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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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TUESDAY,
DECEMBER 5, 2000

The Panel met at 8:00 a.m. in the Grand Ballroom of the Gaithersburg Holiday Inn, Two Montgomery Village, Gaithersburg, Maryland, Dr. Cynthia M. Tracy, Acting Chairperson, presiding.

Present:

CYNTHIA M. TRACY, M.D., Acting Chairperson
SALIM AZIZ, M.D., Consultant
MICHAEL D. CRITTENDEN, M.D., Member
ROBERT A. DACEY, Consumer Representative
MICHAEL DOMANSKI, M.D., Consultant
RENEE HARTZ, M.D., Member
GARY JARVIS, Industry Representative
MITCHELL KRUCOFF, M.D., Consultant
WARREN LASKEY, M.D., Consultant
TONY SIMMONS, M.D.. Consultant
MEGAN MOYNAHAN, Executive Secretary

# I N D E X

P R O C E E D I N G S

8:06 a.m.

DR. TRACY: I'd like to call to order this meeting of the Circulatory System Devices Panel.begin by reading the Conflict.

MS. MOYNAHAN: I'd like to begin by reading the Conflict of Interest Statement for today. 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. The Agency reviewed this admitted agenda for this meeting and all financial interests reported by the Committee participants to determine if any conflict existed. The Conflict of Interest Statue prohibits special government employees from participating in matters that could affect their or their employer's financial interests. However, the Agency has determined that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government. The Agency would like to note,

therefore, that a waiver is currently on file for Dr. Renee Hartz for her interest in a firm that could potentially be affected by this Panel's recommendations.

A copy of this waiver may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

For the record, we wish to note that the Agency also took into consider other matters regarding Drs. Cynthia Tracy, Salim Aziz, Mitchell Krucoff and Warren Laskey. These Panelists reported interest in firms at issue, but in matters that are not related to today's agenda or have now been completed. The Agency has determined, therefore, that they may participate fully in all 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 firm whose products they may wish to comment upon.

DR. TRACY: Can I ask the Panel Members to please introduce themselves?

MR. JARVIS: Gary Jarvis, Industry Representative.

DR. KRUCOFF: Mitch Krucoff, Duke University Medical Center, Cardiology Division.

DR. DOMANSKI: Mike Domanski, Cardiologist, NHLBI.

DR. LASKEY: Warren Laskey, Cardiologist, the University of Maryland.

MS. MOYNAHAN: Megan Moynahan, Executive Secretary of the Circulatory System Devices Panel.

DR. TRACY: Cynthia Tracy, Electrophysiologist, Georgetown University Hospital.

DR. CRITTENDEN: Michael Crittenden, Cardiac Surgeon, Harvard University.

DR. AZIZ: Salim Aziz, Cardiac Surgeon, University of Colorado.

DR. SIMMONS: Tony Simmons, Cardiologist, Wake Forest University.

MR. DACEY: Robert Dacey, Longmont, Colorado, Consumer Representative.

MR. DILLARD: Jim Dillard. I'm the Director of the Division of Cardiovascular and Respiratory Devices, Food and Drug Administration.

MS. MOYNAHAN: I'd like to read the appointment to temporary voting status for today. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 18, 1999, I appoint the following people as voting members of the Circulatory System Devices Panel for this meeting on December 5, 2000: Cynthia Tracy, Salim Aziz, Warren Laskey, Tony Simmons, Mitchell Krucoff and Michael Domanski.

In addition, I appoint Dr. Cynthia Tracy to act as Temporary Chair for the duration of this meeting.

For the record, these people are special government employees and are consultants to the Panel under the Medical Devices Advisory Committee. They

have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Signed, David W. Feigal, Director, Center for Devices and Radiological Health.

DR. TRACY: At this point we'll move to the open public hearing. There are scheduled speakers, but if there's anybody who would like to present some data or information, please identify yourself and come to the microphone.

(Pause.)

In that case, we'll begin with the sponsor presentation and I'd like to remind the speakers to introduce yourselves and state any conflict of interest you have and also whether you have an honorarium for today's presence or travel award.

DR. STANTON: Good morning. I'm Dr. Marshall Stanton. I'm Medical Director for the Medtronic Cardiac Rhythm Management Division and for the record I'm an employee of Medtronic.

On behalf of Medtronic, I want to thank everyone for taking the time to review our submission of the Model 7250 Jewel® AF for the "AF Only" clinical

evaluation.

This is the Model 7250 Jewel® AF and I want to begin by emphasizing that this is the exact same model that this Panel reviewed and recommended for approval, and FDA did grant approval earlier this year for the indication of ventricular tachyarrhythmias with or without concomitant atrial arrhythmias. We're here today requesting an expansion of that indication.

The Model 7250 Jewel® AF is a ventricular ICD. It can detect and treat ventricular arrhythmias. It's comparable to other Medtronic ventricular ICDs.

Additionally, it has features that are intended for the treatment, prevention and monitoring of atrial tachyarrhythmias. For termination of atrial tachyarrhythmias it has pacing therapies including antitachycardia pacing and high frequency burst pacing.

It also has the capability of delivering atrial shocks. The atrial shocks can be delivered automatically or can be patient-activated. For automatic shocks, the time of delivery can be

programmed in such that for example the shock can be delivered in the middle of the night while the patient is asleep. The patient-activated shocks allows patients to deliver an atrial shock when they choose.

The Jewel® AF will not allow delivery of a patient-activated atrial shock unless it confirms that the patient is indeed in an atrial tachyrhythmia.

The algorithms designed for prevention include atrial rate stabilization which functions to prevent the pause that typically would occur after an atrial premature complex and switchback delay which allows a gradual reduction in rate after determination of an atrial arrhythmia. The device also has memory capability for storage of both asymptomatic as well as symptomatic episodes of atrial and ventricular arrhythmias.

These are the patient activators. This is the 9464 and this is the 9465. The 9465 is a downsized version of the 9464. The patient activator or patient assistant allows the patient to self-administer atrial shocks for termination of atrial arrhythmias.

The 9464 was used during this clinical study. We are submitting those data for -- and asking for approval of the 9465. Also, as part of this submission, we're seeking approval of the Model 6937A, defibrillation lead. This is a 9 French unipolar, high voltage lead that's designed for placement in the coronary sinus or the superior vena cava. It does not do pacing or sensing. It's similar to the already approved 6937 SVC lead, except that its defibrillation coil is five centimeters compared with seven centimeters and it has additional insulation for added stiffness.

I want to emphasize again that the Model 7250 Jewel® AF is already approved for use in ICD patients either with atrial tachyarrhythmias or those who are at significant risk of developing atrial tachyarrhythmias.

Based on the results of our clinical trial, we propose the final indication for use. The Jewel® AF system is intended to provide pacing, cardioversion and defibrillation for treatment of patients with symptomatic, drug refractory atrial

tachyarrhythmias and/or life threatening ventricular tachyarrhythmias.

I believe that device-based therapy for atrial tachyarrhythmias is part of an overall treatment strategy that physicians can offer to a very specific patient population. That is, those with symptomatic drug refractory atrial tachyarrhythmias. We estimate that this would compose approximately 5 percent of the total atrial defibrillation population and it is specifically designed for patients who need more control of their arrhythmia. The device also provides monitoring capability to provide information to clinicians.

Our presentation today will consist of the clinical study results which will be presented by Dr. Michael Gold of the University of Maryland. This will be followed by some brief case presentations by Dr. David Schwartzman of the University of Pittsburgh. We also have available, if you have questions, Dr. David Newman from the University of Toronto who has performed the Quality of Life Analysis that's part of the submission. And finally, there are additional

people available from Medtronic to answer any other questions that you may have.

At this point I'd like to turn this over to Dr. Michael Gold.

DR. GOLD: Thank you and good morning. Again, I'm Michael Gold from the University of Maryland. I have no financial interest in either this device or this company. I am being reimbursed for my travel and paid an honorarium for my presentation this morning.

As mentioned, I am here to summarize the results of the Model 7250 Jewel® AF, "AF Only" Study which was recently completed. The purpose of this study was to demonstrate the safety and efficacy of this device in a specific patient population suffering from symptomatic drug refractory atrial tachyarrhythmias, but who were without standard ventricular ICD indications.

This was a multi-center IDE study with prospective follow up to evaluate the safety and efficacy of this treatment therapies. There was also a randomized crossover component of this study, the

evaluation of prevention therapies. That included three month periods in which prevention therapies, both of them were programmed on and three months when both of the prevention therapies were programmed off.

To be included in this study, patients needed to have experienced at least two episodes of atrial fibrillation and flutter within the previous three months and at least one of those episodes had to be documented electrocardiographically. The episodes were required to be symptomatic.

In addition, patients were required to be refractory or intolerant to anti-arrhythmic drugs. Patients were required to have failed at least one anti-arrhythmic drug for inclusion in the study.

Finally, patients were required to be in sinus rhythm at the time of implantation. For those patients who were in atrial fibrillation, cardioversion could be performed, but they needed to maintain sinus rhythm for at least one hour before they could be enrolled in the study and implanted with the device.

With regard to the exclusion criteria,

patients were excluded if they were in chronic atrial fibrillation which was defined as the inability of maintaining sinus rhythm for at least one hour. They were also excluded for a history of uncontrolled angina, a history of sustained ventricular tachyarrhythmias. They were excluded if they had New York Heart Association Class IV heart failure or cardiac surgery within the previous one month.

For safety reasons, patients were also excluded if there was any evident of atrial thrombus detected within the preceding six months prior to implant, or if they had had a history of a stroke within the preceding one year.

Finally, patients were excluded if they were unwilling to give informed consent, if they had a mechanical tricuspid valve which precluded the placement of leads for this device, or if they had a life expectancy less than one year.

One hundred forty-four patients were implanted out of the 146 patients who were enrolled in this study. The study ran from November 1997 to November 1999. There were 107 implants in the United

States, 33 in Europe, and 6 in Canada. Of the two patients who did not get implanted, one had high atrial pacing thresholds and no place to be able to adequately pace the atrium could be found. The second patient had unacceptably high ventricular defibrillation thresholds. One of these patients was from Europe. One of these patients was from the United States.

With regard to the data base for follow up, the cut off date was May 31, 2000 which allowed for a mean follow up of just over one year. The cumulative patient follow up was 1,835 months.

The patient characteristics for this population is show on this slide. It's a fairly typical population of those with atrial fibrillation. Seventy-one percent of the patients were male. The mean age was 62 years and about a third of patients had a history of coronary artery disease.

Myocardial infarction had occurred previously in 19 percent of patients and 29 percent of patients had a history of congestive heart failure. The mean left ventricular ejection fraction was 51

percent, including 31 percent of patients with ejection fractions less than 40 percent. And a mean left atrial size was 46 millimeters.

With regard to the characteristics of the atrial fibrillation, 35 percent of patients had paroxysmal atrial fibrillation which initiated and terminated spontaneously, while the remaining 65 percent of patients had incessant atrial fibrillation which was defined as that atrial fibrillation which required cardioversion, also often referred to as persistent atrial fibrillation.

The primary arrhythmic indication for device implantation was atrial fibrillation in nearly three quarters of patients. In 23 percent of patients, there was a history of atrial fibrillation and atrial flutter. And only 3 percent of patients in this study had a history of atrial flutter only.

The primary objectives of this study were divided into safety and efficacy criteria. With regard to safety the objective was to estimate the relative risk of a system or procedure related complication for the Model 7250, using as a control

the Model 7219D which is a single chamber ventricular defibrillator which was the only available comparable data base at the time that this study was initiated.

The hypothesis was that the 95 percent upper confidence bound would be less than 3.0 to meet the primary objective.

With regard to efficacy, the objective was to estimate the efficacy of atrial tachyrhythmia termination therapies for this device in this patient population, hypothesizing a 95 percent lower confidence bound would be greater than 75 percent for episodes that incorporated shocks as part of the treatment strategy.

With regard to the comparison of historical controls, as already mentioned, this was performed with the 7219 Jewel® PCD ventricular defibrillator. The primary safety endpoint which was complication-free survival was compared between the two devices. The secondary objective was to compare survival from all-cause mortality.

Because these were somewhat different populations, one of ventricular defibrillator

population and the other an atrial tachyrhythmia population, there was adjustment for differences in baseline patient characteristics in the two populations using Multi-variate Cox Proportional Hazards Regression Models.

The variables that went into the final model to evaluate complication-free survival were the region in which the patients lived, their gender, the presence of coronary disease, hypertension, cardio-myopathy, New York Heart Association Class, previous bypass surgery and a history of sustained ventricular tachycardia.

The variables that went into the final model for survival from all-cause mortality was quite similar, including gender, coronary disease, myocardial infarction, hypertension, cardiomyopathy, heart failure, New York Heart Association Class, heart surgery, both bypass surgery and valve surgery, history of atrial fibrillation, history of atrial flutter and sustained ventricular tachycardia. These parameters were chosen for the model based on univariate analysis that suggested differences in the

two populations.

With regard to the primary safety endpoint, the relative risk of a system or procedure-related complication for the Model 7250 in this study compared with the Model 7219 Jewel® PCD was 1.31 with a lower confidence bound of 0.76 and an upper 95 percent confidence bound of 2.25. Thus, the safety objective was met in that this upper confidence bound was less than 3.0.

If we look at the actual complications that were noted, by far and away the largest number of complications were lead dislodgements and again, this device differed from the 7219 in that it was a dual chamber device with an atrial lead. Most of the lead dislodgements were, in act, atrial lead dislodgements. There were 11 lead dislodgements, 3 episodes of atrial fibrillation, 2 hematomas, 2 infections and then a variety of other complications which led to the total of 26 complications in 23 patients.

With regard to the system procedure related complication-free survival, at 6 months this was estimated to be 86.6 percent in the present study

of the 7250 device compared with 91.6 percent for the 7219D control. These differences were not statistically significant.

This device classifies rhythms, atrial rhythms as either atrial tachycardia or atrial fibrillation based on both the rate and the regularity of the rhythms. Very rapid atrial arrhythmias are classified as atrial fibrillation, relatively slow atrial tachyarrhythmias are classified as atrial tachycardia and then in the overlap zone the rhythm is classified as either atrial tachycardia or atrial fibrillation based on the regularity of the rhythm. The programming of these zones are up to the investigator and are, in fact, programmable.

With regard to how we defined efficacy, the device classifies a successful termination of therapy as five consecutive sinus beads or atrial pace beads within 3 minutes of therapy delivery without redetection of another atrial tachyrhythmia. The therapy efficacy are reported in two different ways. The accrued proportions is simply the episodes terminated by a specific therapy divided by the number

of episodes treated with that type of therapy.

To try to control for patients who may have very many episodes which disproportionately contribute to these estimates, the Generalized Estimating Equation or GEE was also computated, computed for all these endpoints which is looking at the probability that a randomly selected episode from a randomly selected patient will be terminated. Again, this corrects for multiple episodes in individual patients.

With regard to the primary endpoint results, there was a 91 percent efficacy for atrial tachyrhythmia termination therapies. This was an evaluation of all therapies and all episodes that had at least one shock in the therapy sequence and included the termination of 1,092 episodes of atrial tachyarrhythmias out of 1,200 episodes in 107 patients. The crude proportion was 91 percent as mentioned above. The GEE estimate was 85.9 percent with a 95 percent lower confidence bound of 81.7 percent which is greater than the 75 percent postulated and therefore, the efficacy objective was

met.

With regard to the number of shocks delivered, this slide shows the number of atrial shocks given per episode of atrial tachyrhythmia in the 1200 episodes that occurred. The mean number of shocks per episode was 1.19. A vast majority, 86 percent of patients only received one shock per episode. Another 10 percent received two shocks. One can see here it's very unlikely that patients received more than three shocks in this study. And in fact, the only patients who received a sixth or the ten shocks, those were patient-activated shocks where the patients intentionally gave themselves that many shocks.

I would now like to move on to the secondary objectives and additional analysis from this study. The efficacy of atrial shocks for atrial fibrillation episodes was very high; 92.4 percent of atrial fibrillation episodes were terminated with shocks. This included 1,868 atrial fibrillation episodes in 102 patients, including 723 who were treated with shocks, 668 of which were successfully

terminated. The crude proportion was 92.4 percent with a GEE estimate of 88.4 percent.

Of those shocks that were delivered with patient-activated therapy, the efficacy of this approach was 92.8 percent. This again is evaluating all episodes that included at least one patient shock in a therapy sequence, but restricted it to those in which the patient was activating shock therapy. This was 519 of 559 atrial tachyrhythmia episodes, again, with a crude proportion of 92.8 and a GEE efficacy proportion of 89.1 percent.

This chart here shows the pacing efficacy using low power, painless therapy to pace terminated arrhythmias. The overall proportions of atrial pacing therapy using either atrial anti-tachycardia pacing or high frequently burst pacing for atrial tachyarrhythmias had an efficacy of about 35 percent with a GEE efficacy of 28 percent.

If we break that down into atrial tachyarrhythmias, the efficacy by GEE estimate was 35.5 percent of episodes were pace terminated. If we then look at pace termination of atrial fibrillation

and of note here, this is only high frequency burst therapy, anti-tachycardia pacing could not be programmed for atrial fibrillation episodes. The termination rate was 14.1 percent by the GEE method.

Quality of life was followed in this cohort of patients over time. What's shown on this slide are the SF-36 scales looking at changes over time for the eight major parameters in the SF-36. Shown are the baseline measurements, the 3-month measurements and then the 6-month measurements. One can see that all eight measurements showed an increase in quality of life over the 6-month period of time and five out of the eight parameters, this reached significance, either at 3 months or in four of the parameters, at 3 months and 6 months, there was significant improvements and increases in quality of life during the course of the first six months of this device therapy.

Not only were there changes in quality of life, we also looked at the frequency of symptoms and the severity of symptoms, using a standardized symptom checklist score and both the frequency of symptoms and

the severity of symptoms significantly decreased over the course of study, both at three months and this benefit persisted after 6 months.

The mortality of patients in this study was estimated as a relative risk compared to the previous control group, the 7219 as mentioned before. The adjusted relative risk for patients with the 7250 device was 0.51 in this study with a lower confidence bound of 0.12 and an upper confidence bound of 2.17.

The survival curves are shown on this slide. Not a very effective slide, but one can see the very good survival of patients in the 7250 "AF Only" cohort shown in the solid line.

Kaplan-Meier all-cause survival rates were computed for this group of patients and showed the estimated 6 month survival in this study of the 7250 "AF Only" population was 98.6 percent. The Kaplan-Meier estimates for the 7219 control was 96.4 percent at 6 months.

I'd like to move now to the detection of atrial tachyarrhythmias. There was a 98.8 percent positive predictive value for detection of atrial

tachyarrhythmias. This included the evaluation of 4,913 spontaneous atrial episodes detected by the device, 4,859 of which were appropriated detected as an atrial tachyrhythmia. This gives a positive predictive value of 98.8 and a GEE estimate of 98.6 percent.

Prevention therapy was evaluated in a randomized portion of this study. This was an evaluation of both atrial rate stabilization and switch back delay, two features that were incorporated in this device. Seventy-five patients completed the randomized portion in which they had three months of these features, both being turned on or three months of these features both being turned off.

There was no significant difference in the prevention and the incidents of atrial fibrillation with the atrial prevention therapy.

With regard to atrial DFTs, atrial defibrillation thresholds were measured with a step up protocol, a two-tiered step up protocol. At implantation the mean atrial defibrillation threshold was 6.8 joules.

Importantly, there was no incidents of atrial shock induced ventricular tachycardia or ventricular fibrillation. Specifically, there was no pro-arrhythmia associated with any of the atrial therapies delivered to these patients. The 95 percent confidence interval for the zero percent observation was zero to 0.3 percent.

Very interestingly, 11 patients or 7.6 percent of the population experienced 67 spontaneous and appropriately detected episodes of ventricular tachyarrhythmias. Sixteen of these episodes were classified as ventricular fibrillation and 51 of these episodes were classified as ventricular tachycardia. Of these VT, VF episodes, 57 occurred in 6 patients and were successfully treated with ventricular therapies, either anti-tachycardia pacing or defibrillator shocks.

The additional 10 episodes occurred in 5 patients and these terminated spontaneously, 9 to 220 seconds after detection. The reason why some of these episodes went so long was because therapies were turned off by the investigators in the ventricular

tachycardia zone. Ventricular fibrillation therapy was required to be on but ventricular tachycardia could be set up as a detection zone with no therapy on and that's why we see some long episodes of ventricular tachyarrhythmias that did not receive therapy.

Atrial shock programming to deliver shocks to the termination of atrial tachyarrhythmias was consistently programmed over the course of this study. What's shown here is that there was an 85 percent of patients had atrial shocks programmed on at the initial baseline of this study. There was very minor changes over the course of this study, but at least contact, 85 percent of patients still at atrial shock therapy programmed on.

I'd like to switch now briefly to the additional components of the system, specifically the 9464 Patient Activator. Sixty-seven patients used this activator to treat 559 episodes of atrial tachyarrhythmias. There was a 90.5 percent of episodes were treated with one shock.

The success rate was 92.8 percent for the

termination of these arrhythmias, the GEE estimate there being 89.1 percent. And over 70 percent of patients have patient-activated shocks programmed on at their last contact in this study.

Again, if we look at the use of this activator, specifically to look at the number of shocks that patients were activated for for episodes that lasted greater than 30 minutes, this cutoff was used because short duration episodes, it was very unlikely that patients would either be able to use their activator or would want to use their activator.

If we look over the course of this study, initially about 52.1 percent of episodes, patient-activated was used for, there was a slight nonsignificant dip at 42 percent at 3 to 6 months and then a persistent and consistent use of patient activator over time which showed no statistical difference over the course of this study. The GEE estimate was 46.6 percent of all episodes greater than 30 minutes were treated with patient-activated shocks.

The 6937A lead was an investigational lead used as part of this study. Fifty-five percent of

patients in this trial, the "AF Only" trial and 7 percent in the VT/AT patients were implanted with this lead. Of the 114 patients who received this lead, it was placed in the coronary sinus in 101 of these patients. The mean follow-up for this group was slightly greater than one year. And there were three adverse events noted, three atrial leads dislodgements and subclavian vein thrombosis. The 3-month complication free survival was 97.3 percent for this lead. The atrial defibrillation threshold in the patients who received this lead was 6.2 joules.

In summary, with regard to safety of this device, we feel that the safety objectives were met. The reported system procedure related complications are consistent with previous device studies and did not differ from the control group evaluated. The system was successfully implanted in 98.6 percent of patients and there was no incidents of atrial shock-induced ventricular tachyarrhythmias.

With regard to efficacy, once again, the efficacy objectives were met. There was a 98.6 percent positive predictive value for the accurate

detection of atrial tachyarrhythmias. Overall, there was a 91 percent success rate for the termination of atrial arrhythmias when shock therapy was used. And I think equally interesting, about one third of episodes of atrial tachyarrhythmias was successfully pace-terminated with painless, low energy therapy.

Quality of life improved over time and symptom burden decreased consistently over the course of this study.

Spontaneous ventricular tachyarrhythmias were detected in 7.6 percent of patients and appropriately treated in all patients in which therapy was activated.

And finally, the sustained use of the patient activator, I believe is evidence for the acceptance of shock therapy in this patient population.

With regard to the benefits versus risks of this device, clearly, I think one of the benefits of this device is it allows for the early restoration of sinus rhythm. The pacing therapy offers incremental efficacy for the treatment of arrhythmias

with little or no measurable risks.

This device also allows for the monitoring of both symptomatic and asymptomatic tachyarrhythmias providing important data for the physician. It also gives patients control of their therapy to allow them to be able to choose and decide when and if they want to receive treatment for their atrial tachyarrhythmias. There's a reduce symptom frequency and severity with the use of this device as well as improved health related quality of life.

Finally, I think the last benefit that was clearly seen is that there was protection from ventricular tachyarrhythmias even in a population with no history of sustained ventricular tachycardia or fibrillation.

The risks of this study are the morbidity associated with device implantation which is similar to those risks associated with other ventricular defibrillators.

In conclusion then the 7250 Jewel® AF "AF Only" defibrillator clinical evaluation shows that the Jewel® AF system is safe and effective in the patient

population with atrial tachyarrhythmias.

Thank you.

What I'd like to do now is I'd like to introduce Dave Schwartzman from the University of Pittsburgh. Dr. Schwartzman was the lead investigator and has the largest experience with this device. He was going to present several very short clinical vignettes to highlight the use of this device.

DR. SCHWARTZMAN: Good morning. My name is Dave Schwartzman. I direct the Atrial Arrythmia Center at the University of Pittsburgh. I'm an employee of the University of Pittsburgh Health System. My role today has been compensated for both honorarium and travel and I am a member of the Atrial Arrhythmia Advisory Board for this company and compensated in that role. And there are portions of my basic and clinical research program with contracts with Medtronic.

Appropriately, you've heard today of the interface between the heart and the device in the context of the atrial fibrillation only study. I believe that a full accounting of the aspects of this

device for evaluation require some sort of elaboration on the interface between the device and the patient or the clinical syndrome.

What I hope to accomplish with these vignettes is to give you that elaboration. In addition, the clinical care of patients with this device is not static. There have been things that we've learned along the way, an evolution of therapies in the context of the device to base strategy, if you will, and I hope to transmit that message as well.

First slide, please. The first patient is a 52-year-old and these are rather typical patients that I've chosen for a rather large cohort in our Center. A 52-year-old man with concentric left ventricular hypertrophy and a mildly reduced ejection fraction, paracysmal atrial fibrillation for 8 years in which the atrial arrhythmia attributable symptoms were severe. He is cardiac disabled and was a construction worker. Clinically had failed and/or had been intolerant of multiple drugs including 1A, 1C and type III drugs. Post-implantation of the device he had frequent events initially which necessitated

ancillary propathenode therapy and then a gradual tapering of the events and since the 6-month post-implantation point, he has had only the occasional events including patient-activated shocks and all my patients have patient-activated shocks programmed on. No automatic shocks. He remains on low dose propathenone, about half of the dose on which he was tried with failure before. And he is working full-time.

There are several lessons which I take from a patient such as this. The first one is one I'll call delayed gratification. And that is in the device-based strategy, what we find more often than not is that control of the atrial arrhythmia takes time to achieve. The science behind that is not exactly clear. For example, a training effect on the atrium may be at play although this study does not lend itself to scientific evaluation of that concept. There's a common need for what I'll call adjuvant anti-arrhythmic drug therapy, relief of disability and a number of my patients have returned to work after being disabled based on arrhythmia. And atrial

arrhythmia events do not disappear. This does not cure. It allows control.

Next slide, please. The second patient is al 64-year-old male with ischemic cardiomyopathy and a severely reduced ejection fraction, 21 percent, pre-implantation of the device. His atrial arrhythmia attributable symptoms are mainly exacerbation of a congestive heart failure syndrome and episodes have been going on for a period of time. In the year prior to the implant he had had 18 in-patient hospital days attributable directly to his atrial arrhythmia with exacerbation of heart failure. Failure of multiple drugs. After implantation, interestingly, we noted that he had frequent events which were pace-terminated and in addition was required to activated his device approximately bi-monthly and this pattern continues. He remains on low dose propathenone. He has no in-patient days in the past calendar year and his ejection fraction at one year reassessment was 34 percent.

We have several lessons to take from this. First of all, serious structural heart disease in our

experience has not necessarily been a deterrent to implanting this device. There are, particularly in the structural heart disease population we're finding frequent pace termination of atrial arrhythmias, whether that relates to more uniform atrial tachyarrhythmias early in the structural heart disease group or not remains to be seen. There's a reduction in hospital days and an amelioration of left ventricular dysfunction in this particular case.

Next, please. The third patient is a 47-year-old man with a structurally normal heart who is post A-V node ablation. This was several years back. Referred with a syndrome of frequent paroxysmal fibrillation which has been going on for over a decade. His problem was that despite the A-V node ablation with a mode switching rate response of pacemaker, he had persistent symptoms which were severe during his atrial arrhythmia event. The device was demonstrated to be functioning effectively, that is, the pacemaker device with prompt, accurate mode switch. He had had failure and/or intolerance in that context of multiple Type 1 and Type 3 anti-arrhythmic

drugs including amiodarone and so his system was changed to include the Jewel® AF system.

Post-implantation, we noted that pace termination of his atrial tachyrhythmia general events generally failed and so he was required to activate the device for shock about every three months and he's on no standing anti-arrhythmia drug therapy at this time.

A couple of lessons. Pre-implantation atrial fibrillation syndrome, that is, frequent paroxysmal AF in that case is not necessarily a deterrent to this device-based strategy. And in addition, the duration of the atrial fibrillation syndrome, in this case over a decade, is not necessarily a deterrent to the Jewel®-based strategy.

Next, please. The final patient is a 54-year-old woman, post mitral valve replacement for rheumatic heart disease with a normal left ventricle. Episodic persistent atrial fibrillation for over 8 years. Severe symptoms attributable to the atrial arrhythmia and failure or intolerance of multiple drug including amiodarone. She is now 29 months

post-implantation. Again, frequent events initially noted in this patient which necessitated patient activation which was frequent and for that reason the addition of amiodarone again. Gradual tapering events over time such that we are now anti-arrhythmic drug free. This was the case at one year and since. Event frequency is stable at about every two months and this is really shock. And there has been no change in the event frequency of note for the past 12 to 29 months on the mean.

The lessons I take from this case are that the strategy of maintaining sinus rhythm appears to maintain its effectiveness at least thus far, 29 months, what I consider a reasonable follow-up duration.

I would like to take -- again, in order to illustrate the interface between the device and the patient and the clinical strategy of atrial rhythm control in this context, I would like to take this opportunity to invite two patients that I have asked to attend this meeting to address specifically their experience with the patient activator and the concept

of commanded shock. I would like to ask my two patients to come up now if they will.

MS. JONES: I'm Jane Jones. I'm a retired high school teacher from Pittsburgh, Pennsylvania. Have had the 7250 device for about 13 months now. I have my travel and honorarium has been provided for me for this day.

First, I need to say that I don't like to be out of rhythm. I am tired. I am out of breath. I am sweaty. I am clammy. It's not nice. Until I got the defibrillator, my only choice was carioversion. I probably had seven or eight of them in the hospital in the last few years. Now that I have the defibrillator in about a second I can be back in rhythm and on about whatever I have to do that day.

Cardioversion in the hospital was not a pleasant day for me. It took the entire day because usually they were working me into their schedule. It also meant that another member of my family had to take off work because you cannot drive home from a cardioversion. So two of us would spend a long day in the hospital, but I would be back in rhythm. Now I

can do it myself.

As far as learning how to use my activator, it was not difficult. The day after the device was implanted, I sat in my hospital bed and Dr. Schwartzman put the heart out of rhythm and showed me how to place the activator on top of the defibrillator, push the button, the shock was delivered and he showed me that I was back into rhythm. It's not very complicated.

At home, now when I go out of rhythm and choose to put myself back in, I have a very specific plan. I go to my family room and sit in my La-Z Boy chair by myself. I don't like anyone else around. In fact, there have been times I've done it when my husband hasn't even been in the house. That's how sure I am that all it's going to do is put me back into rhythm. I put my feet up in my La-Z Boy and I tell myself you have to do this. The sooner you do this, the sooner you can get on doing whatever you plan to do today. I push the button. There's an immediate beeper system that tells me, a series of beeps, that tells me the signal has been received. In

the two to five seconds that it takes for the shock to build up, I set the activator back down in my lap, put my arms on the arms of the chair and tell myself to relax. I don't think I do, but I try. As soon as the shock is delivered and what it does to me and I tried to think back to describe it to you. I must close my eyes. I never see anything. I know I jump and the sound I make is something like "uh" and then it's over. I take my pulse immediately and I literally can get out of the chair and go and do whatever I plan to do that day. I don't take drugs. I don't take wine to calm me down and I think the main reason is I don't want to have to go to bed. I want to be able to get up and go and do whatever I need to do. That's what I do.

The area that I think maybe I appreciate it as much as not having to go in for cardioversions is vacations. Now that I'm retired, I'm free to go places. My husband and I went to Florida for three weeks last winter. Not having my defibrillator the choices that we would have had to deal with when I went out of rhythm were not really acceptable. Come

home early. Live with it out of rhythm. Neither of those I like. I would have to try a hospital in Tampa to do the cardioversion, but with strange doctors and a strange hospital and it would have taken a day of our vacation. Now I take my activator with me wherever I go. We're going to Scotland next year. I hate the thought of trying to find some place over there to be cardioverted. And I decide when I'm going back into rhythm.

It's a good feeling. It's a feeling of power, but it's power over me, over my heart and I can put myself back into rhythm whenever I choose.

That's kind of my story. Thanks.

MR. CARLSON: Good morning. My name is Donald Carlson and my travel has been paid for. I'm a public school teacher in Waterford, Pennsylvania, just south of Erie. I had my implant last October, October 22nd. My story is about the same as Jane's. When I'm out of rhythm, I feel tired, I'm sweaty. Before I had it implanted when I would come home from school I would just kind of crash and go to sleep. Not have much energy to do anything. Since the

implant now I can put myself back in rhythm and you feel better almost instantly, about 20 minutes I think it takes.

I went to school one day and had -- was having an arrhythmia thing. During my prep period I sat in my school chair and shocked myself and by the time the prep period was over I was feeling a lot better. So it's something you really can do anywhere. I prefer not to do it at school. I prefer to do it when I'm relaxed, either sitting on the couch or lying in bed. And it seems to work the best then for me. But you feel better almost immediately and like Jane said, you don't have to go to a hospital to have it done.

So I really appreciate the work that Dr. Schwartzman and Medtronic and how it's affected my life and I would like to thank them for that.

That's about all I have.

DR. STANTON: Thank you. That concludes our presentation.

DR. TRACY: Thank you very much. We'll move on at this point to the FDA presentation.

MS. TERRY: Good morning. My name is Doris Terry. I'm the primary review for P980050 Supplement 1.

To the Circulatory System Devices Panel, ladies and gentlemen, the manufacturer, Medtronic, Incorporated, is seeking approval for the Medtronic Model 7250 Jewel® AF implantable cardioverter defibrillator in the "AF Only" population.

Acknowledgements to the members of the FD Review Team who were instrumental in completing the review of the PMA application.

The Model 7250 Jewel® AF is an implantable cardioverter defibrillator that detects and treats episodes of atrial and ventricular tachyarrhythmias and bradycardia by delivering defibrillation, cardioversion, antitachycardia pacing, albradycardia pacing. Atrial arrhythmias are detected by the Model 7250 either as atrial fibrillation, atrial tachycardia by monitoring the cycle lengths and regularity of the atrial intervals. We should note that this is a first of its kind ICD intended for use in the "AF Only" population.

The system consists of the commercially available pulse generator model 7250, approved under P980050, the Model 9465 Patient Assistant, the Model 6937 ACSSEC lead and other commercially available leads and accessories.

The proposed indications for use of the Model 7250 Jewel® AF only study are as follows: The Jewel® AF implantable cardioverter defibrillator is intended to provide pacing, cardioversion and defibrillation for treatment of patients with symptomatic, drug refractory, atrial tachyrhythmias and/or life threatening ventricular tachyarrhythmias.

As mentioned in the Medtronic representation the study design involved a multi-center perspective IDE study that evaluated safety and effectiveness of the Jewel® AF. Also, there was a randomized crossover study for evaluating prevention therapies. The primary and second objectives were called out in the Medtronic presentation.

The PMA population consisted of 146 patients enrolled. One hundred forty-four actually

received the device. The mean follow up was 12.7 plus or minus 6.1 months. The primary indication was ATF only in 97 percent. The New York Heart Association Class was 53.4 percent Class I; 34.2 percent, Class II. The mean ejection fraction was 51.1 percent.

For data analysis, the time to first system-related complications was analyzed using the Cox Regression Model. The study requirement is meet when the analyzed data is less than or equal to 3. The relative risk of system in procedural related complications for the Jewel® AF versus the control was 1.31. The complication-free survival results were compared to the model 7219D Jewel®.

The episode treatment effectiveness, the GEE equation was used to adjust more multiple episodes.

The adverse events were categorized as those occurring at implant, system-related complications requiring invasive intervention, observations, events without invasive intervention and events that were not device related.

A summary of the adverse events: 11

events occurred in 11 patients at implant. There were 26 system-related complications in 23 patients. Two hundred twenty-one system related observations were reported in 97 patients and 322 nonsystem adverse events such as chest pain, fatigue, congestive heart failure were report in 95 patients.

Kaplan-Meier estimates compare the complication-free survival of the Jewel® AF Only population and control at 3 and 6 months. The estimates and percent confidence intervals are shown. There's a Panel question regarding the survival rates of the Jewel® AF Only population.

Eight deaths occurred in the PMA population. Seven nonsudden cardiac and one death categorized as unknown. Kaplan-Meier estimates also compared survival from all cause mortality of the Jewel® AF Only in control at 3 and 6 months. The estimates in 95 percent confidence intervals are also shown here.

Episode treatment effectiveness for atrial tachyarrhythmias, the requirement was that for lower 95 percent competence bound is greater than 75

percent. For atrial tachy therapies treated with atrial shock, 107 patients had 1200 atrial episodes that were treated with atrial shock. Ninety-one percent were terminated. The adjusted atrial therapy's effectiveness was 85.9 percent with a lower 81.7 percent confidence bound.

Episode treatment effectiveness was reported for ATF episodes treated with ATP. Success reported at 38.6 percent; 32.1 percent adjusted.

For AF episodes treated with higher frequency bursts, success was 18.2 percent and for AT episodes treated with high frequency bursts there was a success rate of 11.7 percent. The success rate are noted also in a Panel question.

The positive predictive value for the atrial detection algorithm was reported as 98.6 percent.

The effective prevention therapies on the frequency of atrial tachyarrhythmias with the randomized crossover study that included 75 patients reported no statistically significant difference in frequency reduction.

The Model 9464 patient activator is hand-held. It's a hand-held device which can be placed over the Model 7250 to trigger delivery of an atrial shock. This is the first of its kind of device which can be used by the patient to initiate atrial shocks to treat their atrial arrhythmias.

The clinical experience, of the Model 9464 Patient Activator is being used to support approval of the downsized model 9465 Patient Assistant, 71 percent of the patients were programmed for self-activated shocks. The effectiveness for the self-activated shocks was 89.1 percent lower bound of 84.6 percent.

Twenty-seven adverse events with use of the Patient Activator in 71 patients were reported. Thirteen of the events in 12 patients were considered as device-related. Of these were 9 cases where the patient was unable to initiate a shock and 4 cases of failure of the activator to deliver warning tones of pending shocks. Fourteen events occurred with use of the activator and were not considered devise-related. Most of the events involved cases where there was an activated shock that failed to defibrillate due to

insufficient programmed energy.

The 6937 CSSVC Lead, 114 patients were implanted with this lead. The mean atrial DFT was 6.2 plus or minus 6.6 joules. The lead parameters remained stable through 3 months.

Regarding the lead-related adverse events for the 6937A, there were no events at implant; 3 complications, lead dislodgement in 3 patients and one lead-related observation in 1 patient.

The Panel questions. In evaluating device safety, Medtronic reported 3 and 6 month complication pre-survival results were lower when compared to adverse event results from previous ICD studies. You can see this in Table 1 of the Panel questions.

In addition, four patients had a stroke during the course of the study. The risk of stroke, possibly as a result of frequent cardioversions raises an important issue when evaluating safety of atrial shock therapy.

Please discuss the clinical significance of the complication-free survival results and the occurrence of stroke in assessing the safety of the

Jewel® AF for the new indication of treating patients with atrial tachyarrhythmias.

Number two. In their investigational plan, Medtronic prospectively specified the Model 7219D as the safety control. It appears from the demographic co-morbidity data that the Model 7219D population was sicker than the Jewel® AF only population. To address this Medtronic performed a risk factor analysis intended to take into account baseline differences in cardia health. Given the choice of controls, do the clinical results of the Jewel® AF only study demonstrate device safety for the intended patient population?

Number three. As reported in the clinical study, Medtronic met their specified effectiveness hypothesis for atrial shock. Additional effectiveness results were also reported as in Table 2 of the Panel Questions.

The study also examined the effectiveness of atrial prevention therapies on frequency of atrial tachyarrhythmias using a crossover study. Medtronic reported that the reduction in AT/AF frequency when

atrial prevention therapies were programmed ON versus OFF was not statistically significantly different from zero. Based on these effectiveness results, please discuss whether you believe the potential benefits of atrial tachyrhythmia termination and prevention therapies outweigh the risks of implanting the Jewel® AF in the intended patient population.

Number four. The clinical experience from the Model 9641 Patient Activator is being used to support approval of the downsized Model 9465 Patient Assistant. Given the experience, do you have comments or concerns regarding the clinical use and labeling of the Model 9465?

Number five. Given the proposed new Indications for Use for the Jewel® AF and the likelihood that the patients will be healthier than the ICD patient population, please discuss whether you believe that the potential benefits of implanting the Jewel® AF in patients with atrial tachyarrhythmias outweigh the possible risk associated with the implantation and therapies of the device.

Number six. Of the two enrolled patients

who did not receive the device, one patient had no atrial capture during the implant procedure. Also of the 10 reported device explanations, 6 of the reported reasons suggest that the device therapy in these patients was either ineffective or poorly tolerated. Medtronic reported that 13 patients had an ablation procedure, an alternative therapy, after being implanted with the Jewel® AF. Please comment on whether you believe the Jewel® AF provides adequate AF prevention and/or treatment therapy for this patient population, and whether you believe that the therapies, particularly atrial shock therapy, may be poorly tolerated in some patients. Please provide your clinical impression of these potential intention-to-treat failures and discuss how this clinical information should be presented in the Jewel® AF's Instructions for Use labeling.

Number seven. The Jewel® AF System is intended to provide pacing, cardioversion and defibrillation for treatment of patients with symptomatic, drug-refractory atrial tachyarrhythmias and/or life threatening ventricular tachyarrhythmias.

Please provide your clinical impression of Medtronic's proposed Indications for Usage and comment on whether they are clinically appropriate for the Jewel® AF indicated population.

DR. TRACY: Thank you. We'll move on to the Open Committee Discussion and the lead reviewer for this product is Tony Simmons.

MS. MOYNAHAN: Members of the Sponsor can approach the table if they'd like.

DR. SIMMONS: Okay. Tony Simmons. I guess I have difficulty beating around the bush, so let me go right straight to it and say I have a lot of problems with this particular proposal and I hope you can convince me otherwise.

Let's start off on page 1-35 under the FDA summaries, okay? This is a table of adverse events and complications.

DR. STANTON: Which section is this in?

DR. SIMMONS: This is under the FDA summaries. Section 4. Page 1-35.

Atrial fibrillation is a common disease. We see -- I get more atrial fib consults than I ever

thought I would ever see in my lifetime. And certainly, it's a very complicated disease with lots of causes and lots of potential therapies are being proposed right now. In fact, there's a multi-center study trying to decide it's even safe to treat atrial fibrillation and maybe we just should be anticoagulating these patients and leaving them alone.

So I think we have to at least get on the same framework, the same common ground that this is a nonfatal disease, with serious quality of life issues, serious aggravations to patients, but it is not a life-threatening disease. Can we start there?

DR. STANTON: I'd agree that it's immediately not life threatening. I think there are data to show that people with atrial fibrillation are at an increased risk of mortality, but I'll concede the point for discussion.

DR. SIMMONS: Okay. You know, if we look at this table here and we just start off with -- a lot of these complications and serious adverse events are just things that I'd expect to see, things like shoulder pain and patients have congestive failure,

they get more congestive failure, early recurrence of atrial fibrillation. I'm going to throw all those things out. Let's just look at the ones that I consider serious complications like two patients with no device implanted, okay? So you took two patients to the operating room and because of the substrate, whatever, you couldn't implant the device. That's a complication. Inappropriate detection, oversensing, 11 lead dislodgements, 2 infections, 1 device explanted because of anxiety, lead failures, patients unable to tolerate therapy, serious undersensing. I mean if we just add up those and throw out all the other ones, pacemaker syndrome, things like that. We end up with about 25 significant complications or as serious adverse events which adds up to about 13 percent. So you're talking about taking patients who don't have a life threatening disease and you're subjecting them to multiple operations and you're ending up with a serious complication rate of approaching 15 percent. I mean is this realistic?

David, is this realistic? I mean FDA is going to ask me this at the end of this time. They're

going to ask me is this realistic. I mean, really, is this realistic? A 15 percent serious complication rate for a nonfatal disease?

DR. SCHWARTZMAN: You say nonfatal as if it's the only arbiter of care in these patients. These patients are highly selected. I think it's fair to say the burden of this entity directly attributable to atrial fibrillation, take away all of the bunting, this is atrial fibrillation attributable symptoms is tremendous. I'm not saying that this is applicable to the broad swath of atrial fibrillation, I agree with you. It's a major public health problem, but in terms of the patient perceived benefit of something like this, this is small across the board. But for a select group of patients, it is not small and I would submit that the benefit is real and worthwhile in the face of the complication rate. Some of the complications that you mentioned I would not describe as therapy-limiting. They're realistic. They're IDC like, but again my orientation has been and continues to be that this is a reasonable and effective strategy in the right subgroup of patients with atrial

fibrillation.

DR. STANTON: I think a real important point is that this device therapy is aimed at a very specific limited group of patients with atrial fibrillation and we've been very careful to specify that in our study inclusion criteria and in the labeling that we think is appropriate for this device. In no way are we trying to say this device and device therapy is appropriate for everybody with atrial fibrillation.

What I believe is that this offers physicians another tool in their armamentarium for treating these highly symptomatic patients with recurrent atrial fibrillation and the complications that you point out here, we acknowledge, and they are complications of device-based therapy. And in fact, if we looked at published literature on a blatant pace therapy has similar types of problems with lead dislodgement, infection, etcetera.

Michael?

DR. GOLD: I think to try to put into perspective at least for me this device is part of a

treatment strategy for maintaining sinus rhythm in drug refractory, highly symptomatic patients. If you take everything you point out about failures, those are failures for the treatment strategy, if you take the patients who you can't implant a device in, if you take the patients who can't tolerate the therapy, if you take the patients who you give up and do A-V junction ablations, if you take the patients who explanted devices for infections, if you take all of them and say we failed on those, you're still talking about a success rate in this population of being able to maintain sinus rhythm on the order of close to 90 percent at one year. We actually have a slide that we can put up where we looked at that data because we were very concerned about that, but I think if you, from a clinical perspective when patients come to me with recurrent drug refractory atrial fibrillation, the chance of me with yet another drug or yet another treatment strategy being able to keep them in sinus rhythm is extremely low. I have never -- know of any of other therapies that approach this sort of success rate. So is there a price to pay in this high risk

population? Absolutely. But I think rather than looking at the complication rate, when I look at the success rate, I think we actually had a remarkably high success of being able to maintain a strategy of sinus rhythm in a group of patients who most physicians and most of us would have thought the horse was out of the barn and we'd already lost the battle of trying to control their atrial fibrillation. This is the curve here showing at 2 years. We're at 89.9 percent of therapy, device therapy survival calling a failure anyone who had their device either turned off, if atrial therapies were turned off, or their device explanted, removed or any A-V junction ablation. If we take all of them lumped together, we still have 81 percent of patients at two years receiving therapy which I think really is a testimony to how effective this therapy approach is in this group of patients.

DR. SIMMONS: I'm not sure I buy that. If you did nothing with this patient population and you did enough EKGs on most of them at two years, you'd find out that a lot of them are still going back and forth between sinus rhythm and atrial fibrillation,

wouldn't you?

DR. GOLD: I don't think so. If 65 percent of these patients were in atrial fibrillation, I assume that in that group who are already drug refractory, at two years, certainly placebo-controlled studies have suggested in the absence of anti-arrhythmic drugs or failed anti-arrhythmic drugs, I think the proportion of those patients who would be in sinus rhythm at two years would be a small minority of patients. I'm not saying it would be zero, but it certainly would not approach 81 percent.

DR. SIMMONS: Well, that's if you gave up trying to treat them and bringing them in to cardiovert them and I guess if you gave up all therapy and just didn't do any type of treatment for that group of patients, I'm still not sure it would be a minority. I mean the placebo-controlled trials I remember would suggest that probably 50 or 60 percent of them are still going to remain going back and forth between sinus rhythm and the paroxysmal group.

DR. STANTON: Which is only a third of this patient population. Two-thirds were persistent.

DR. GOLD: Whether the total number would be 30 percent, 15 percent, 40 percent, I would be -- I don't think the literature would support that a majority of patients would be in sinus rhythm in who years at this population. And 81 percent at two years, I found actually very reassuring.

DR. SIMMONS: You know, I'm not denying that I guess that the device has effectiveness. I'm just not completely convinced that this is the device, that this is -- that the price that you're willing to pay, I guess, at this point in time I'm not completely convinced that the price for the device is worth the effectiveness. Do you understand what I'm saying? These are significant operations.

Now you guys are doing them, so you're taking care of the patients, so you are somewhat emotionally involved in taking care of the patients, but when you stand back and look and see how many reoperations these patients had and how many of them ended up with their devices explanted and how many of them ended up with A-V node ablations and I mean it's a significant number.

DR. STANTON: I think it's also -- you can look at the glass as being partially empty or mostly full. These, again, I want to come back and say this is a very select patient population. This isn't all comers with a-fib that you see in an a-fib clinic. These are highly symptomatic people who have failed on an average of three drugs prior to coming to this point and these patients, I think now can and should be offered an alternative that for many of these patients, in fact, the majority of these patients works very well with known complications that are in the same range as device-based therapy. I think when clinicians offer any therapy, be it surgical, drug, ablation, you have to go through a list of what the complications are. With anti-arrhythmic drugs, you have to talk about pro-arrhythmia, the chance that a person is going to die from the treatment you're initiating for a nonfatal arrhythmia, as you point out. Nobody died because of device therapy in this trial. With the surgical maze procedure there's certainly a lot of morbidity associated with that. For appropriate patients, it's an appropriate thing to

offer.

DR. GOLD: And I may again to reemphasize, tomorrow I'm going to be seeing patients as well and just as you are, I can guarantee you that in my clinic tomorrow I'm going to be seeing patients with atrial fibrillation coming there. When a patient shows up in my office with atrial fibrillation do I recommend an atrial fibrillator to them, to most of them? Certainly not. We've estimated about 5 percent of the population of atrial fibrillation patients, those who remain highly symptomatic, who have failed drugs, who are very motivated as we heard from the couple of patients we heard today, patients who are really debilitated symptomatically from their arrhythmias. For those patients to accept the chance that there's a 10 to 20 percent chance over the course of two years that this therapy may fail, to give them an 80 percent chance of being in sinus rhythm and in fact, 94 percent of this population was in sinus rhythm at one year. That group of patients, I think, not only would benefit, but would jump at the opportunity for that. But it's a very select group of highly motivated,

highly symptomatic patients in whom this invasive therapy is a useful therapy with very low, at least no mortality measured, A-V node ablation which we do commonly in this group, clearly has some measurable mortality and sudden death associated with the anti-arrhythmic drug therapy which I give to these patients has some measurable pro-arrhythmia mortality associated with it. So it's a cost to all of our therapies and I think in a selected group of motivated, highly symptomatic patients, they are more than willing and they benefit from the therapy.

DR. SIMMONS: I guess, you know, I can understand what you're saying and I appreciate what you're saying. When you, however, release this device to say it is now an atrial fibrillator and it's being released to every physician who can get a license to implant, I'm not so sure that the device will necessarily be applied and I don't know of any way to get the device to be applied to that select, less than 5 percent of patients who are going to be -- you know, really beneficent, because I think you're right. I appreciate what you're saying, that there are

motivated people with high pain tolerances who can learn to live with this thing and make it work and in that very small group of patients, yeah, I could see this could be a very valuable thing. But as a therapy for atrial fibrillation and have an indication this device can be impacted for atrial fibrillation, I don't know.

DR. SCHWARTZMAN: Let me try to address that, Tony, because I think that's my concern as well, based on now interfacing with communities surrounding my Center.

I think that, first of all, this is not a -- I'm not selecting patients here for high pain tolerance, if you will. I think patients look at it as risk reward and again, at least in my cohort we have a large representation of age, group and gender co-morbidity, for example. We've had no explanations for intolerance. People use shocks variably and their thinking on it evolves with the study, but shock use is the rule rather than the exception.

In terms of how this will be applied in the community, it is my feeling that the patients will

drive the utilization of this device and by that I mean if physicians begin implanting this in patients in whom the risk reward is not there, particularly those who get shocks that are automatic, for example, that will not be tolerated and in no uncertain terms that will return to the physician and the physician will stop prescribing that therapy. So I personally believe that this will be relegated to the shelf of electrophysiologists who deal with referral type atrial tachyarrhythmias who have considered all of the therapeutic options and who have taken the time to establish that the symptoms are attributed to atrial arrhythmia and severe enough to warrant considering it. I believe that's the way it will evolve. I don't think it's going to go out there and these things are going to go in willy-nilly and let the chips fall where they may. I really think that it will constrain itself because of the risk reward issue.

DR. SIMMONS: Let's go on to another topic. On that same page under Table II, Lead Dislodgements, if we look at the lead dislodgements for this study, overall you had 12 out of 254 leads

dislodged which is 4.7 percent which is high. If we look at just the atrial leads and the CS leads, the dislodgement was 11 out of 218 which is around 5 percent which is pretty high. And then if we give you the benefit of the doubt and throw out the 6937 data and just look at the 6937A data for the atrial and CS lead dislodgement, you're talking about 10 out of 200 which is about a 4.7 percent atrial or CS lead dislodgement. So I actually went to the library, actually I sent the EP Fellow to the library --

(Laughter.)

-- and had them look up lead dislodgements over the last few years, atrial lead dislodgements and certainly Parsonette's database, the European database and these actually include surgeon's putting in atrial leads, was only around 2 percent. I expected to get a comments from the surgeons when I made that comment, but I didn't get it.

(Laughter.)

It was a joke, it was a joke. It was only about 2 percent. So you're talking a significantly high lead dislodgement rate than is in the reported

literature.

When we met for the 7250, we were concerned about the atrial lead dislodgements and actually proposed that there should be a post-marketing surveillance for this led. Do you have any data from that, anything you want to comment about that?

DR. STANTON: Yes. The 6943 lead has just begun a post-market study as FDA asked for. We don't have any data from it yet.

The lead dislodgement rate is 6.9 percent which is about the same as it was in the VT/AT study that you're referring to.

DR. SIMMONS: Don't you think that's -- that's very high.

DR. STANTON: Yes. It's certainly higher than the 2 to 3 percent that's reported in the literature.

DR. SIMMONS: Do you guys want to comment?

DR. GOLD: I may comment. I absolutely agree that it's high, a very high rate, not a rate that we normally accept or want to see. Most of those

lead dislodgements were due to putting defibrillation coils in the atrium or in the coronary sinus. That is not a requirement for the implantation of the system. I think it's important to point out to implanters and investigators that there's different ways to skin a cat.

David and I differ, I think, a little bit in terms of our implantation approach, but I'm of the approach that the simpler, the better and the -- I don't use this lead at all. The lead system that I use is the simplest, easiest to implant lead system to try to minimize my complications. And the lead complications with standard leads and standard positions are no different with this system than with other type leads. So one has the option of an adequate well functioning system with different lead complications with lower complications --

DR. SIMMONS: So what system do you use?

DR. GOLD: I use the standard dual coil defibrillation lead and a standard atrial pacing lead. I don't use a coronary sinus lead. I don't use an atrial coil. I use the same lead system that I used

--

DR. SIMMONS: I do think that's interesting because that was going to be one of my later points is that if we look at the defibrillation thresholds as reported with the coronary sinus lead in the coronary sinus versus the atrial defibrillation thresholds without that lead, they are .2 joules difference and you're recommending programming this thing at twice the atrial DFT which is going to be around 12 to 15 joules as a first shock for the average patient, so why are we even bothering with this lead? Why are we even asking for approval for this lead?

DR. SCHWARTZMAN: Because there are individuals who require that vector, presumably for effective atrial defibrillation.

DR. SIMMONS: Maybe, maybe huh.

DR. STANTON: Tony, it wasn't randomized for looking at does the coronary sinus lead change defibrillation thresholds. This was at the discretion of physicians and in some cases they may have added it to try and lower the defibrillation threshold, so

those are the numbers of the DFTs, but I don't know what they mean in comparison.

DR. SIMMONS: Okay.

DR. GOLD: But I think simple lead systems have low lead dislodgement, low lead complication rates. Investigators and implanters need to know that more complicated lead systems and more coils in the heart increase complication rates and lead dislodgement rates and it becomes, I think, if approved their choice of is the benefit worth the risk in that situation.

DR. SIMMONS: Well, maybe there should be something in the packaging, an insert or something to suggest the fact of just exactly what you said. If we do decide to approve the lead, based upon its high dislodgement rate is still a question, but if we do decide to approve the lead, whether or not it shouldn't come with a warning that there is a high dislodgement rate and there is no proof that adding that lead right now actually does much for you.

DR. STANTON: Tony, I'm sorry, I missed some of that. Were you talking now abut the 6937A or

the --

DR. SIMMONS: Yes.

DR. STANTON: The lead dislodgement rate was 2.5 percent for the 6937A which is the coronary sinus lead and that's actually acceptable.

DR. SIMMONS: Right.

DR. STANTON: Right, and with the 6943, were you raising a question --

DR. SIMMONS: No, whether or not just -- you know, let me back up for just a second. Out of your 146 patients, only 86 had atrial defibrillation thresholds done, is that what I saw? I mean why so low? I mean that's terrible. That's for any clinical study. Those are significant protocol violations, aren't they? Sixty percent of your patients went through the protocol the right way?

MR. BROWN: My name is Scott Brown. I am a statistician with Medtronic. All of the patients with the exception of one did go through an atrial defibrillation threshold testing process. For the purpose of analyzing DFTs, we only reported those numbers if they followed precisely the two-step

protocol which included the precise use of increased thresholds as they went along. So there were a vast majority of patients who did have testing. Not all the data was analyzed as such.

DR. SIMMONS: Okay. Well, that makes me feel somewhat better.

What we were talking about is you have no proof that adding that coronary sinus lead is really going to improve your defibrillation thresholds significantly, then maybe if we do approve it, at the very least that lead should come with some warning that's there no evidence that it actually does anything as far as improving thresholds. Do you want to comment on that?

DR. GOLD: Well, I think the coronary sinus lead was not the culprit for the increased lead dislodgements.

DR. SIMMONS: No, right, but still if you're going to program something to 15 joules and you can put in a coronary sinus lead and drop the joules down to 10, the patient is not going to perceive any difference.

DR. STANTON: Yeah, I would say we certainly are not making any claim that the 6937A does anything different to atrial defibrillation thresholds and if you want that in the labeling we can put it in. We did not test that as part of the study protocol.

DR. SIMMONS: Okay. I must say I'm disappointed there's no data from that post-marketing surveillance. When did you go on the market with this?

DR. STANTON: The device was approved in June of 2000 and we did not start to release it until late August, so with rolling out the investigational protocols and getting IRB approval it's just starting for that study.

DR. SIMMONS: Okay. A few other things and then I'll let it go for other people.

One thing I wasn't clear about is I noticed in the manual a couple of times it says a rapid ventricular rate precludes therapy. If the patient has a rapid ventricular rate and it's atrial fib. or atrial flutter, then giving them therapy should be beneficial. If it's ventricular

arrhythmias, then giving them therapy at the very least shouldn't hurt them. Why does rapid ventricular rates preclude therapy?

DR. STANTON: Are you talking about the -- there is a safety features that prevents delivery of an atrial shock during rapid ventricular rates and the reason for that is so that you don't have the possibility of when you're delivering relatively low energies as you might during atrial defibrillation, possibly hitting during repolarization of the ventricle.

DR. SIMMONS: So what are you defining as a rapid ventricular rate that you can't -- is this like a programming lockout?

DR. STANTON: Yes. It's programmable and the minimum value is 400 milliseconds. So nothing -- it won't deliver if the RR interval is shorter than 400 milliseconds. It's a safety feature.

DR. SIMMONS: One hundred fifty beats a minute. All right. Do you guys agree with that? Does that make sense to you?

DR. GOLD: I do. I think obviously safety

is the number one concern and since we all induce ventricular fibrillation routinely by shocking low energy on T waves, the concern was that if patients with a very rapid response and it's not a regular 150, they're in atrial fibrillation, that with a long short coupling interval that a shock synchronized to an R wave could still be a vulnerable period from the preceding beat somewhere else in the heart and there's been concern in the literature about inducing ventricular tachyarrhythmias, ventricular fibrillation with such shocks. So it seems to be, I think, a reasonable safety approach and the data show there were no pro-arrhythmia events with shocks, so clearly the way it's now designed it's very safe for delivering shocks.

DR. SIMMONS: It just seems like a couple of the patients that you just brought up here on no antiarrhythmic drugs could very easily have an RR of 155 beats a minute and then they wouldn't be able to get their therapy.

DR. SCHWARTZMAN: As a matter of strategy, it has happened. It happens occasionally. But in

terms of the way it generally plays out, depending on what the patient is doing in part, obviously, if they're more active or upright. And so the device, the activator will tell them if the device cannot delivery therapy. Generally, that's because of the rapid rate and what will happen is they lie down and relax for a few minute or take a single dose of a beta blocker, for example, and those patients in which the problem has been a persistent problem, they get put on standing drugs, such as a calcium channel blocker or a beta blocker. So as a matter of incidence that has happened, certainly a minority of patients and in terms of responding to it, it's not a big deal.

DR. STANTON: And, Tony, just to clarify, it's not an average rate of 150, so 400 milliseconds, it's any interval short than. So if you have one interval that's longer than 400 milliseconds, that's the programmed lockout, then it would be able to deliver. But as David points out, there are going to be cases where people are going to be going rapidly and consistently be over 150.

DR. SIMMONS: Just one or two other little

quick things. Under your indications section and we can talk about this later, but certain atrial tachyarrhythmias, I mean I don't think I could ever vote for a device that's going to be labeled as therapy for atrial tachyarrhythmias. I mean this is an atrial fibrillation device. I can't even imagine wanting it to say this is a primary therapy for atrial flutter and certainly not for regular superventricular tachyarrhythmias. So just as a matter of housekeeping, certainly we are talking about an atrial fibrillation device, not an atrial flutter device. You only have 3 percent of your patients so I don't think you can make very many claims for -- this is therapy for atrial tachyarrhythmias other than atrial flutter and atrial fibrillation. Do you want to comment on that, David?

DR. SCHWARTZMAN: I would like to, mainly as a function. I agree with you in terms of uniform rhythms whether pharmacologic or catheter ablation-based solutions, but what I would submit is that -- and based on what we're learning from these devices is that these syndromes are not static or describable as

a single entity. For example, patients that you would swear were in persistent atrial fibrillation will have periods of flutter or atrial tachyrhythmia that are minimal to base termination. On the contrary, patients with primarily uniform syndromes like flutter will be in fibrillation. Part of the problem is our inability to define from the surface of an electrocardiogram what is going on and part of the problem is that these are hybrid syndromes and that is turning out to be the rule rather than the exception. A perfect example is atrial flutter which, in my opinion, is rarely a solitary rhythm. It is generally fibrillation that happens to have a combination of electrophysiologic features and probably anatomical features in the right atrium that support a macro re-entrant rhythmia such when you remove that possibility sooner or later you're left with an atrial fibrillation syndrome.

So I think it's not that simple. I would agree with you wholeheartedly that if you can define a uniform rhythm, then this device is certainly not the way to go, but I would also submit to you and

again with a large experience in an atrial arrhythmia center it is very rare to see patients with pure syndromes relative to those with impure syndromes.

DR. SIMMONS: Yes. And I have no problem with patients having atrial fibrillation and atrial flutter being candidates. Clearly, you're right, atrial pacing and even the high burst may turn out to be very effective therapies for those arrhythmias, but to put this device in as a therapy for atrial flutter which now has probably a 90 plus percent cure rate with ablated therapies and other therapies, I don't think you've prove that that kind of risk benefit ratio exists.

DR. GOLD: Yes. I think we agree or at least I agree. The distinction is probably more for the treatment of the arrhythmias. When we separate the arrhythmias as the device does into regular atrial tachyrhythmias, atrial tachycardias from atrial fibrillation, there's obviously a very different success rate in terms of case termination and other treatments of those arrhythmias. So they're concomitant arrhythmias with the atrial fibrillation

that the treatment is more effective and we have effective ways of being able to deal with the, at least periods of more organized rhythms in these populations of the patients, but I don't think there are many people who would suggest that for a patient with paroxysmal SVT or atrial flutter, we're going to start implanting defibrillators.

DR. SIMMONS: One other quick question and then I'll quit. Under your -- look at page 5 in the package insert. It says whenever the patient has an A-V node ablation, antitachycardia pacing and frequency burst pacing therapy should be disabled. Why is that?

DR. STANTON: I'm sorry, which was it again?

DR. SIMMONS: It's at page 5 under the package insert. A-V node ablations, patients receiving A-V nodal ablation after implant should have atrial anti-tachycardia pacing and atrial high frequency burst therapies disabled.

DR. CONLEY: My name Dennis Conley from Medtronic. The reason we put that in there is because

during ATP pacing in the atrium we did not have backup ventricular pacing in this device. So we thought once this is out in the marketplace, that is the most conservative warning that we could have in that device. Does that make sense?

DR. SIMMONS: Yes. I guess I didn't appreciate that. So you have no backup ventricular packing when you're doing anti-tachycardia pacing?

DR. CONLEY: In the atrium, that's correct, in this particular device.

However, you could speak to your experience maybe with A-V nodal ablation?

DR. SIMMONS: Maybe I'll have about half a dozen patients with nodes either prior to or subsequent to the device implant and that's obviously a problem.

What we've done is we've programmed the antitachycardia pacing durations to be a second or less. And none of the patients are perceived that brief period of withdrawal of ventricular support pacing.

The shock therapy, obviously, has nothing

to do with the trial anti-tachycardia pacing. Whether the briefer duration of atrial tachycardia pacing is less effective than the generally multiple second atrial antitachycardia pacing is hard to say with such a small group in the context of the larger group of patients with ATP ON, but as a matter of strategy, A-V node ablation does not preclude the use of the device.

DR. SIMMONS: Maybe I'll give somebody else a chance.

DR. TRACY: Dr. Aziz?

DR. AZIZ: Well, I think some of my questions are from a surgical type perspective.

Do all these patients, are they on anticoagulants for the duration of the therapy?

Do you recommend that they should be on anticoagulation?

DR. STANTON: Sixty percent of the patients were taking Coumadin at various points during the trial. That was left up to the clinician.

Michael, do you want to make some comments?

DR. GOLD: Yes. I think it was not

mandated that patients be on warfarin. Certainly, my clinical practice is that patients with atrial fibrillation and structural heart disease should be on warfarin and should be persistently on warfarin and I put all my patients on that. I think they probably should be on it.

DR. AZIZ: And from the analysis of your data, could you sort of give some ideas as to whether the initiation of the atrial fibrillation was from the right atrium or left atrium? Do you have that sort of data? No.

DR. STANTON: No.

DR. AZIZ: Do you think that has any bearing on the success of your termination of atrial fibrillation as to where the etiology starts from?

DR. SCHWARTZMAN: That's a very interesting question, obviously, because of how the field is unfolding, but the best answer would be paroxysmal versus persistent, for example. So if you take the patients with relatively well preserved hearts, relatively small left atria, paroxysmal atrial fibrillation syndrome, I think most

electrophysiologists would tell you that it is likely that the initiation of that entity is left atrial and depending on who you talk to, I think most of us are gravitating toward atrial fibrillation being more of a left atrial disease or not, so I don't know that that kind of data even makes sense.

The point is that regardless of clinical syndrome and regardless of cardiac structure, my experience and the multi center experience certainly demonstrates that the strategy -- the efficacy of the strategy did not change significantly. So my sense of it is that mechanism, trigger mechanism doe snot have a major influence on whether or not this strategy should be used.

DR. GOLD: I think if we at least use analogies of ventricular tachycardia literature, what we know, tachycardia, ischemic heart disease are coming from the left ventricular, pace termination is very successful from the right ventricular as long as you can entrant an arrhythmia. If it's a re-entrant arrhythmia you have a reasonable chance of being able to terminate that arrhythmia. So being close to the

arrhythmia origin probably gives you relatively little benefit, incremental benefit for pace termination, at least for ventricular tachycardias assuming the same thing where atrial flutter has been shown that you can pace terminate it anywhere, whether or not you're in the circuit. So we can say very little about where these arrhythmias are coming from, but it probably has a minor impact in terms of the efficacy of therapy, at least pacing therapy.

DR. AZIZ: You know, I think there were four patients who had a CVA during the course of the study. I think some of them had just stopped Coumadin and some hadn't.

What do you think the etiology of that was?

DR. GOLD: Of the four patients who had strokes during the study, three of them were not on warfarin at the time of their strokes. One of them had had several shocks several days before that. The others had not had recent, or at least immediately recent shocks. Again, this reemphasizes to me the importance of warfarin therapy and people with atrial

fibrillation, we don't understand all the mechanisms for why patients with atrial fibrillation have strokes. But we do know in many, many very well controlled, large, randomized studies that they benefit from warfarin therapy to reduce the risk of stroke. The AFFIRM Study, which is a large NIH study looking at treatment strategies mandates warfarin therapy whether you're in a rhythm control arm or a rate control arm. And I think the field is evolving to the point that we should not be reassured by the fact that we have a patient on an anti-arrhythmic drug that appears to be working, we should not be reassured that we have a device that may be able to treat these arrhythmias quickly. Atrial fibrillation is a pro-thrombotic state that leads to strokes and at this point we have no data, no evidence in my mind that any treatment of atrial fibrillation, whether mechanical or drug is, in fact, reducing that risk of stroke, which is why I strongly advocate that all patients should be on warfarin if they have atrial fibrillation with a history of structural heart disease regardless of what treatment strategy we take.

DR. AZIZ: Do you think the greatest danger period is the time when you convert the patient from atrial fibrillation back into a regular rhythm for am emboli dislodging?

DR. GOLD: That's certainly been the traditional teaching from Dr. Lown and others, but the data to support that, the risk may go up during that period of time, but my anecdotal experience with the firm where we've had many patients in that, I've now had collected, unfortunately four patients who are in the rhythm control arm of a firm, who have only documented sinus rhythm, never documented atrial fibrillation on their drugs and four patients who have had strokes. Whether they're going in and out of atrial fibrillation, whether atrial fibrillation is an epiphenomenon and they simply have atrial myopathies that lead to strokes, I don't know. We just don't have sufficient data. But we do have overwhelming data in support of the use of warfarin. So I think we need to hopefully use evidence-based medicine to guide us in terms of our clinical management and these patients, bottom line, should be on warfarin,

regardless of whether we shock them in two minutes, two hours, two days, whether they're on anti-arrhythmic drugs or not. Whatever we do to them, we know warfarin works and until we can prove otherwise, that's certainly my recommendation.

DR. STANTON: I'd like to make a quick comment. I think there's some interesting considerations in this regard. As you know, the American College of Chest Physicians recommends that if a person comes in with atrial fibrillation of less than 48 hours duration, then it's okay to go ahead and cardiovert them even if they're not on anticoagulants. I don't personally agree with that. I have used 24 hours and I'm not even sure that that's right.

All the shocks delivered in this study were within 24 hours.

DR. AZIZ: I mean you're not aware of any TCD type monitoring at the time that these shock therapies are being done to see if you do have increase blips going up in the middle cranial or anything like that, a trans-cranial Doppler monitoring, you're not aware of any studies of that

nature?

DR. GOLD: No, I'm not.

DR. AZIZ: One other question. How do you sort of decide whether to put the SVC lead versus a coronary sinus lead, what sort of predetermines -- not being an EP guy, which lead do you put in?

DR. GOLD: I think it depends on whether you get implanted in Baltimore or in Pittsburgh.

(Laughter.)

It's largely investigative preference. I think the lead systems -- I think David may want to comment on some of those decisions.

DR. SCHWARTZMAN: I don't want to leave the beaten path. We've used the coronary sinus lead routinely. It was and remains my preconceived bias that the success of a twice DFT defibrillation will be higher with a right atrial coronary sinus circuit than with a circuit that does not incorporate the left atrium, i.e., the coronary sinus lead. That data is being played out now.

Based on our preceding conversation though I would agree that certainly that that data does not

prove promising, that the coronary sinus portion of the circuit should be left at the discretion of the physician for those patients in whom adequate atrial defibrillation cannot be achieved with circuits not incorporating the coronary sinus lead.

DR. STANTON: Dr. Aziz, I just want to correct a statement I made before about the number of shocks that were within 24 hours. That was 95 percent, not 100 percent.

DR. AZIZ: In your experience has the size of the left atrium had an impact on how successful your defibrillation has been or do most of your patients have a small left atrium?

DR. SCHWARTZMAN: We're in the 40s now and we've seen no relationship and obviously there's a biased sample in that (a) these patients need demonstrable maintenance of sinus rhythm after trans-thoracic cardioversion if they were persistent prior to the implant; and (b) we stay away from the enormous left atria so given that bias, we're talking about under 6 centimeters, but within that cohort, we've seen no significant difference. We've certainly

seen no difference in the ability, 100 percent of our patients have had an adequate defibrillation threshold utilizing a right atrial coronary sinus circuit. In terms of the specific threshold we've really seen nothing compelling regarding a correlation between the actual energy and the volume of the left atrium, if you will.

As in ventricular DFTs I think it's not so simple. A lot of it has to do with orientation, anatomy, probably things extrinsic to the heart and so that I think the structure correlation between energy and structure gets washed out because of these other competing influences.

DR. GOLD: We have actually looked at that in a little more detail, not in this series of patients, not with this specific lead system, but using a uniform lead system and testing protocol with a dual coil lead with one coil in the right ventricle, the other coil in the SVC right atrial junction and then an emulator in the left pectoral region, so a classic triad type of shocking configuration for induced atrial fibrillation in over 100 patients now,

there is a correlation between left atrial size and atrial defibrillation thresholds. It's not a strong correlation, but it's statistically significant, but again, as David has pointed out, we can uniformly defibrillate patients. So large atrium may have defibrillation thresholds of 7. A smaller atrium may have a threshold of 4, that sort of range with mean thresholds of around 5 joules and are sort of large prospective evaluation of this. So it does affect the amount of energy, but it doesn't preclude the ability to uniformly defibrillate atria in patients within the established amount of energy that are provided with these devices.

DR. AZIZ: In the patient cohort that you have, I think there were 80 percent of patients with a New York Heart Association Class I or II. If you could sort of put your futuristic hat on, if you had patients who have lower and I think you excluded New York Heart Association Class IV, but a lot of the times patients in heart failure obviously do get trouble from atrial arrhythmias. In the future, do you see these devices playing a beneficial role,

particularly in giving people the atrial kick with bad EFs? Do you see that as an application?

DR. SCHWARTZMAN: Well, I can address my own experience. We actually have had a lot of interest from our heart failure group for their patients with reduced ejection fraction atrial arrhythmia attributable difficulties in controlling their heart failure syndromes and we have now 18 patients of various degrees of follow up with congestive cardiomyopathy, whether ischemic-based or not. And if you put them into the analysis mix with patients with structurally normal hearts or preserved ejection fraction, there's no difference in efficacy. Again, I don't think the metric is six months. I don't think it's 12 months. It's probably significant. But some of the issues that we're looking at and have had anecdotal results that are promising regard hospitalization. That was one of the cases. Preservation or improvement in ejection fraction, possibly related to a tachycardia mediated component of left ventricular dysfunction in these patients. Obviously, the patients have attributable

symptoms and so quality of life issues.

And so the way it has played out thus far, is that that is a particularly interesting population and I think as device-based therapies evolve we will gravitate more and more to the patient with cardiac co-morbidity, i.e., congestive heart failure, reduced left ventricular function.

DR. GOLD: I'd like to echo a similar sentiment. I have the most enthusiasm for using this type of therapy in patients with the most underlying heart disease. Our interest has been largely in applying this to patients of coronary disease and particularly congestive heart failure.

We've had the same experience that it works well having the backup ventricular defibrillation is reassuring, particularly in patients with a lot of structural heart disease and low ejection fractions and we are beginning an IDE-approved study through the FDA to, in fact, evaluate the use of this device in a randomized fashion in patients with congestive heart failure. So our experience anecdotally is that it works well and

I think it's going to be a very important substrate for the use of rhythm stabilization in which drug therapy is fraught with problems of limited use because of contraindications, increased para arrhythmia and other problems in that population.

DR. AZIZ: Just two quick small questions. In a surgical type population you've excluded obviously patients with mechanical tricuspid valves, but biological prosthetic valves I presume it's okay to use that?

DR. SCHWARTZMAN: Yes.

DR. AZIZ: By the same token, sometimes people with heart transplants who have repeated biopsies done, you don't see any problem using this sort of device in those patients who luckily don't get a lot of atrial arrhythmias on this? What do you say about that?

DR. SCHWARTZMAN: These are biopsies --

DR. AZIZ: Heart transplant patients who obviously have repeated heart biopsies with the boptome being put through the tricuspid valve. Do you see that patient population as being a

contraindication to its use or haven't you addressed that?

DR. STANTON: None of the patients had heart transplant prior to having the device implant so we don't have any data on it. I'm not sure if it would necessarily contraindicated, but it would certainly be a rare occurrence.

DR. GOLD: Surely, there's a long literature for pacing those patients if they need pacemakers. So putting leads across the tricuspid valve in a transplant patient requires frequent biopsies is well established. These leads are slightly larger, but certainly placing leads across those valves are commonly done.

MR. BROWN: Just one last -- the incidence of atrial fibrillation in cardiac surgery patients, obviously, is very variable and I see in your protocol you exclude patients within a month of cardiac surgery.

Do you have experience with patients who have a very persistent fibrillation tachyarrhythmias a month or more after cardiac surgery in this mix of

patients?

DR. STANTON: We haven't been able to slice the data that way to answer that question right now.

I think as you point out though the reason we had that as an exclusionary is one third or so of people after thoracotomy having atrial fibrillation, that's not the patient group we wanted to include.

DR. TRACY: Dr. Crittenden?

DR. CRITTENDEN: Tony and Salim really asked the questions that I was concerned about, but I just have one kind of educational question is -- can you tell me that none of these patients seem to get symptomatic relief from the examples that you had this morning. As soon as they were cardioverted they felt better. I was under the impression and maybe this is a wrong impression that conversation to sinus rhythm, electrical conversion to sinus rhythm doesn't always translate into an effective atrial transport mechanism. We see a lot of symptomatic relief based on the SF-36 scores. Can you kind of correlate all of that for me to help me understand a little better?