic root replacement because when we were starting our homograft series here, at the time we got the valve, the homograft data was showing more insufficiency, as you know, and subcoronary techniques were employed. So we used exclusively the aorta root replacement techniques and have had incidence of bleeding of less than 2 percent, and incidence of mortality of 4.4 percent. So I think, in summary, it has to do with surgeon skill some, having

repetitive attempts at being able to do root replacement. It also has to do some with the patient's pathology.

DR. AZIZ: Do you think use of anti-fibrinolytic agents would be advisable, or do you use that routinely?

DR. KON: We use Amcort [phonetic].

DR. AZIZ: All right. I think we talked a bit about the mortality being increased. Again, I think the numbers of patients who got the 19 mm valves is small. I think there were few, if any, in the root-inclusion group and only 7 in the full-root replacement and more in the subcoronary position. I believe you addressed that.

I think the data that has been presented is very impressive. Clearly the data only goes out for about 3.5 years, and I hope that what we have seen so far will obviously go out to 8-10 years. I think that is really what we are all hoping for.

I think it would be very important, at least from my point of view and probably from the Panel's, that there be very close follow-up of these patients to detect maybe increasing AI's, and I hope it doesn't occur; leaflet degeneration, the rate at which the valve degenerates. Clearly, these are glutaraldehyde-treated, sort of tanned leather in a sense, valves with non-living cells. So there should be a rigid mechanism for following these patients,

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and I think the Panel members may have something to say on that.

From my point of view, I think it is a more complex technique of valve implantation than stentless. I think the surgeons who are going to get involved, and I hope they are, obviously would need to get fairly extensive hands-on training, I think more than just a video and the like. I know that you put up a slide showing the ways that you are proposing to do that, but I would recommend that surgeons have somebody on hand as they are doing some of the more complex procedures.

I would also suggest that surgeons who have a lot of experience with doing just the Bentel [phonetic] procedure for root replacement, again, need to get more homograft experience rather than going from Bentel to putting these in, even though they feel they can deal with the aortic root.

The other word of caution that I think one might see in the future is that it seems that with reoperations, and I am sure some of these patients in 10, 15 years might come to reoperation, likely the homograft reoperation, it is going to be a more tricky technique than just dealing with a stentless valve reoperation. So I would presume that some mechanism would be in place whereby, if one is faced with

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reoperating on somebody in whom you put one of these in, maybe special techniques or assistance is on hand.

Actually, from my point of view, in summary, I think the preoperative and early mortality rates are in an acceptable range. The perioperative and postoperative complications are similar to what we have seen with other valves, and in some cases are less than the complications that we see with other valves.

I think the incidence of thromboembolic events is similar and, if anything, less than is seen with other prosthetic valves.

The incidence of bioprosthetic thrombosis, degeneration, dysfunction to date are really remarkably low. The in vitro animal testing is also encouraging.

I might just add that I think another place where this valve might have a role is in patients who are having their Ross procedure done using this for replacing the pulmonary -- maybe in pediatrics for pulmonary valve replacement. Thank you.

DR. CURTIS: The other primary reviewer was supposed to be Dr. Brenker but he had an emergency and he couldn't make it but, fortunately, Dr. Domanski can go ahead and take his place.

DR. DOMANSKI: Thanks. You know, I actually have

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some questions. I guess I need some education about the statistics. I don't claim to be a brilliant statistician but I wonder if there is someone who is either from the FDA or perhaps the company, and I would like to address a few questions to them.

Perhaps we could turn to page 501. If one looks there to Table 2 -- now, I am going to accept for the moment that the historical controls that were set up are reasonable for the purpose of this part of the discussion. I will move on to them ultimately but I would just like to start by assuming that they are reasonable. Look at Table 2 under "all deaths." I want to make sure that I am reading this properly because I may not be. This is, of course, freedom from death. If one looks to that, we find the Freestyle estimate is 91.6 and your confidence intervals are 89 to 94.2. As I read over to the control, I assume that 91 percent, 95 percent, 95 percent, 97 percent represent 4 different studies. Is that right?

DR. EICKHOFF: That is correct.

DR. DOMANSKI: Well, absent the 91 percent, if one looks at all of these other studies, it lies outside the 95 percent confidence interval so it seems to me there is a statistically significant increase in mortality with your valve. Why isn't that true?

DR. CURTIS: Can you identify yourself, please?

DR. EICKHOFF: Christine Eickhoff. I am a statistician at Medtronic. As Dr. Sintek pointed out in her presentation, the article that the 91 percent came from was a similar population of patients as far as age to the Freestyle valve. The rates quoted there for the other controls are from a much younger population.

DR. DOMANSKI: Well, you know, I don't know that is enough statistical analysis to do it. I think if we are going to take that position -- you know, we are getting away from randomized, controlled trials because of the obvious problem with ever getting a better valve and trying to approve it by that technique, but I am not so sure that that represents sufficient discussion of why you are throwing out a whole series of studies. There are other potential confounders and I guess I would like to hear a discussion of those studies if we are tossing them out. Could we have somebody do that? I am concerned about this because, I mean, you picked the one study that makes the valve look good and you are saying, well, gee, it looks to us like maybe they are younger. But it would be interesting to hear a better discussion -- not better but more extensive discussion of why it is reasonable to throw the three out to make the valve look like it increases mortality. Younger is one, but

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perhaps we could add to that.

DR. CURTIS: Were those studies included in the PMA?

MS. CAFFERTY: They are in Attachment 4. Dr. Elkins will address that.

DR. ELKINS: I am Ron Elkins, from the University of Oklahoma. I am occasionally paid as a consultant for Medtronic. I do have a very small amount of their stock personally, and my expenses to this meeting will be met by Medtronic.

I have had a long interest in homograft and autograft valve experience, and I can tell you that if you take these studies that are in the PMA pack and look closely at the studies, there are really two controls that are there that involve patients that are similar in age groups, all root replacements that are two of the most outstanding controlled series in this country, something not met by most other investigators in the country, without question. And this is Nick Kukutza's [phonetic] study and Ben Scott's study that involves the root replacement.

The second thing is that there is little question that if one looks at certain patient age populations that this study would look very poor. And those are patient-related factors that affect death, and I can

demonstrate to you studies that would show a 1 percent mortality for a similar group of patients but age quite different, who have had an aortic valve replacement.

We can move to the other end of the spectrum and aortic valve replacement in a wide range of patients, those that have significant aortic root pathology; those that have endocarditis; and those patients that are reoperative patients, requiring their second aortic valve replacement. But this mortality is certainly within range for that age group of patients. And I think every surgeon in the room recognizes that aortic valve replacement, as we do it in advanced age and with increasing morbidity prior to surgery, i.e. a New York Heart Association classification of III or IV, is quite clearly a riskier operation and these mortalities fit with what is acceptable. And that is certainly the way I would answer it as an investigator and as someone reviewing the data from outside.

DR. DOMANSKI: Okay. That is certainly a reasonable answer, to say, gee, they are older and so they are not comparable. But I think it goes to the problem of deciding whether we are really considering appropriately matched populations, and I think that is very difficult in this kind of non-randomized setting. Age is certainly one thing that goes into it. Whether there are others that make

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those populations at high risk is a little bit harder to know but, from my point of view, that is a pretty reasonable answer.

What about thromboembolism? If you come down to the next one, now all of the studies fall above the confidence intervals. And, again, please understand that I am a real amateur as a statistician. But if one looks at thromboembolism, which is just the next entry down, all of the studies fall beyond the 95 percent confidence interval. So it seems to me that you are statistically significantly worse with respect to thromboembolism than all the other studies.

DR. SPYKER: Dan Spyker, FDA. As one of the architects of this strange idea of putting controls into this, I want to say that we would never permit a sponsor to make these kind of comparisons. I think your point is very well taken but we would not permit a non-randomized comparison of this post hoc. It was done for illustrative purposes and even though I forced them to put confidence intervals on there, they did it kicking and screaming. But this is a problem and you have clearly pointed out the problem.

DR. DOMANSKI: Yes, but the problem may also be a real one. See, we really are not going to be able to gather

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enough data in a reasonable way to see a clear difference. I mean, it would require a tremendous amount of data unless the valve were markedly different. But one begins to wonder whether these are significantly different if, with a small amount of data, they fall this far outside the confidence intervals.

You know, I was going to go right down the list and say the same thing. It looks the same for bleeding. The bleeding is statistically significantly worse if you use the confidence intervals that are printed in this table. Perivalvular leak, I suppose the same comment. I mean, you are talking about two standard deviations; it is not that it is just a little over; it is way out. Then it is not different for endocarditis; not different for reoperation, and so forth.

So I think that is a bothersome table. If we are going to use the data, we have to use them. If we are not, then I don't know -- I guess we don't have anything if we don't. But that is quite bothersome, actually. I am not sure what to do with data like this.

Let me move on now to --

MS. CAFFERTY: Dr. Domanski --

DR. DOMANSKI: Yes, ma'am?

MS. CAFFERTY: Gary Grunkemeier will address the

question or the issues that you have raised.

DR. DOMANSKI: Sure, I would appreciate it.

DR. GRUNKEMEIER: I a Gary Grunkemeier, from Portland, Oregon. I am attending this meeting as a consultant to Medtronic.

You are right, Dr. Domanski, I think that this is a difficult way to compare these valves when they are not randomized, using literature or historical controls, but it has been determined that as of this date, in 1997, that seems to be our best effort.

I would point out to you that these patients in the Freestyle study are 71 years old on average, and except for about 1 of the studies, the patients are much younger. As far as survival, age itself -- first of all, I am not sure that survival is a good measure of valve performance. I think it is more a measure of the condition the patients are in. One of the main conditions is age of the patient which exquisitely separates survival curves after valve replacement.

Also, I think that as patients age the thromboembolism, the background rate of strokes goes up to the point that for patients of about 75 or so it approaches what we are used to seeing with prosthetic valves. Some large population studies have shown that.

One other point, I am not sure these are statistically different, even though you pointed out accurately that the upper 95 percent confidence interval of the study valve is below the point estimate for the other series. They also would have some variability and the confidence intervals might overlap.

DR. DOMANSKI: Yes, I think actually what we are running up against is that we probably have a totally inadequate series of controls. I think that is going to be the real bottom line.

DR. GRUNKEMEIER: It could be. Another point is that in an FDA study, such as this, all events are counted. As you know, the data are scrutinized.

DR. DOMANSKI: Well, they should be.

DR. GRUNKEMEIER: Whereas, in the average published series, I don't think that they are scrutinized quite to that level.

DR. DOMANSKI: Oh, I think they are. I think it depends on the study. I don't agree with that.

DR. GRUNKEMEIER: Well, there is variation. On the average, I think some of the best ones; other ones, I don't think they have quite the follow-up effort that is in place in a company like Medtronic to scrutinize these patient records back and forth..

DR. DOMANSKI: Well, I think, first of all, with respect to Medtronic, I have known Medtronic for many years and they are a wonderful, wonderful company. It is a remarkable place. I have been up there, actually, in the past and they are a monument to technology and so forth. So I will certainly stipulate that.

But I still think that there is a real problem with these data because I think what you are saying may well, in fact, be correct. That is, you don't have an adequate control and what you have is a valve and just not real controls to match the population. But that is really a problem because I am not sure what we are considering in that case.

I think in principle establishing, for this purpose, parameters from the known literature is a good idea. In fact, I thought it was a good idea when I was kind of in at the beginning of that. The question is whether it has been done or not. That is the issue, and it is an issue for the FDA as well. But that is more the issue. No, I take your point and I have no doubt that we have no earthly idea whether these populations are the same. In fact, they probably aren't, as you point out. Thank you. I take your point.

Forgive me for going a little bit slowly. I would

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like to look, in fact, pursuing that just a little bit, at page 514. Let's go down this list. I am looking at the bottom under "background." I think that these controls -- you know, these are limitations in effect but I just want to go down that list. Most notable was the absence of several safety controls, that is, death, reoperation or explant. I mean, those are really key things to be in place if you are considering a valve. Now, this is not necessarily just for the company. I am just pointing out a problem in the OPC. But to not have death, reoperation or explant when you are considering valves is a little hard. Again, I really stand to be educated on this. I don't mean to sound argumentative at all. I probably am just not being clever about it but I don't understand how we can consider controls complete when they don't have those three things: the absence of any effectiveness controls; the lack of any OPC values; and the lack of sufficient patient population information to ensure an adequate comparative group.

In fact, if you go down how the articles were selected -- you know, we go through this when we try to do meta-analyses and things, and obviously this is not something you do a meta-analysis on but one tries to not bias one's review of the literature and I am a little bit concerned about this. I believe at one point in here, and I

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am having trouble finding it now, they talk about the article and they don't have enough information, and then they go back to an earlier year and try to develop their quality criteria. That is kind of a data-driven approach to establishing a control group. So I am a little concerned about the standards by which this is being compared.

Let me go to 527. One of the things I think they did in the statistics there, and I may be misreading this but it looks like they included perioperative explants. I wonder why in the data analysis one would do that. I would regard that as an event of sorts, or am I wrong about that? What is the thinking behind that?

DR. EICKHOFF: We did acknowledge the patients that had attempted implants as the definition is applied to them, but they were not included in the operative event. But on page 522 the patients are listed with attempted implants and the reasons why.

DR. DOMANSKI: But shouldn't they be included if you are going to do the analysis? I am not sure that I understand not so much each one of them and why you excluded them, but just in general why it is not sort of an intention-to-treat analysis.

DR. EICKHOFF: We actually looked at the analysis including those patients in there, and there were no

differences in the results.

DR. DOMANSKI: Okay, fair enough. Now, let me go back to 406, which is in the FDA summary. This is the summary of our statistical reviewer. If one looks to the second paragraph under "introduction," they indicate that because of the small numbers in the other groups the review was limited to the subcoronary implant. Does that suggest that the FDA reviewer felt that it wasn't appropriate to review the other levels of implant?

DR. DAWSON: I am John Dawson. I am the FDA reviewer on this application. The reason I didn't get into the other implantation techniques is because of the failure to meet the overall 800 person year requirement. I didn't actually realize until today that there were specific valve sizes that had met part of the OPC requirements. If I had to do it over again, I would go back and look at those sizes.

While I am here, let me also indicate about the control articles. One of the questions that we have for you is what you think about this technology or this technique in the absence of prospective, randomized controls. My approach to these articles, and I feel that they were selected on an appropriate scientifically rigorous basis and I had some role in that myself, and you will not find any calculations in comparison of the Freestyle with controls simply because

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I don't know of any that I think are appropriate. Basically what these numbers do is to show you whether things are drastically worse or drastically better. For anything in between you are not going to get a good answer, it seems to me.

DR. DOMANSKI: Again, I am an amateur statistician but I begin to wonder what "drastically" means when it is outside the confidence interval.

DR. DAWSON: I think it is really a subjective reading of the numbers. I can't give you a concise calculation that would be worth doing.

DR. DOMANSKI: You know, if I were kind of looking that and trying to say, gee, is this okay, I would say, well, you know, from just sort of stepping back and looking at it, is this really a clinically significant difference, it seems to be fairly small numbers -- actually, I am not sure whether they are real small, particularly considering that we are looking at fairly small numbers of valves. You wouldn't expect to see much difference. I mean, there could be a pretty big difference and you wouldn't see a difference.

I mean, if you did a randomized trial, you would randomize these people. With these kinds of numbers, even if there were a very substantial difference you wouldn't be

powered to see it.

DR. DAWSON: Right. Well, one of the things that we don't get to do with these articles is tell you what to make of them, and because I don't have a machine to put the numbers through, then I expect you to have a different reaction to them than somebody else will. That is part of the problem we are up against in using controls.

DR. DOMANSKI: I understand, although, you know, one works with historical controls sometimes and tries to at least generate hypotheses. Here, I sort of hear you telling me, you know, there is no real interpretation of these numbers possible.

DR. DAWSON: Well, I wouldn't say possible; not that I want to put forward.

DR. DOMANSKI: Well, maybe not that any of us should put forward. I mean, that is my concern. The concern is do we have anything?

DR. DAWSON: Well, if we drop out the control articles, then the only thing I have to offer is looking at the table of the safety factors for OPC's. And if you tell me or somebody else tells me that these articles are inappropriate, then the use that I have made of them is something I would withdraw.

DR. DOMANSKI: I guess the concern usually with

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these sort of analyses is not so much that the articles themselves are inappropriate but just in general in doing the OPC's -- now, this doesn't apply to this application but I think I would be more concerned about the ones that you don't have, or how they are excluded rather than included because I suspect the articles you have included are good ones. The question is how they were picked in a non-biased way. That is more the problem with this sort of analysis.

DR. DAWSON: Right. Well, that problem of being selective about articles is something that we were conscious of and attempted to take into account as much as possible.

On thing that happens I think is, in the literature, if something has gone terribly wrong it is going to show up in some of the articles you look at. If you look at enough of them and something terrible has happened, you will find out about that.

DR. DOMANSKI: But, you see, the question is when they are outside those confidence intervals like that, has something gone terribly wrong and are we just not able to see it more clearly because the numbers are so small?

DR. DAWSON: Well, I really would want to discourage you from trying to line things up with confidence intervals because the differences among those various studies in the protocols and the patient exclusion and

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inclusion criteria -- I just don't really see how you can do that.

DR. DOMANSKI: I understand that, and it goes back to what I was saying before. It is not at all clear that the population that we are considering for these controls is adequately comparable at baseline. In fact, it probably isn't. I think the point that was raised, that is, that they are older patients probably is correct, as a matter of fact, but it is worrisome to be presented with controls that really aren't comparable because, I mean, what have you got? You really don't have controls at all. I mean, we might as well just consider it a non-randomized thing and not kid ourselves that we have something here because we may not.

DR. DAWSON: Very true.

DR. DOMANSKI: It may be that we are really back to doing what we did historically, and that is considering really a non-randomized study and asking whether we have a reasonable value, and not fussing around with an attempt at controls that looks like it didn't work at all. I, frankly, think that is what the Panel needs to do with the application. That is, look at it and say, gee, does this look like a reasonably safe device? You know, is there reasonable assurance that it is comparably safe and effective compared with what is out there, and not kid

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ourselves with thinking that somehow you have done a controlled study. But I may be wrong.

Let me ask just a couple more questions and then I will get off the floor.

DR. DAWSON: Excuse me, before you go on, let me just repeat that any advice that you have for us on how to deal with the literature controls would be very welcome. Also, if there are specific questions with the numbers that you can identify that are bothersome to you, it would be good to know that too.

DR. DOMANSKI: Sure.

DR. SAPIRSTEIN: Michael, I am largely responsible for the selection of the articles, and the basis for the selection is given in that long list of the articles --

DR. DOMANSKI: Sure.

DR. SAPIRSTEIN: And this is just an addendum to provide some sort of road map to you of what is available out there in clinical practice. You make your judgment based on the hemodynamic data, the New York Heart Association classification and OPC, which you were involved in generating. If you want to use these control articles, you are welcome to; if you don't want to use them, don't use them. But don't hang too much on these control articles. They are there for additional information.

DR. DOMANSKI: Okay. Let me look at 4-6 and if it looks repetitive in terms of picking at statistics, we will stop it because that is really not the intent. But looking at 4-6, what is the one-year survival -- oh, I guess we have that on page 5-1, don't we? That is just all deaths? Is that the answer to that question?

DR. EICKHOFF: That is correct.

DR. DOMANSKI: Okay. Now, the other thing is that in this analysis I think you eliminated the low implant rate centers. Is that right?

DR. EICKHOFF: No, that is not correct. All implants were included, all centers.

DR. DOMANSKI: Okay.

DR. DAWSON: I can just very quickly tell you why that came up. When we were looking at poolability I wanted to focus on the main implant centers, and we just hit about 30 cases as sort of a cut-off.

DR. DOMANSKI: But I wonder about doing that, and a little bit of this is a methodologic discussion I suppose. What is going to happen when a valve goes out there? Is, in fact, a great spread of the population of centers going to be using it, and, you know, I feel uncomfortable with eliminating those centers. Now, if you said only the best centers, or only the highest volume centers, or only the

people off the learning curve are ever going to use this valve, then that sort of approach would be reasonable, but I am not sure that pulling out the centers just because they are low in recruiting or low in implanting is easily defended.

DR. DAWSON: Well, I think that is a valid point. There are different criteria that could be used for selecting the centers for evaluating poolability. I had one thing in mind, which was really just the precision of estimation of the various statistics we were looking at, and for that I wanted a reasonable sample size.

DR. DOMANSKI: Okay.

DR. DAWSON: In fact, one of my colleagues suggested, and I am sorry to say I didn't follow through with it, to look at the rest of them combined and see how poolability would work out. I just couldn't get beyond the problem of having adequate precision.

DR. DOMANSKI: Okay. One last question, there is a table on page 4-5. Again, I stand to be embarrassed on this one, but it has study at one year and it has rates for a variety of things. Then it has controls at five to six years. It would seem to me that the controls at five to six years are roughly comparable to the study at one year, and I am not sure how you can compare the study at one year to

controls at five to six years, or am I misreading the table?

DR. DAWSON: I can't take the blame for that.

DR. DOMANSKI: I wasn't blaming.

DR. DAWSON: I am not sure. Here comes the
culprit!

[Laughter]

DR. SAPIRSTEIN: I will take the blame for that.
The reason why it is four to five is that these statistics
were taken out of published articles and they were the best
available. There were none available at one, two or three
years.

DR. DOMANSKI: Because in some cases "all cause
death" -- I realize there is no statistically significant
difference in the means in this case but if one looks at,
there are already more of them dead at one year than there
are in the highest mortality in the control thing at five
years. I mean, you have 90.4 percent survival at one year
and you have 91 percent survival at five to six years, and I
know we are probably going to end up saying it is an age
thing again and I am sure they aren't comparable at
baseline, because I really don't walk away thinking this is
a bad valve, or that it is worse, or something like that. I
think it is probably just kind of in the data but those data
would, you know, kind of make you wonder if these things are

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better at five to six years than you are doing at one year.

Does anyone want to comment on that?

DR. EICKHOFF: I think we are having some difficulty with the page that you are referring to.

DR. DOMANSKI: Oh, I am sorry. Excuse me, it is page 4-25 and it is a table at the top.

DR. EICKHOFF: We have different page numbers.

DR. DOMANSKI: That is not good news. It is FDA summaries, page 4-25. That is what they gave me.

DR. EICKHOFF: For us, I think it is 4-29.

DR. DOMANSKI: I am sorry, it is 4-25 for me; for Dr. Gilliam as well.

DR. ELKINS: Can I just take one control article and look at it?

DR. DOMANSKI: Sure, please.

DR. ELKINS: And call your attention to one fact?

DR. CURTIS: Would you identify yourself, please?

DR. ELKINS: Dr. Elkins, again. Causes of all death is rated at 91-95 percent at 5-6 years. If you turn to one of the articles relating to full-root replacement and your postoperative year, actuarial survival by preoperative New York Heart Association classification and you look at 5-6 years, that number is down in the 70 range. It is not up at the 95 percent range or 91 percent.

So one of the problems when you do this is what piece of information you have taken off of what graph, and in some of these the actual curve of survival includes operative survivors. It starts from operative survivors. It does not include operative deaths. Some of them do.

This data that you have for this valve includes all deaths, including operative deaths. I think when one begins to break it down into the classification of patients that you are dealing with and the age of patients it is a very acceptable survival rate. I think to take the controls and take those numbers you have to go back and read the articles carefully and say, gee, what does that mean?

And the same case can be made for the thromboembolism rate. If you look at the same article, there is not a single patient with TIA that is counted as an incidence of thromboembolism in it. Now, we counted all TIA's. So as you look at this and try to compare it to controls, you have to go back and do your homework on the articles.

DR. DOMANSKI: It sounds as though the populations really aren't comparable. I think that is the take-home rather than that there is some problem with the valve. So I want to say that as I close. I mean, it is not that I really think there is something wrong with the valve; it is not

obvious to me that there is.

DR. CURTIS: Okay. I would like to start going around the Panel members before we take a break. We will start on this side of the room this time. Dr. Tracy, do you have any comments to make?

DR. TRACY: I will try to make my comments fairly brief. As I was reading through this I was struck that some of the implants were in a fairly young population, and that the expected duration of survival of this valve may not be as good as a mechanical valve, at least the way the controls look and we have had a long discussion about controls. We don't have data really past three years for this particular valve. How do you envision using this valve in a younger population? Is that at all appropriate?

MS. CAFFERTY: Would one of the surgeons, Dr. Huysmans or Dr. Sintek, address that?

DR. HUYSMANS: Of course, I have to give a personal answer because you can't find it in the data. You just see that there are some surgeons that have used it in younger patients. From the experience known to me, I know that in some cases this, again, was a matter of a homograft not being available. That is one thing.

The other thing is that we know from animal studies that we performed ourselves that the durability of

an unstented valve is far better than that of a stented valve. So our expectations are good.

To me, that is insufficient reason to use it in young people, but some people have said, well, we use a bioprosthesis in patients; it could as well be this one, that has hemodynamic advantages, as the other one that doesn't have the immediate advantages and where we certainly know that it will not last very long. I think that is the answer as things stand now.

DR. ELKINS: Dr. Elkins again from Oklahoma, and I apologize for taking the podium a lot but one of the issues that comes up is specific patients in the younger age group and what to do with those patients. Specific groups were those patients, for instance, where you must avoid anticoagulation or would like to avoid anticoagulation, and in the absence of an available homograft the classic example would be a young female of child-bearing age in whom you might elect to implant a valve such as this. She gets through child bearing and it comes time for replacement, at that point the valve may or may not be a prosthetic valve. We do know that the death rate in patients with prosthetic valves in the age range of 16, say, to 30 is much higher than the death rate of tissue valves in these patients of the autograft type.

So there are some things that are very encouraging but it is going to take time to answer that. Exactly where this valve fits in terms of which patients in the younger age group I can't tell you, but the patient who is not a candidate for long-term anticoagulation would be a patient for it. The patient with endocarditis is certainly a patient for it. There is a number of different specific situations, and in these younger groups this probably represents in some of the situations the patient.

DR. TRACY: What is your level of confidence -- I wasn't totally clear where the calcification was seen. Was it seen on the residual aortic wall tissue? In the patient's aorta? On the pathology specimens that you have, where is that calcium?

MS. CAFFERTY: Fred Schoen will answer that question.

DR. SCHOEN: On the clinical explants, of the 31 clinical explants that were analyzed, all calcium was seen in the native aortic wall. There was no calcium seen either in the implant cusps or the aortic wall.

In the experimental material, the preclinical studies, there was substantial mitigation, and you have those data, of calcification in the implant cusps but not clear mitigation in the implant wall.

DR. TRACY: That is really all I have for now.

DR. CURTIS: Dr. Weintraub?

DR. WEINTRAUB: I think I blew everything on the first valve.

[Laughter]

I don't have a lot to say but just a couple of questions for the surgeons. What is your preference for implant technique now? We have three options here. The inclusion seems to be the least popular. Obviously, the full-root is for certain dilated aortas. But for sort of the standard aortic valve replacement, what do you all do at this point?

MS. CAFFERTY: We will at least start out with Prof. Huysmans answering that because he does use all three implants.

DR. HUYSMANS: I think you might need the answer of all the surgeons present here because everyone has a different opinion. As I pointed out at the beginning, every surgeon has his experience with homograft and feels safe with one technique especially. So he will try to use that technique as much as possible. That is one thing.

The other thing is if you look at it from a theoretical point of view, and that is what I am doing based on a lot of experimental work with biological valves, I do

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prefer at the moment, and I want to state that that is certainly not forever because we just have to wait for further results -- at the moment I prefer the root-inclusion and the reason is that you don't have the potential problems you might have with full-root replacement.

Also I do use the full-root replacement in cases of very pathological aortas. But I think if we don't have that, I prefer the root-inclusion, and the reason is that it has that rib of tissue above the tops of the commissurae that assure you that you perfectly preserve the original anatomy of the valve. In our experiments, that has been shown to be very important for durability.

On the other hand, it is much more difficult. So if we have a patient that is at high risk for other than surgical reasons, we will choose the shortest procedure, the easiest procedure, and that is the subcoronary implant. So personally I feel the need to have all three implants available because you can optimize your choice of technique according to the total situation of your patient.

MR. WESTABY: Stephen Westaby from the Oxford Heart Center in U.K. Medtronic paid my airfare. I have no other interests.

I would just like to say I have now used this valve in 200 consecutive, unselected patients that required

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a bioprosthesis, including young patients who were ineligible for anticoagulation. My object was to demonstrate that this is a versatile valve that can be used in any patient, irrespective of the degree of operative difficulty, and also to demonstrate that it could be used in an acceptable time and safely.

My cross-clamp time mean for this valve is a little more than 40 minutes, and I would not like to hear operative difficulty overemphasized. It is really a very easy valve to use when you are well organized.

In the 200 consecutive patients, all but two had a subcoronary implant, the modified subcoronary implant, and two with porcelain aorta had an aortic-root replacement. I think the consecutively selected series does demonstrate the versatility of this prosthesis.

I know I am not allowed to expand on data that hasn't been presented, but the hemodynamics of this valve is absolutely exemplary, and one would have to say that in my context of Great Britain I could no longer justify using a stented prosthesis in the aortic position, and that is because of data that has been accrued over four years now looking at left ventricular mass regression and improving performance of this prosthesis with time.

DR. CURTIS: Excuse me, Dr. Domanski has one

additional question.

DR. DOMANSKI: One quick question, do you think in your experience, which is substantial with this valve, are there patients who you think are better served by this valve and this prosthesis than any other prosthesis that is out there?

MR. WESTABY: My opinion is that apart from the aortic homograft in infective endocarditis, in elderly patients with aortic stenosis this would be the prosthesis of choice for many European surgeons as it stands.

DR. WEINTRAUB: You are to be congratulated on your cross-clamp time. I don't think a lot of us could do that.

[Laughter]

I don't really have too much more to add. I think the thing of interest will be a longer-term follow-up because with all the tissue valves available today, stented or unstented, homografts or not, I think if there is any choice to be made it will probably be on long-term valvular survival and we can't wait around for 15 years to make decisions about that. So I think that it will be important to follow a cohort of patients for a really long time so that we have appropriate data to make those decisions.

DR. CURTIS: Dr. Skorton?

DR. SKORTON: I will follow the trend of giving little talks about philosophy here. I think that there is a problem because we don't have randomized trials, and I think this is actually not hugely different from what we talked about for the earlier application today. It is just a matter of degree and not a matter of qualitatively different.

So I think there is no need, with deference to my colleague, to really reinvent the wheel. We know that non-randomized controls is not an effective way to detect little differences between groups. We have known that for 20 or 30 years, and there is just no way to make that any different. We don't have any true control procedures for this study. We don't, in my opinion.

It is unclear to me what causes different survival curves when multiple variables are involved -- age, valve type, surgical skill and so on, all those things being lumped together in a multicenter trial. So all those things, to me, indicate that the Panel itself has to accept the precept, as Dr. Domanski said, that we don't have controls on this.

On the other hand, I believe that the control articles that were chosen by some criteria-based mechanism is better than the very old-fashioned consensus method of just getting a bunch of people around in a circle and hoping

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that their combined personal experience is representative of the field. So I believe that what we have today is the aggregate personal experience of the panelists plus some attempt by the FDA staff and Medtronic to select articles. So I think it actually is helpful.

I guess I think the panelists themselves need to make two decisions. The first one each of us has to decide for him or herself is are we comfortable operating in a pre-randomized trial mode where we are basing our decision on an aggregate personal experience of the people here plus our deference, whether they are paid or not, to consultants like Dr. Elkins who, we know, has a world of experience doing this and wouldn't put his reputation on the line for a few bucks from a company.

I, for one, am comfortable making such a decision but I think we should recognize that all of the things that we are doing, as stated in the earlier application, whether we have OPC's or not, we are not dealing with a situation in which we can compare at various points in time, for various valve sizes, for various populations a statistically significant difference whether we use lumped OPC data or not. So I don't actually see this as very much different from the first application. It is just a little bit newer device in a field with a little bit smaller N even than the

first time.

So I, for one, when I looked this over prior to coming here felt that we had to make a decision based on our own experience and whether the descriptive data submitted by the company looked like anything big was jumping out or not compared to just what our experience is in reading the literature. And I do think it is helpful to have some of these articles selected but I think by no stretch of the imagination should we derive any numbers of any kind and claim to be making direct statistical comparisons. So I have no questions of the company about that.

DR. CURTIS: Actually, I thought we might go ahead and take a break now, about ten minutes, and come back to continue the discussion.

[Brief recess]

DR. CURTIS: All right, I would like to go ahead and continue with Dr. Pluth.

DR. PLUTH: Thank you. I notice that in the warning label on the Medtronic Freestyle it states that accelerated deterioration due to calcific degeneration of a bioprosthesis may occur in children and adolescents and, of course, those with calcium metabolism abnormalities. But as I look at the data presented I see that we have very few patients below the age of 15 included in our data. As a

matter of fact, there are only two patients who had entire root-inclusion, and 2.2 percent of patients with subcoronary implants that were below the age of 15. Can we really recommend the valve in patients below the age of 50? Is there enough data present here that can say that we don't have accelerated deterioration in that age group?

MS. CAFFERTY: I will ask if one of the surgeons wishes to address how they identified their patient population for this bioprosthesis. Dr. Sintek?

DR. SINTEK: Well, my personal experience has been to pretty much reserve this valve for patients aged 65 and above. I think that the recommendation is based on what has been recommended in the past for tissue valves in general, and I think most surgeons do tend to not use bioprosthetic valves in patients under the age of 50, with the few exceptions that were state earlier, unless we don't have a homograft available. So I would say that basically the recommendation is following what we recommend for tissue valves in general.

DR. PLUTH: In the subcoronary implants I do not see, or I do not see if that was broken out, what number of patients actually had valves implanted in which the non-coronary cusp or wall was included versus those which had scallops of all three cusps.

DR. HUYSMANS: I can tell you that 79 percent were implanted with the so-called modified technique, that is, where the non-coronary sinus was left in place, and 21 percent had a fully scalloped implant.

DR. PLUTH: Do you feel that is an important consideration, as O'Brien did when he changed his technique about four years ago?

DR. HUYSMANS: I am in preference of anything that helps to preserve the valve geometry. So leaving one sinus in is at least the beginning of that.

DR. PLUTH: Has that recommendation been made?

DR. HUYSMANS: So far it has been on a very individual basis. Each one speaks from his own experience with homografts. As you know, most people nowadays use the Ross-O'Brien methods of implantation which, to my feeling, are, indeed, the better methods. But, as you are well aware, it is difficult to make a certain technique obligatory to a surgeon.

DR. PLUTH: As I look at the data, the incidence of valvular regurgitation at 42 months appears to be quite good, but is this adequate follow-up? If you note on 5-52 in our brochure here, even with stented valves, they all look good for about four years and for that reason I question whether or not a 42-month follow-up is adequate. I doubt

that we can really compare the structural deterioration.

MR. WESTABY: I have four-year follow-up now on the modified subcoronary that you made the inquiry about. The reason I feel that is reliable is because it allows you to very accurately position the commissural pillar so that our incidence of valvular regurgitation has been very low indeed. The method also suspends the valve from a transverse aortotomy which helps prevent regurgitation.

What I will say is that we have looked in great detail at our incidence of regurgitation. I have a couple of cases on the learning curve where we had mild to moderate regurgitation, and we have looked most carefully to see if that has been progressive. In no case has aortic regurgitation been progressive, and in many cases the so-called trivial aortic regurgitation, which I feel is closing volume, has actually disappeared. On one occasion, and this is obviously anecdotal, a patient presented two years after a Freestyle implant with acute Type A dissection and some aortic regurgitation. Inspection of that particular valve at two years showed very adequate coaptation of the leaflets; no calcium in the aortic wall; and resuspension of that valve, as for a normal human valve in aortic dissection, restored full competence. So in about 220 cases in total now, I would say that regurgitation is never

progressive in my experience.

DR. PLUTH: I am glad you brought that up because you said in your learning curve, and that was a question I had also. I commend you about the training program as far as Medtronic is concerned. On the other hand, myself and a lot of my colleagues feel that it may take 10 to 12 patients before you really feel confident of getting a valve into the proper position and have it be competent, and not have a leak associated with it. I am wondering if one or two cases on a wet lab somewhere is going to help the patients that will have this done in the future, or whether we are going to put the first ten patients at risk.

MR. WESTABY: From my perspective again, my modified subcoronary method was designed in a wet lab, but I must say I haven't modified the technique from patient 1 to patient 218. We teach the implant method in Oxford. We have taught virtually all the surgeons in Scandinavia now. The way we do it is for the surgeons to come into the operating room and watch two implants on, again, completely unselected patients. They may have dilated sinotubular junctions, severe calcification in the aortic sinuses and so on. They watch two. They are given a video of the operation so they can watch the video of an operation on many occasions, and also a written account of how to do the operation and the

pitfalls of the operation, and they take all that away and study it. In Scandinavia, in particular, that has worked very well, indeed, and there are a lot of reliable implanters in Scandinavia as a result of that education process.

DR. PLUTH: A little bit ago we heard that amino oleic acid was useful to prevent calcification of leaflets but when calcium did occur it was in the aortic wall. If you notice, on 4-26 there seems to be an increase in valve area and a decrease in gradient present at one year as compared to post-implant. Now, I agree that this could be related to improved cardiac performance, but it can also be related to an increase in root size. Do you have any echo data at all to support the fact that the prosthesis is not increasing at that one-year level, or what will happen in the future with that aortic wall that becomes calcified?

DR. DUMESNIL: Actually, we measured the aorta and we have no evidence that there is an increase. The other thing, for improvement in hemodynamics there are two possible mechanisms which have been proposed, which are the regression of perivalvular edema, and in support of that hypothesis is that improvement is noted only in the root-inclusion technique or in the subcoronary technique but not when you do the full-root replacement. So you see it

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only with the first two techniques, not the other one. The other hypothesis is the regression of left ventricular hypertrophy.

DR. CURTIS: Excuse me, did you all shift positions at the table? Were you sitting there before?

DR. DUMESNIL: I was sitting here. I am Dr. Dumesnil.

DR. PLUTH: This was with the total root replacement?

DR. DUMESNIL: With total root replacement the hemodynamics don't improve over time.

DR. PLUTH: No, it said that it did improve, that your valve size became larger and the gradient became less at one year.

DR. DUMESNIL: With the subcoronary.

DR. PLUTH: With the total root replacement. That is on 4-26, as I recall, the effective orifice area.

DR. DUMESNIL: Well, our copies are different from yours.

MS. CAFFERTY: I think all we need to do is add four to the number you state and then we will have the right page number.

DR. PLUTH: Okay, then it will be 4-30.

DR. MILLER: Fletcher Miller from the Mayo Clinic.

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My expenses were paid to come here today. I consult for Medtronic and my time away from my clinical practice is reimbursed by Medtronic.

If you note there, the cardiac index there also increased in males from 2.4 to 2.5, and from 2.7 to 2.8 in females. The stroke volume is the numerator that we used in the continuity equation for the echo calculation of the effective orifice area. So that improvement in cardiac index then leads to the improvement in the effective orifice area.

DR. PLUTH: The last one I have is a comment that was made that the durability of unstented valves is better than of the stented valves. I guess I am missing that data. I can understand if you are trying to compare apples to oranges because we are comparing glutaraldehyde preserved valves to perhaps non-preserved valves and O'Brien's series, of course, sort of indicated good durability but I don't know where that data lies as far as glutaraldehyde-preserved valves are concerned.

MS. CAFFERTY: Are you referring to a specific statement in the Panel pack?

DR. PLUTH: It was made earlier this afternoon, that the durability is improved in unstented valves.

DR. HUYSMANS: That was from animal experiments, as I said, from my individual experience.

DR. PLUTH: But it is not included in the data?

DR. HUYSMANS: It isn't.

DR. PLUTH: That is all I have.

DR. CURTIS: Dr. Crittendon?

DR. CRITTENDON: The afternoon has gotten late and, fortunately, Dr. Pluth has asked a lot of questions that I wanted to. He has really stolen my thunder.

One thing I am quite concerned about is the issue of calcification. Apparently we don't have enough data to really look at that closely. I would like Dr. Schoen to comment on that perhaps in terms of what he thinks, if he might speculate, or what he has seen with explants in terms of palpable calcium. I guess I am concerned, particularly with the full-root replacement and even with the subcoronary that there is going to be a rigid piece of calcium left there, and if you had to go back and replace it perhaps in that young female that Dr. Elkins talked about who was not a candidate for anticoagulation and then later on comes to a re-replacement.

DR. SCHOEN: From the clinical explants that we have analyzed, just 31 valves, there was no calcification seen in either cusps or aortic wall, except in those few cases where there was endocarditis and calcification, of course, occurs in endocarditis irrespective of a

degenerative phenomenon.

I am not sure that it is reasonable to assume that aortic wall calcification will be a problem long term in these valves. There is no evidence to indicate that. We did see aortic wall calcification to some extent in the experimental studies. But recall that the model that is used in experimental studies is a rapidly growing juvenile sheep, which is much more akin to a very, very young human individual than it is to an adult individual. So I think this may be very different in the human situation. We have no way to know but I don't think we can necessarily assume that aortic wall calcification will be a problem.

There is increasing evidence that calcification of the aortic wall in stented bioprostheses, again the same sort of system other than mechanics, is much, much diminished in adult humans who have stented porcine valves. There is a study that we did that shows that the calcification in the wall is much, much diminished compared to the calcification on the cusp, and it is not likely that it will be an issue, anti-calcification or no anti-calcification.

So I think the only way this is going to be found out is on a long-term basis, looking at what happens, and by postmarket surveillance studies to look very, very carefully

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at explants to make sure that this is not progressive.

DR. CRITTENDON: I have a question about the implantation technique as well. It is my understanding, and I am not a homograft surgeon so I have learned from listening to Dr. Elkins and Mr. Ross, etc. I would just like to know, it seemed to me that the Ross registry had shown that we were getting away from doing subcoronary implants and doing more full roots. I think one surgeon commented that his group does full roots and not the subcoronary technique. I was just wondering if you all could comment on that. I guess I am skeptical from this point of view, you know, presume that the subcoronary technique was abandoned because of aortic insufficiency, and the good physician from The Netherlands said that he was concerned about the subcoronary technique. He did better using the mini-root inclusion because it did maintain the geometry a little bit better. So could you elaborate on that a little bit more and tell me why there seems to be some incongruence between what the Ross registry talks about and what is proposed here?

DR. ELKINS: Well, let me comment about this and I will put a little historical perspective to it as well, if that is all right. The issue with the Ross implantation technique, and for those of you who have never done a Ross or do not know what it represents, it is simply the use of

the patient's pulmonary valve to replace his aortic valve, and that involves using this pulmonary aortic and its contained valve. It can be implanted in three techniques, the similar three techniques that are used here.

When one implants the pulmonary valve, it is very viable tissue; it is very soft; it is very thin-walled; and it has little rigidity to it at all. It is something quite different from the valve we are implanting today or describing today at the time that it is implanted. So that valve becomes quite difficult to implant when one has to guarantee normal anatomic arrangements for competence of the valve. As time has gone on, people have moved to the root replacement because it is technically an easier operation to ensure the normal anatomic orientation and anatomic function of the valve which winds up with a good physiologic function.

Homograft valves have moved to some extent in the same direction, and it has been roughly about four years ago that Mark O'Brien at the AATS recommended that all homografts be implanted as a root replacement, which has not been accepted worldwide by any means.

In this valve, because of the structural integrity that occurs with the glutaraldehyde fixation of the aortic valve, you do not have the problems with an ability to

actually fix the orientation of the commissurae. So it has significant usefulness from that point, and I think the inclusion technique is a superb way to implant this valve, personally.

You have heard that the modified subcoronary technique has been absolutely superb in Mr. Westaby's hands, and we have heard about root replacement techniques, and I think one is going to use all three. I have here photographs from the only four-year explant of an inclusion cylinder valve that has been available in this country that the Panel could look at. I do not have slides to show you. It is an absolutely pristine valve, without any evidence of calcification of the aortic wall.

We may have a treatment here in a glutaraldehyde-treated valve that clearly delays calcification. It is going to take ten years to know that. But if it happens, then something very significant has happened and the only way we are going to know this is to collect ten years of clinical experience because there is not an experimental animal that will provide us that data.

DR. HARTZ: Jut out of curiosity, how old was that patient when you implanted it?

DR. ELKINS: This patient was 81 at the time of death, and it is an older individual; it is not a patient.

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With the permission of the Panel, would they like to see it?

DR. CURTIS: Was that part of the PMA?

DR. ELKINS: No, it wasn't. This simply was provided today.

DR. CRITTENDON: I don't think anything else.

Thank you.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: I don't have any questions for the company. I just want to agree with Dr. Domanski's statement earlier that this is something that is new to all of us, how we are getting the data presented to us for the valves. I think it would be interesting to see the progression of how we approach this and then, in the coming future, as we get more and more data that is going to be required to be presented without statistical methods that we are all going to be perfectly happy with.

DR. CURTIS: Dr. Simmons?

DR. SIMMONS: I really don't have any questions. I guess for a non-surgeon this presentation was very good and the data I think speak for themselves, at least on the surface being very exciting. I don't want to get too confused. There are still problems that maybe we can address. You know, the time; three years of follow-up is nothing; and there are certain sizes that have no data. I

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think there are some issues to be resolved but I have no questions.

DR. CURTIS: Dr. Hartz?

DR. HARTZ: Yes, I have a few comments. I will take Dr. Weintraub's tack from this morning. Number one, do the data presented permit assessment of the safety and effectiveness of this device? I have no question that this is a superb device for the early-term that is presented here. It is absolutely better than anything we have seen. The obvious sort of precaution about late calcification -- in the subcoronary group the mean age was 70 years. We felt the same way when the first Hancock pig valve came out to six or seven years post-implant. Just a word of caution. Other than that, I think the data supports that this is an outstanding hemodynamic choice.

I do have concerns about safety, not of the prosthesis but of the implant technique. Along those lines, I have several recommendations for questions for the Panel labeling information.

First the same thing as I mentioned earlier, I think that the counseling section should say "must have" antibiotic prophylaxis, and the same comment about the patient getting a temporary wallet card at the time of implant until the permanent card is ready.

Page 1-5, under introduction questions, how certain is the manufacturer of the sizes of these prostheses? These are taken from actual animals. We have sizes 19, 21, 23. I am not certain that you have told us what sizes we should use. Are you supplying sizers? Is there a size range you are going to recommend for each given sizer? In other words, if the annulus is size 20, which of the two prostheses would you recommend? I think that is an important issue, especially in view of the fact that regurgitation is a little bit easier to get with this implant technique.

Much more important is page 1-6, physician training. The function of a stentless bioprosthetic valve is sensitive to surgical implantation. I think this should be stated much more emphatically, that this prosthesis takes a longer implantation time. There will of necessity be a longer ischemic time, and I think very few surgeons in this country will be able to implant this prosthesis in the subcoronary position with a 40-minute ischemic time. I can't do it. I think it is worth the extra time but we have to point out that it is going to take longer.

To that end, in the labeling the suture technique section is notoriously inadequate because there is not a recommended implant technique, and if we all took Mr.

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Westaby's recommendations to have on-site training and videotapes, that would be wonderful. What is the company going to do to ensure that, indeed, happens? I can imagine surgeons in this country, many of whom who have never implanted a homograft in contrast to other countries, we don't train our residents for homograft implantation. We don't let them do them -- taking a valve out and thinking it is just similar to a stented valve and not knowing exactly how to even trim the prosthesis, and that is not included in your labeling information.

A couple of other comments come from the other prototype that is used as contrast, and that is the Carpentier-Edwards valve. The questions I had were about cautions concerning the use of a bioprosthesis in severe hypertension. I have not previously read this Carpentier-Edwards insert and I wonder if that is a concern of yours. Should we be concerned about patients with extreme hypertension using this particular prosthesis?

Another very important issue that is in this Carpentier-Edwards insert is the issue of anticoagulation. They use reference 1 which I think is very outdated. We need to have some recommendations from you. Are we required to anticoagulate patients? Using Orzulak's [phonetic] manuscript from the Mayo Clinic, in Attachment 5, there is

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pretty strong data that these patients may not need anticoagulation at all, especially with warfarin derivatives, especially in the early postoperative period when we are thinking about bleeding. So we need to have a little bit more clarification in your insert. Must we anticoagulate, and for how long?

I would say that I think most physicians in this country implanting any type of bioprosthesis in the aortic position have gotten completely away from anticoagulation with Coumadin. So we would like a little bit more clarification on that issue.

On instructions for implantation, a little further, on 2-3, you state you do not invert the bioprosthesis when suturing. Again, for the novice implanter who has never done a Ross, they may not know what you mean by inversion of the prosthesis. So I think you should have a diagram and not just invert the prosthesis into the ventricle. Then, as I said, just a little bit more on the suture technique.

But I hope that you will come up with some sort of an implant process, a training process so that we can get the good results that have been obtained by Dr. Elkins and Mr. Westaby.

MS. CAFFERTY: Did you want a response on that?

That is definitely the approach that Medtronic is taking, and it is also one that, in order to receive the valve, should we have approval for it, the distribution center in Minneapolis has a list of surgeons who have attended training programs and it is from that list that the valves are released.

DR. CURTIS: What does that training program consist of? I am sure you have a whole list but if somebody goes up there, what do they get?

MS. CAFFERTY: The very minimal would be the wet lab and also the video and also the technique monograph. That would be the very minimum. I think it would be dependent on surgeons, as you had identified, if someone comes to us with homograft experience versus someone who doesn't have homograft experience. I think what the training material would include would vary on the surgeons.

DR. CURTIS: So you would not sell the valve to somebody who had not gone through that training?

MS. CAFFERTY: That is what is being recommended at this time.

DR. HARTZ: Is that an FDA approved process, like an LVAD?

DR. SIMMONS: At the time of the ICD implant, when they were first approved, didn't we have to go through a

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mandatory training program and didn't FDA mandate that? I mean, is this something that is new enough that consideration could be given for a mandated training program?

MS. CAFFERTY: May I ask for clarity what is done for homografts?

DR. HARTZ: There is no such training process for homografts in this country.

DR. CRITTENDON: There is no requirement.

DR. HARTZ: Maybe I am being overly protective but it may be handled by labeling instructions but there really is nothing in this that told me how to sew this prosthesis in. I learned today from listening to the other presenters, and have a good idea how I would do it but if I hadn't been at this presentation and read their papers I wouldn't know.

MS. CAFFERTY: Mr. Westaby?

MR. WESTABY: If we could speak from the European experience, everyone in Europe and Scandinavia has had to come to a training program before they have been allowed to implant a valve. I briefly described the training program in Europe. It included at least one or two implants, at least the program in my center. I think it does help a great deal if surgeons can actually stand next to an experienced surgeon doing this. The videos help; the detailed

descriptions help but what you really have to get over to the surgeons that haven't used it before are the potential pitfalls and how to ensure a good, competent implant without complications, and that is easiest done from surgeon to surgeon.

But, certainly, I will reiterate that in our center every single surgeon that has come has had to watch a couple of implants before they tried it themselves.

DR. CURTIS: Dr. Gooray, do you have any comments you want to make?

DR. GOORAY: No, I don't.

DR. CURTIS: Mr. Jarvis?

MR. JARVIS: No, I don't.

MS. CAFFERTY: Prof. Huysmans would like to add to the training.

DR. CURTIS: Go ahead.

DR. HUYSMANS: Well, I think it might be useful to your understanding to tell you what we have done in the last few years. We organized a series of workshops on the implantation of stentless valves. That includes sort of background information, starting with experimental findings, going to clinical experience with homografts and other stentless devices, a lot on the physiology of valves. It also includes live TV interactive operations of all three

techniques, and wet lab, and I think it is a fairly complete program of two days. After that, we offer to assist people in their first series of implants.

It has been very interesting to see that the feedback of this program was enormous, much more so than with any other subject that I have dealt with before. It is interesting to see that sometimes one of the big chiefs somewhere in Europe will present one of his younger residents to come and see the workshop, but the next time he will be there himself. I think that shows that such an educational program, when you set it up properly, has an enormous influence and everyone feels that he has to do that before he starts implanting. I think such a thing would be feasible in the United States as well.

DR. ELKINS: The question was asked about education for homografts, and I probably have been to more educational seminars for homograft implantation in this country than any surgeon in the last, certainly, ten years, and I can tell you that we are going to take that experience, and we discussed this for hours, and the people who are responsible for the educational system plan to reproduce in many ways exactly what has occurred in Europe and what occurred in the U.K.

You know, I think any direction that you all have

for us, we will do. But there is no question that this is a great concern of all of those who are involved in implantation now and we are in the process of developing a series of workshops that will probably be anywhere from half a day to two days, and this is an ongoing, continuing educational process, and I think it will vary. My residents implant homografts. They are going to be quick to take this up. Some residents have no experience and it will take longer.

But it is a doable project because I am convinced, just as I think we have demonstrated with the Ross procedure and the Ross registry, the Ross procedure can be learned by American surgeons and good results can be produced with it. And I think the same thing will happen here.

DR. WEINTRAUB: Could I just ask a question? Has the Panel mandated proctoring in other areas, like cath. angioplasty, etc? I seem to remember that we have done that.

DR. HARTZ: Sure, all kinds of things.

DR. WEINTRAUB: Has the FDA mandated proctoring?

DR. CALLAHAN: I don't think we have actually mandated it, no. Some of the training programs certainly advocate it.

DR. HARTZ: You can't get the devices unless you have done the training, some of them.

DR. STUHMULLER: Actually, at the last meeting a condition for approval for one of the devices was that a physician who was an experienced operator be present during the first two uses of that device by a new investigator. So that was a condition of approval for a device at the last meeting.

DR. WEINTRAUB: It is a little bit of an uncharted area with valve replacements, but I actually think it is a good idea. Perhaps the staff could work with the sponsor to have some sort of mandated program. This is going to come up again whenever homografts get free of their legal entanglements and are presented to the Panel, but I am sure it will come up again.

DR. SPYKER: Dan Spyker. As one who will probably get saddled with implementing these things, I would simply remind you that we want very much to hear your opinions and recommendations, and we will do what we can and we will figure out a way to get them done as quickly and as expeditiously as possible. And if we can't, we will whine and we will try to get some professional organizations to help us. But I think you have a responsible sponsor and they are certainly going to try and do what you think is appropriate.

DR. CURTIS: It sounds to me like just because you

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know how to do a homograft doesn't mean you know how to do one of these things and it is going to require at least some training. I am speaking as a non-surgeon but I think we are going to have some sort of a requirement there.

Taking my turn here, one of the things I was interested in is training, which I think we have discussed enough but then, secondly, I wanted to talk a little bit about the indications because they are extremely broad. Basically, the proposed indication is if you need an aortic valve and you wanted the option of an aortic root replacement, then you would use this.

Yet, I heard some discussions about patient age groups. Normally we think of using mechanical valves more often in the younger patients and the bioprosthetic valves maybe in the older patients. Should the indications be a little bit more specific? Should we not favor these in younger patients? Should that be stated? Should there be some sort of an age range here? Because it is extremely broad the way it is written. Would you want people to be broadly implanting these to all-comers, all patients who need a valve?

MS. CAFFERTY: I will ask one of the surgeons to address that. Dr. Krause from Portland?

DR. KRAUSE: My expenses for the meeting were paid

for by Medtronic.

As an investigator implanting this valve over the past five years, my indications have been in patients in whom I would otherwise use a tissue valve. The average age of my patients was 76. I felt, because this was an investigational device, that I should limit the use of the device to older patients in whom tissue valves were appropriate.

I think that with all of the tissue valves that are currently available, one should not assume that one is going to last any longer until we prove that. I think that the indications for using it should be similar to other tissue valves that now are approved.

DR. KON: I think to put age restrictions on this valve would sort of be a mistake because our approach has been to look at what we think the patient's expectancy is rather than their age. Occasionally, you know, you end up doing a valve replacement in a patient with metastatic cancer that is getting treatment and a bioprosthesis is a better option, and often a bioprosthesis where you need excellent hemodynamics would be the choice. To restrict somebody just because of age, I don't think would be a good idea. Our experience has been, personally, in patients who are young that need a bioprosthesis, less than 45 years of

age, to do a pulmonary autograft or a Ross operation. In patients that are 45 to 65, and this is just based on what the life expectancy would be, to put a homograft in. In patients over 65 to use this valve. I think as a general recommendation that might be a good idea. Age restriction would eliminate the surgeon's judgment in terms of life expectancy, and I think that would be a mistake.

DR. CURTIS: Yes, I wasn't meaning an age restriction. Sometimes we say, you know, you should consider -- we don't know how long these valves are going to last. So I think people have to think about that. I never would consider it a restriction, more that you have to consider these things when you are picking a valve, and there are ways to say that, to, you know, make people consider carefully, as you mentioned.

DR. HUYSMANS: It is part of the workshops to tell people that they should be rather conservative about the indications because we don't have the long-term follow-up and until that time we will have to be careful in considering your ability and maybe the effect of calcification. Nevertheless, I do agree that you do have indications where younger patients might benefit.

The other problem I would like to mention is that we have been faced several times recently with patients that

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demand this valve because they have heard about the better hemodynamics, and were impressed about what they had heard from their cardiologist. That is another thing that makes it difficult to withhold it from a patient. I think that is something we should be aware of.

DR. CURTIS: Okay. If we could go around now and see if anyone else has specific questions for the company. Anything else you want to address to the company?

[No response]

Okay. You can step back then. In directing the rest of the discussion this afternoon, I think we need to do what we did this morning, which is to go through the questions for the Panel and answer them the best we can and eventually come to a motion and a vote on this. That is in our Panel packet on page 1-3.

The first question was already addressed briefly by Dr. Hartz when she mentioned the data and whether it permitted an assessment of the safety and effectiveness of this device. That is really just a question asking us if there is enough information here to make a judgment. My impression was that she was positive to that. If anybody feels otherwise, I would like to hear that. This is just, you know, do we have enough information. My assessment would be that we do.

Then the specific questions that were asked of us, number two says, does the following indications section adequately define an appropriate population for use based on the data presented?

What we were given was that the bioprosthesis is indicated for the replacement of impaired native or prosthetic aortic valves with the option of aortic root replacement. Any comments from anybody on that indication? Go ahead.

DR. HARTZ: You can compare it to what we have seen in other summaries today, the option of aortic root replacement when the patient's life expectancy exceeds the life expectancy of the prosthesis. If you just modify it, then the issue of age does not have to be considered. And we have seen that in another place today.

DR. DOMANSKI: Could I just ask about that? I mean, it is conceivable that someone whose life expectancy is shorter actually might benefit from it, that is, somebody who is hemodynamically compromised in some substantial way might benefit from this device even though their overall life expectancy were short.

DR. WEINTRAUB: Greater.

DR. DOMANSKI: Well, I may have said that backwards -- no, no, if their life expectancy were shorter

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for other reasons but they were sufficiently hemodynamically compromised so you just plain had to do it. I mean, I am not sure why the limitation.

DR. HARTZ: Yes, and I think that is what one of the other surgeons raised, and it is an important issue, and that is exactly the group the very elderly patients fall into. They really need those hemodynamics, or malignancy patients, or young women of child-bearing age is an exception, but for this particular indication, for aortic root replacement when the life expectancy of the patient is longer than --

DR. DOMANSKI: I am sorry, yes, you are deleting that.

DR. CURTIS: What would be the life expectancy of the prosthesis?

DR. HARTZ: Because, you see, autograft is an option.

DR. CURTIS: Yes. I know as a surgeon you make judgments like that but what would we judge then the prosthesis to last? If a patient had a life expectancy of five years you would probably feel comfortable putting this in, I would think.

DR. HARTZ: Well, see, we don't have that data.

DR. CURTIS: I know that.

DR. HARTZ: We have very limited data. So the only way that we can safely say when this prosthesis should be used is to say when we know -- we don't know if it is going to be five or ten years, or whatever it is going to be. We do know that the autograft will last longer than that period of time. So I am just trying to think of a thing that you can put in the indications section for the surgeon and let the surgeon make the decision what he or she thinks the life expectancy of the patient is and the life expectancy as a prosthesis as the next three, four or five years go by.

DR. WEINTRAUB: Yes, but we put prostheses in patients all the time and we think the patient is likely to outlive the prosthesis. Sure, we do. We do it all the time. A 55-year old guy that wants to ski, we know he is going to outlive his prosthesis.

DR. HARTZ: Yes, once in a while a patient will tell you that they will not be anticoagulated, or is vigorously exercising, so you will choose a bioprosthesis over a mechanical valve.

DR. WEINTRAUB: Well, I think you have to assume that surgeons are going to use some intelligence.

DR. HARTZ: That is exactly what I am saying.

DR. WEINTRAUB: So why say anything?

DR. HARTZ: Well, we are being asked for an age

cut-off.

DR. CURTIS: Oh, I don't know if I am asking that. I am saying that if we leave it vague, then I don't know if it adds anything to the current thing, and I don't know that we can't do anything but leave it vague.

DR. CALLAHAN: One of the things we have been doing recently is just putting the data into the labeling on which the information was based so the surgeon would know that this data was based on patients 50 years and older, or whatever, and he or she would know where the data was coming from and make the appropriate decision. So you don't necessarily have to put an age limit in the label per se but it is in the data.

DR. CURTIS: I think that would be fine.

DR. GILLIAM: In the Carpentier-Edwards they just suggest a certain population of people who could not or should not be anticoagulated, not necessarily stating an age but just more or less suggesting a patient population where this valve may be particularly suited for. Because I think age is going to get you into trouble.

DR. PLUTH: Why don't we say the durability of this valve is suspect in patients less than "blank" years of age. I don't know that suspect is the right word -- is indeterminate.

DR. CURTIS: I think it comes up later when we talk about specific patient populations and not knowing how long the valve actually lasts, which is really the big unknown. So maybe it will be sufficient to leave it the way it is and then have that addressed later on in the labeling.

Is the proposed contraindication section appropriate? Namely, that there are no contraindications? Are there any?

DR. CRITTENDON: Is it contraindicated in somebody who is inadequately trained?

DR. CURTIS: To receive it!

[Laughter]

DR. TRACY: But the Carpentier-Edwards has some contraindications listed. This may be the place to address the fact that you may be better off with a mechanical valve and bioprostheses -- wait a minute, I am reading the wrong thing. Do you use if the surgeon believes it would be contrary to the best interests of the patient. So it kind of opens up the door; you have to consciously make the decision that even though the patient wants not to be anticoagulated, maybe you should talk them into it; it would really be in their best interest to have a valve with proven durability. So I think some wording similar to that would be appropriate.

DR. CURTIS: It really in a way covers that whole issue. You don't want to use it if it is not in the best interest of the patient rather than saying, hey, anybody can get one. Go ahead.

DR. SKORTON: Will all deference to my colleague, I think that is the kind of statement you should have to make with every device and drug ever approved. I think the thing to do in this case is somewhere, and I don't know where the right place is, mandate a training program, and I am eventually going to suggest mandating some postapproval surveillance. I don't think the right place to put those things in is the indications and contraindications. I think about contraindications as something that would stop you absolutely from using it and I don't think this falls into that category.

DR. CURTIS: Okay.

DR. SIMMONS: I don't think you should just leave the wording that there are no contraindications to this device though. I agree with Dr. Tracy about saying something similar to the one that is in the Carpentier-Edwards, that there are contraindications but that they are up to the discretion of the surgeon to decide, something like that. Otherwise it sounds like it is an advertisement.

DR. DOMANSKI: But what does that tell you? What

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does that tell somebody reading the package insert, to say that there are contraindications and you have to decide what they are?

[Laughter]

DR. SIMMONS: Well, what does it say to say that there are no contraindications? Do you believe that there are no contraindications?

DR. DOMANSKI: Well, name one.

DR. SIMMONS: Very young age.

DR. DOMANSKI: Well, then maybe that should be listed. I think we should be explicit in what we say, and we also ought to say what "very young" means.

DR. SIMMONS: Well, I am just saying I don't think you can define it very well, and to say that there are no contraindications is sort of like giving it a blank approval. You know, if you are going to hedge at least say it in a way that won't prevent people from doing it but you are not advertising the device either.

DR. SKORTON: I have a suggestion. Maybe where we are disagreeing is that we can't find a contraindication specific to this product --

DR. SIMMONS: I think there are contraindications that are specific to this product but not for every individual.

DR. SKORTON: Just to finish the thought, if there is not a contraindication specific to this product and your concern is to remind people that you have to sort of use judgment when you are putting in a bioprosthetic valve, I think we can find a more eloquent way than is in the comparison thing. Perhaps something like contraindications beyond the usual judgment necessary in deciding on the use of a bioprosthesis, something like that; I think something where you say you should use your best judgment in taking care of your patient. I don't know, I just don't understand how that got into the other one.

But isn't that what you are talking about? You are not talking about what you know about this product; you are talking about just taking into account the general class of the thing.

DR. CURTIS: Actually, I think the way you just worded it is probably pretty close to what would work.

DR. WEINTRAUB: If you are concerned about age, one could make statement that some tissue valves have been known to calcify early in the young, something along the lines of a generic statement, if you really wanted to do it. But I would hope that surgeons who would be thinking of putting this in would know that. But if one wanted to put it in, you could.

DR. CURTIS: You know, there are plenty of things we know though that wind up in the labeling because they have to be there for one reason or another. Yes, it is not a contraindication. There is no reason why you can't put it in a young person; it just is not a smart thing to do.

DR. CRITTENDON: It is a relative contraindication.

DR. CURTIS: Yes.

DR. WEINTRAUB: We don't really know that. Generically, tissue valves in general tend to calcify and deteriorate more rapidly in the young, but we don't know that specifically for this valve but a statement to that effect might cover it.

DR. TRACY: The other issue is what about renal failure patients or people with altered calcium metabolism? Does that belong as a contraindication or is that a warning?

DR. CURTIS: That actually was included. It is on page 2-2. It is listed as a warning in the product label on page 2-2, number 4.

DR. WEINTRAUB: That is perfect.

DR. CURTIS: I think that will work. Number four, the patient counseling information -- we talked about the "must" and the "should."

There are different issues of anticoagulation here

than in the mechanical valve, and we know that.

A temporary wallet card was talked about. I think that is a good idea.

Number six, do the data presented support approval of all three configurations? If not, what additional data would be required to establish the indication for the other configurations?

That is three different techniques of implantation. I was actually interested that none of the surgeons on the Panel have really touched on that very much. Obviously, the numbers are much greater for the subcoronary than for the other two. Are they small enough that that is a concern to anybody?

DR. WEINTRAUB: Frankly, if you release the valve surgeons are going to put it in the way they want to put it in.

DR. CURTIS: True.

DR. WEINTRAUB: So I think that probably is not an issue, honestly.

DR. CURTIS: I mean, there are numbers for all three techniques; they are just not the same numbers.

DR. WEINTRAUB: Yes, they are not the same numbers.

DR. CURTIS: The same magnitude.

DR. PLUTH: Follow-up duration I think is the biggest concern. When you talk about aortic root replacement, total root replacement, and you don't have the normal aortic wall covering the prosthesis and you have a wall that may calcify, who knows what might happen down the road? You break up the elastic fibers and you start to have aneurism formation, then what?

The question in my mind is I am not sure there is enough data about what the implant is going to do in the future.

DR. CURTIS: So which one are you talking about?

DR. PLUTH: The full root.

DR. CURTIS: You are concerned about that?

DR. PLUTH: Yes.

DR. CURTIS: You would do something different?

DR. PLUTH: I think the data isn't there to tell us what the long-term results on that are going to be.

DR. CURTIS: Okay. Would that be necessary before approving it? I mean, it is true, people put it in however but you always have labeling too.

DR. WEINTRAUB: Part of the problem though is that you may have to wait seven, eight, ten years --

DR. CURTIS: Right.

DR. WEINTRAUB: -- to get that.

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DR. PLUTH: Or maybe four.

DR. WEINTRAUB: How many?

DR. CURTIS: Is that an issue that would be taken care of by postmarket studies? Surveillance? Any other comments about the three different techniques?

[No response]

So it doesn't sound like so much of an issue. Okay, number seven, the specific patient populations. Under 8.1 for specific patient populations it says the safety and effectiveness has not been established for longer than three years. Probably everybody is going to be happy with that, I would think, because we know that is true.

All right, number eight, do the data presented support approval of all five valve sizes? Is there a size -- we ran into that specifically this morning -- is there a particular concern with any of the sizes that we don't have enough information on?

DR. AZIZ: I think for the root-inclusion we tend to have small numbers in the 19 and 24 size, 0 and 6, I think.

DR. CURTIS: Right. So that would sway you against approval of that?

DR. AZIZ: I don't know if I would disapprove it but it is one of those difficult things because usually, you

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know, you sort of do a root enlargement or something of that nature so your good judgment would sort of have to come into that. I wouldn't exclude it but there are few numbers for the root-inclusion technique in the 29's and 21's.

DR. CURTIS: All right. Other comments on that issue?

DR. SKORTON: I have a comment. Not being a surgeon, maybe I can be talked out of this but, given that we don't have controls, don't have randomization, and it is even less controlled than the earlier situation today, I am concerned about those two sizes in the root-inclusion.

DR. DOMANSKI: How sure are you -- I am not a surgeon either -- how sure are you when you go in what size valve you are going to end up using? I mean, if you don't have those things available could you ever get in there and say, oh gosh, I wish I had that size?

DR. AZIZ: You know, on the echo you can get a rough idea as to what the annular size is --

DR. DOMANSKI: Sure.

DR. AZIZ: -- so that would give you some idea. Now, if you had an old lady, you know, and you didn't want to do a root enlargement you might just put in a 19. I am not saying that you should but you might do that because it is not so complex.

The only thing against, you know, what you were saying is, see, there are 19 mm valves put in the subcoronary position so I think there is some data on using this valve in the subcoronary position. The root, obviously, makes it slightly more complex. It is not like this valve has not been put in at all.

DR. SKORTON: No, I was really talking about the root inclusion.

DR. HARTZ: This is why I asked the question earlier about sizers, and we really don't know that those valves are exactly 19 because they come from an animal. But this is the impetus for using this prosthesis, 19's and 21's. This is exactly the reason that this prosthesis is so attractive to us. We don't have homografts for everyone; we have this which is just the same thing hemodynamically, and those are the sizes we are concerned about. The only reason we don't have more in those sizes is because that is the size of the patient's native aortic annulus. That is the best hemodynamics you can get in that given patient. I think that is truly an issue here. When there are more patients we will have the data. It is as good as you can get.

DR. SIMMONS: Maybe something could just be put in the warning section that the data is not available for this implantation technique, the root-inclusion and full-root,

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but not exclude it from being available, or something.

DR. CURTIS: I remember the issue was raised before about if you had an annular size of, say, 20 that was in between, do you size up or size down? I assume that that would be clarified, particularly in the physician training.

Number nine, is the proposed physician training section appropriate, or are there any other points you believe should be included? It says you have to be familiar with the technique. I think we all want a little bit more than familiarity with the techniques. I think I was getting a consensus that people would want to mandate physician training. We have discussed some of the issues about the wet lab, about seeing it. Should we talk about requiring that somebody sees a couple of human implants? Do we need to be getting into that kind of detail?

DR. AZIZ: I think so. I think we should really mandate or spell out what the minimum requirements would be. I mean, the ideal thing would be to scrub in with somebody but that may not always be possible. I think you should at least see one clinically being implanted, or somebody should be around when you are doing one. I think we should mandate something like that.

DR. PLUTH: In each position? I mean, each type of implant?

DR. AZIZ: Clearly, the root implantation ideally I think you should do. The subcoronary isn't too difficult to put in. The root-inclusion or the full-root I think would be. Probably in the training session where there is a wet lab you would get that exposure, hopefully.

DR. DOMANSKI: I wonder about the wisdom of doing everybody's QA for them. I mean, people learn differently from different things. I mean, when I learn procedures I find that I have to actually do them and watching somebody else do it has real but limited value. I just feel uncomfortable saying go find somebody to proctor you or you can't do it.

DR. CURTIS: Although if this Panel went to the extent of saying, you know, from the previous Panel meeting that you had to have somebody present there in order to be able to get the device and be able to do that procedure. It seems to me that that issue was simpler than this and that, you know, to say that you have to have somebody sit next to you to use a laser but it is okay just to kind of watch somebody doing the other, I am not sure that is logical. It seems like we have a more complicated procedure here but, yet, we don't want to mandate too much.

DR. DOMANSKI: That presumes it was great wisdom to do that with the laser. I think we can make an

independent decision about this.

DR. WEINTRAUB: I used the term proctor before and I may have used that incorrectly. I am not sure one can even mandate proctoring. That would mean you would have to do it in some other institution or some instructor would have to come to yours. So that was probably not a good choice of words but a course of instruction, I think, we can mandate, as proposed by the sponsors, and with regrets to Dan Spyker, I think we can allow the staff to work that out, perhaps with consultation from the Panel surgeons, as to the details of that kind of an arrangement.

DR. CALLAHAN: The reason I reacted before was just because of that word "proctor." We are treading the line of clinical practice. But in terms of having a training program, we don't have any problem mandating that, if that is what you want.

DR. SKORTON: I wanted to just push back a tiny bit in the other direction. I agree we should stay away from the word proctoring. I don't think we should leave it so vague that someone could just buy a videotape through the mail and consider themselves trained because we just heard from a whole bunch of surgeons, including people who are paid consultants for the company today, that it is necessary to get hands-on training directly with somebody who has done

it. So I would urge the Panel to not back off of that. I don't think we have to have the word proctoring but not back off from the idea that one has to get training on site so that somebody doesn't call an image up over the Web, or videotape, or 50 other technologies that are going to be more and more available, as a shortcut way to do this.

DR. SIMMONS: I agree. You know, the company's own representatives have said the same thing. To not do it -- I don't see the logic of that. It sounds like you are afraid to say, you know, go, get this training.

DR. CURTIS: So it sounds like at a minimum what we are talking about is that there should be physician training; that you have to go to the company; whatever arrangements are agreed upon, wet lab, didactic, etc., etc., at a minimum in order to be able to get the valve. There really doesn't seem to be a big consensus that surgeons have to start flying around helping people implant the first one or two.

DR. CRITTENDON: Can I be the devil's advocate for a moment? How is this different from Medcab? [phonetic]. You can't be mandated to take a Medcab course before you do it. We all know how to put suture in the annulus and have studied anatomy. Again, I think the ideal is to do it the way we are suggesting but I just wonder if we are going to

open Pandora's box in terms of enforcement and a whole bunch of legal stuff about chiefs of surgery having to enforce this type of thing.

DR. WEINTRAUB: There is no device on Medcab. You are not implanting a device.

DR. HARTZ: And it is not the annular sutures, it is the treatment of the prosthesis before we sew it in; exactly now the prosthesis should be trimmed. It is not standard any more. We don't just take it out and sew it in. So that is the part of it that, to me, is going to be the learning curve. Once we know how to trim it we will be able to sew it in.

DR. PLUTH: I think the sponsor himself would be happy to do the training courses because if someone has an unsuccessful result they won't use it again.

DR. HARTZ: Right.

DR. PLUTH: So either they start putting it in the right way or it is just not going to be used.

DR. CURTIS: That is a good point. Before we get to the actual motions and votes, I would like to skip ahead to 14 and 15, the methodology, because we didn't really discuss that this morning with the other presentation.

There has been a variety of comments about the objective performance criteria and we are asked for specific

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comments or suggestions on the use.

I actually think that the process works pretty well. Given the limitations of trying to find literature articles that match exactly whatever study is being presented, I think there has been a real attempt to try to match them as well as can be done. We all recognize that it is difficult to impossible to do prospective controlled trials about a lot of these issues. I actually kind of like the way it worked out overall, not that you can exactly match column for column but really giving us a ballpark for what kinds of numbers you might expect that we might compare to. So I think the process works pretty favorably but if there are any other comments, I think this would be a good time to get them. Go ahead.

DR. SKORTON: I agree with you. I might just restate it a tiny bit differently. I think that the Panel should go on record as saying that when possible we should support the use of randomized clinical trials and not just assume that we are never going to ask for that. I think that would be going too much the other way.

But I think that the stuff that the FDA staff supplied us, even in this case where the controls were very problematic, was useful. And I would call all of these things, all the OPC stuff and these decision aids or

decision crutches for the Panel but not decision replacements. A randomized clinical trial that showed a huge differential, that would be a replacement. We are not going to use our clinical judgment to overcome that. So I think these are decision aids and they are helpful but we should just reaffirm, unless somebody disagrees, that when possible we should still pursue randomized clinical trials.

DR. CURTIS: I think that is a good point.

DR. DOMANSKI: Well, I do have a comment about it. Actually, I think what happened here was that the FDA staff has gone into real uncharted waters in an incredibly difficult sort of thing in trying to establish these objective performance criteria by using the literature, and the literature is obviously extraordinarily difficult to use, as anyone who has tried to do a meta-analysis or anything like that will attest.

I wonder if one couldn't -- this is a very useful first step and a very difficult one but I wonder if this methodology couldn't be pushed further, if we couldn't, in fact, work harder to access databases and so forth and push a little bit further to get more from it. It is hard to do and it is hard to take the first step but they have taken the first step, and I wonder if it wouldn't be worth working more on that because I think it may have something to offer.

DR. PLUTH: I think there is a real problem when you start using data from the literature because most people present their data because they have the better results. So you are sort of seeing somewhat superior data that you are trying to compare a device with. You would be much better off to have databases, such as maybe Summit or something of this type, in which people are not afraid to report their material. Summit is a bad example in that regard, but some other data source would be much better than taking articles out of the literature which may be the most favorable instances.

DR. DOMANSKI: There is certainly publication bias, and there is also a change over time in the management of patients and the effectiveness of doing so. So it is difficult. Perhaps even accessing databases where people have published this stuff -- done sometimes with meta-analysis -- is better than nothing, which is what one has otherwise.

DR. TRACY: is it possible that future data such as that presented today would be part of the comparative data? I think it is true that when you are doing a study you are more likely to write down every single thing that happens. Where there may be a trivial degree of leak, it is reported, whereas in the literature that may have been,

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well, it is so trivial we won't notice that. But this is probably pretty scrupulously collected information. Is there any way that that is going to be incorporated into the comparative literature or source for future products?

DR. GILLIAM: I would just suggest that perhaps postmarketing data, if we can sort of agree in a general way on what data are to be collected, at least the next time, three to five years from now if we have to look at another valve we would have OPC data that really mean something, and it may be something that as a learning experience we may want to sit down with each of the companies, as we have sat down postapproval follow-up period, to say these are data that we want to keep; what are data and what are endpoints that can reasonably be expected that the company keep track of and that we would, indeed, have a database to compare our next group of valves.

DR. CURTIS: Okay. Unless anybody wants to make other points, I think we could move to a Panel recommendation. This means we have to hear the whole thing read all over again.

DR. STUHLMULLER: Dave, it is one of those bureaucratic issues. Panel recommendation options for premarket approval applications: The Medical Device Amendments of the Federal Food, Drug and Cosmetic Act

require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application, or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of use outweigh any probably risk.

Effectiveness is defined as reasonable assurance that in a significant proportion of the population the use of the device, for its intended uses and conditions of use when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows: Option one, approval. There are no conditions attached.

Option two, approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting all the conditions are discussed by the panel and listed by the panel chair. You may specify

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what type of follow-up to the applicant's response to the conditions of your approval or recommendation you want, for example, FDA or panel. Panel follow-up is usually done through homework assignments of the primary reviewers of the application or through other specified members of the panel. A formal discussion of the application at a future panel meeting is not usually held. If you recommend postapproval requirements to be imposed as a condition of approval, then your recommendation should address the following points: a] the purpose of the requirement, b] the number of subjects to be evaluated and, c] the reports that should be required to be submitted.

Option number three, not approvable. Of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to panel deliberations: a] the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; b] reasonable assurance has not been given that a device is effective under the conditions of use prescribed, recommended or suggested in the labeling; c] based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading. If you recommend that the application is not approvable for

any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

Option number four, tabling. In rare circumstances the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to the FDA or the applicant, thereby creating ambiguity and delay in the progress of the application. Therefore, we discourage tabling of an application.

The panel should consider a non-approvable or approvable with conditions recommendation that clearly describe corrective steps. If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

DR. CURTIS: We got a little bit confused this morning about the order of doing things. I think maybe if we could make a motion, and if there are conditions to it we are going to need to specify them. Either Dr. Domanski or Dr. Aziz?

DR. DOMANSKI: I am going to move approval with conditions. I think this is a valve that looks like it may actually have some advantages over other things. So I really think it ought to be approved. I need some help though with the conditions because, you know, it has been a long

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discussion and I think the surgeons could help us out with that part of the motion.

DR. CURTIS: Are there any conditions of data that is missing, or are you looking at postmarket?

DR. DOMANSKI: I am looking at postmarket surveillance.

DR. CURTIS: Okay. So you would move with approval with --

DR. DOMANSKI: Of all of the sizes, each configuration.

DR. CURTIS: Okay.

DR. DOMANSKI: And postmarket surveillance as follows, colon, and I would like them to fill it in.

DR. CURTIS: Okay.

DR. AZIZ: I would second that.

DR. CURTIS: Good. What kind of postmarketing studies would we be talking about?

DR. AZIZ: I think, particularly because the valve has only been in for about three and a half years, it would be nice to have some, if possible, echocardiographic analyses annually because I think as we go out to about seven or eight years that is particularly where it is going to be coming up against the bioprosthetic valves. If that would be possible, not just clinical evaluation, I think

echo.

DR. CURTIS: Echo, and if you say clinical evaluation, what are we looking for?

DR. AZIZ: You know, if you started hearing a murmur or some evidence of deterioration in New York heart classification, but that might be difficult to separate out from, say, coronary-artery disease. But if we could get that data it would be nice to have.

DR. WEINTRAUB: I think I would leave it to the FDA staff to work out the numbers. It really gets to be pretty impractical to follow a thousand patients --

DR. CURTIS: Sure.

DR. WEINTRAUB: -- over a long period of time, and we have done this before, taking a cohort of patients that would be followed very closely. But that could be worked out, I would think, with staff.

DR. CURTIS: Do we get most of the information we need from follow-up echocardiograms? I mean, the only other thing that was mentioned was New York Heart Association class. Is there anything else we would want to know clinically?

DR. AZIZ: Incidence of thromboembolic events. I think it has been pretty low and I am sure it will be low, but that should be collected.

DR. CURTIS: Thromboembolism? Okay.

DR. PLUTH: Do you want to correlate it with age?

DR. CURTIS: Okay, correlation with age. Can anybody think of anything else that we would want to know specifically?

DR. GILLIAM: Freedom from reoperation.

DR. CURTIS: Okay. All right, so the motion has been put forward that we recommend approval -- go ahead.

DR. WEINTRAUB: Mike, can I add another condition, which would be the condition that a training program be established, again in consultation with the staff?

DR. DOMANSKI: Sure, yes.

DR. CURTIS: I am sorry, I missed what you said.

DR. WEINTRAUB: Establishment of a training program to be worked out with the staff.

DR. CURTIS: So postmarket surveillance and the training program is required.

DR. SKORTON: And then the addenda to the labeling that were mentioned by Dr. Hartz and others. I kind of assume that is part of the motion as well.

DR. SIMMONS: Contraindications, warnings.

DR. CURTIS: I think so.

DR. SKORTON: Someone suggested rather than data before approvability that the warnings say insufficient data

to establish safety in the 19 and 21 size for root-inclusion.

DR. DOMANSKI: Sure, let's add that but let's also be specific about the other things that are being added. What are the others?

DR. HARTZ: Oh, the antibiotic must be used, and we will work on that temporary ID card. I do have a question that we have kind of skimmed over. Is there going to be a recommendation for any form of anticoagulation? Or should we just leave that? If nothing else, postmarket studies should include in detail what the patient received, especially for those first few years while we can still get that information. This is the golden opportunity to get it.

DR. CURTIS: So use of anticoagulants --

DR. HARTZ: Or antiplatelet drugs.

DR. CURTIS: Or antiplatelet drugs.

DR. AZIZ: And the last thing, you know, valves that are explanted, is there any way -- you know, if there is peculiar pathology that is picked up, if there is just a way to disseminate that information. So they would have to, obviously, send it to a central place.

DR. CURTIS: A core pathology lab?

DR. AZIZ: It would be nice to have that, yes.

DR. SIMMONS: And the adjustment to the

contraindications section the way it was suggested, to be more in line with the others. I forget how you phrased it.

DR. CURTIS: I think it is in the minutes. Okay, so we have a motion for approval with conditions. We had a second to that. We talked specifically about postmarketing echo follow-up and clinical follow-up with the issues talked about regarding anticoagulation and antiplatelet drugs, thromboembolism, New York Heart Association class, correlation of outcome with age, freedom from reoperation, the need for a training program, the issues of labeling that we discussed earlier, adjustment in the contraindications and all of that. I hope I haven't missed anything. Can we go ahead and vote on it? We will go around the room. Dr. Hartz?

DR. HARTZ: Approval with those conditions.

DR. CURTIS: Dr. Simmons?

DR. SIMMONS: Approve.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: Approval with those conditions.

DR. CURTIS: Dr. Crittendon?

DR. CRITTENDON: Approve.

DR. CURTIS: Dr. Pluth?

DR. PLUTH: Approve.

DR. CURTIS: Dr. Skorton?

DR. SKORTON: Yes.

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DR. CURTIS: Dr. Weintraub?

DR. WEINTRAUB: Approve.

DR. CURTIS: Dr. Tracy?

DR. TRACY: Yes.

DR. CURTIS: Okay, the motion passes. Leave your Panel packs here, Panel members. Don't take them away. We will reconvene tomorrow morning at 8:30. Thank you.

[Whereupon, at 6:06 p.m., the Panel adjourned, to reconvene on Tuesday, September 16 at 8:30 a.m.]