

in a period -- I can't remember exactly, but it was somewhere between one and a half and two years.

And again, just stating the clinical experience, given the number of implants, if valves were really going to fail from fatigue after a period of one and a half to two years, this would be evidenced in the body of clinical information that was presented today.

DR. DOMANSKI: Thanks.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: Just one short, brief comment on, I think that we're -- this is somewhat an unusual case, I guess, in that the valve has been out there for a long time.

I think the engineering -- I appreciate the engineering viewpoints from both sides, the good and bad, if you will, because it sometimes seems such an inexact science, and we somehow feel like the engineering is an exact science, so it's nice to see that at least even in engineering, that we can't count on absolute facts.

One thing that concerns me is the lack of recent data. I think maybe this is -- the valve is still being implanted elsewhere, and our threshold for approval is quite low, given the data requirements for a new valve today.

I mean, were this a submission that you just had on your desk today, and you had to start a clinical study, we don't ask for that many implants, and given the long

journey that this valve has taken to get to this point, I guess, again, I'm -- I feel compelled to ask the sponsor, you know, why, say, three years ago, you didn't just say, okay, fine.

We know what this is. Why don't we get 300 implants, you know, worldwide, and track them and the information requested, you know, to get it approved? I mean, if it indeed is such a good valve, the initial data ought to be pretty easy to come by, if it is used that often.

Could you comment on that?

DR. STUHLMULLER: Well, I would like to interject, I mean, with all due respect to Dr. Gilliam, Dr. Crittenden asked this question, and it's been addressed I think by the sponsor.

Your focus today should be on whether you believe the clinical data before you provides reasonable assurance of safety and efficacy, and the issue of, you know, business decisions by the Company, potentially, isn't what's on the table for discussion today.

DR. GILLIAM: That's not really the question, I didn't mean to ask it that way. I mean, I -- I'm not really asking whether the valve's a good valve or not, I guess I'm --

The real question I'm asking is that, new implants

right now, is there some information we have available from the sponsor, concerning worldwide implants that might say that this valve is indeed being actively implanted, and there are no thromboembolic phenomena, there are no red flags that would --

I think the durability issue is one, and safety. I'm willing to accept -- I mean, the valve has been out there. We've got tons of data, I'm willing to accept that part of it. I guess, more, to make me feel comfortable, I think it's -- that we're not, I guess, looking at a dinosaur.

I mean, I want some information that this is an active implanting -- a valve that is being actively implanted and there are no major issues that are not obvious to the sponsor or someone, now.

I guess that's -- not a question of business decision. I don't really, really have that desire to know.

DR. SAPIRSTEIN: John, since a lot of this information is based on an out of the U.S. study, I think that perhaps Dr. Gilliam's request should be accommodated.

DR. ARMITAGE: I'm going to respond. I'm not sure that I'll answer your question completely. You'll help me out, if I miss any aspects of it.

I would prefer not to cite the exact number, but suffice to say that in recent years, we've continued to sell

thousands of Hancock II per year, and they are being actively implanted outside of the United States, including Canada.

The only two populations that I'm aware of that are continuing to undergo follow-up, are the two populations that you saw today, the seven hospitals in the U.S., as well as the Toronto Hospital System.

I know that Dr. David and Ms. Armstrong are preparing the presentation, it's either 14- or 15-year data, so, you know, they have cited another database closure. They will accumulate their data again.

Their 12-year data was published only three or four months ago, in February. At Medtronic, we continue to follow the patients at the seven hospitals.

In addition to the continuation of this follow-up, which should give us an indication of what's going on now, as opposed to what was going on several years ago, there are other authors around the world who, of their own volition, decide to publish on the valve.

I won't cite data specifically, but there were a couple of presentations at a recent heart valve meeting in London, just one and a half weeks ago. There were at least two presentations on clinical experience with the Hancock II valve, very reassuring presentations. Those abstracts can be given to you, if you so wish.

DR. GILLIAM: You have addressed my question. I think I wanted to hear someone, for the record, say something to suggest that -- I mean, this valve has got a long track record. I think we're looking at something, 15, 16 years, you know, as far as the application process here. And it would -- I guess, I wanted to make sure that this is still a valve that is good for the public.

I think in the public's interest, if someone came up to me and brought a 1984 vintage pacemaker for approval, I would look at them and say, you know, well, why? I mean, compared with the ones now, I wouldn't want to foist that on the public, because they've -- you know, even though it could be safe and maybe effective at that point, I would not think that it would be as effective as I one I would approve today.

And I think that's the assurance that I wanted to have, that this is an actively-implanted valve. That there are data that is still ongoing, that people are using this valve with good results in 1999, as opposed to three years ago, stopped implanting. And that's all I have.

DR. DAVID: May I make a remark as a clinician, perhaps address the issue that you brought up?

We were, myself and my colleagues at Toronto General Hospital, were the investigators for the Mosaic, which is the Hancock II stent, with a free-style leaflet.

We finished the trial. And believe it or not, my surgeons stopped using it. They are using Hancock II again. Simply because most surgeons are senior, they have 17 years' experience with the valve, they say, the patients did very well, why should I try a new one? Let's wait and see what happens to the sample size of the Mosaic, before we all jump on this bandwagon and change to Mosaic.

Indicating that it's a good valve yet. Most of us feel this way.

DR. CURTIS: Dr. Simmons.

DR. SIMMONS: I really don't have much in the way of questions, but I thought there were some questions that the FDA brought up, I thought might give you a chance to respond before we debate them is, why do you want animal data in your labeling?

DR. ARMITAGE: The value of the animal data is just to help the clinicians understand the purpose of the T6 anti-calcification treatment. If that data is not there, there are naturally questions about, well, what is this treatment? Why is it there? Does it work? What does it mean to me?

DR. SIMMONS: I don't know. It sounds like you're going to be using that animal data to promote an indication or an advantage to the valve, that hasn't been shown. Is that -- is that the reason that you include it?

DR. ARMITAGE: Well, we look at it as in, from an educational perspective. We do not plan to promote it. As I indicated before, we feel that we do not have clinical evidence that clearly supports the anti-calcification efficacy of the T6, and the reason for that is, that deriving that type of proof from clinical information is exceedingly difficult.

I've had this conversation with Dr. Schoen on several occasions, and inevitably, I ask him, well, what will it take? How can we prove that T6 works? How can we prove that the AOA works?

And his comment is, well, the best proof that you have, Tom, is the long-term clinical outcomes for the patients. In other words, freedom from SVD, mortality, etcetera. But even when you have that data, you can not positively ascribe those positive outcomes to the anti-calcification treatment.

So, the industry finds itself in a quandary. I think that there is tremendous technical merit to treating tissue with anti-calcification treatments. However, just the nature of valve implants and clinical follow-up make it exceedingly difficult to discern clinically, if it was efficacious. That's why most people refer to animal studies in order to form their own opinion about whether it is useful or not.

DR. SIMMONS: Okay. I guess the other question, just from a technical sort of, why do you want the 21 valve approved, since you have got so few implants, and no real data to support it?

DR. ARMITAGE: The 21 mm valve, I would have to look at the exact number, but in the U.S. Cohort, I believe it represented approximately 20 percent of the implants. It was significantly fewer in the Toronto Cohort. It is, indeed, 20 percent in the Long-Term Medtronic Study at the seven sites in the United States.

As Dr. David indicated, it is their opinion, their practice in Toronto, to up-size the valve. Frequently, you will see in the Toronto clinical data, that in 18 percent of the cases, they did a patch aortic root enlargement, and that was because they wanted to get in a larger valve. Consequently, they put in fewer of the 21 mm valves.

This is not standard practice in the United States. If you take a look at the Medtronic Long-Term Cohort, I think that the frequency of patch enlargement of the aortic root only occurred 1 or 2 percent of the time, and our desire to have the 21 mm aortic valve is that it will be one of the more frequently implanted valves, and the majority of patients in the United States have small aortic annular, and that's who this device is targeted for.

DR. CURTIS: I think to follow-up on that, why

don't you have the minimum 15 assessments of gradient and effective orifice area for the valve size in all the valve sizes? I mean, 15 echoes per valve size doesn't seem like that much of a burden.

DR. ARMITAGE: I agree with that assertion, that given the number of patients who are in the cohorts, we should have that data, but please let me explain how we came about the cohort.

As Ms. Kennell indicated, the earlier data, the FDA found to be unsatisfactory because it had been collected in a variety of ways from a variety of centers, with multiple different protocols, people who didn't necessarily have the expertise.

And we decided that in order to not repeat the sins of the past, that we would try and identify a sub-cohort of patients for whom the data were collected in a very well-controlled fashion, by people who were learned in their craft, with standard protocols, standard methods of evaluating the exams.

And for us, that meant to take the patients from the Toronto Cohort, who were routinely followed at the Toronto Hospital System, and that grouping amounted to 300 and I believe 43 patients, and of those 343, there were not 15, 21 mm aortic valves, there were only nine of them. But those nine --

Proportionally, the nine 21 mm aortic valves in that grouping was representative, or similar to, the frequency with which the 21 mm was used in the total 1112 patients in the Toronto Case Series.

DR. CURTIS: What about the mitral valve, this is all mitral valves?

DR. ARMITAGE: Well, perhaps I'll let Dr. Miller answer that question.

DR. MILLER: I think the mitral data, you have -- this is an unusual experience, I think maybe a singular experience for the Panel, because this history started, obviously, before there were the real rigorous protocols in place for echo, like you have today.

Not only that, but even in clinical practice, we weren't doing, back in -- a lot of these valves were studied in Toronto before 1990, we weren't doing more than pressure half-time. You know, that's why you don't see a continuity method mitral valve area there.

And a lot of times, even today, if you look in the United States within a lot of clinical echocardiographic laboratories, for a mitral valve, if the pressure half-time is normal, there is no regurgitation, the sonographer isn't instructed to take time to measure the spectra for mean gradient, because with a normal pressure half-time, it's a clinically normal prosthesis.

And I think that's what we're seeing. We're seeing the effects -- this was a clinical protocol. The cardiologists and echocardiographers that were supervising the studies were satisfied it was normal without measuring mean gradient, and so they left it at pressure half-time data.

DR. CURTIS: I see. Okay. Mr. Dacey, any comments?

MR. DACEY: There is a consumer perspective, I believe on the FDA Panel Question 6. You have to understand my personal experience of 20 years of preparing patient education materials, and working a great deal with physicians and hospitals and obviously, patients.

There is no shortage of patient education brochures out there. And certainly, there is no shortage of information on the Internet these days. But what I am seeing is a new opportunity, and part of this goes back to my work with the Colorado Personalized Education For Physicians Program, which is, what I hear -- and this is anecdotal, I can't bring any science to this --

That what is needed are communication tools that physicians can use with patients that are patient-appropriate, because the patients have a wide, wide range of ability to comprehend, understand, and we tend to just put words on paper and assume that that is going to translate

into patient knowledge. And that's not true.

And I would like to see if there is some way, and there are multimedia opportunities here, to give physicians tools that they can selectively use with patients. And I'm not asking physicians to make judgments about their patients, as much as I am saying, we have some baseline information.

When I was working on the HCPR heart failure patient education material, I was really beat up, trying to get it to a fifth-grade level, which was the standard I had to work at. But they were right.

Subsequently, a lot of that information now is, again, out there on the web. We have this rapidly-changing demographic going on, where the community where I live, 80 percent of the households are on the Internet, and we have a great many people who are very science-literate. Well, 15 miles down the road, that is about 20 percent of the people are on the on the Internet.

Well, you can imagine what happens in the two different hospitals. When people, especially who are scientists themselves and are diagnosed with a problem, the first thing they do is go to the web and find out everything they can about it, and they cart all this to the doctor's office.

So, I am suggesting here that you consider, rather

than just another brochure, that you look at the whole communication process and see if there aren't some tools that will help people understand, but also give physicians the opportunity to improve the whole process of communication, not only for what's going to happen, but what is going to happen downstream, that people as patients need to know.

And I'll end this by, when I first started working with patients 20 years ago in Denver, I was amazed at the number of valve patients that I saw, who were never told they were going to have to take coumadin until after they had the surgery. And it came as a total surprise to them.

And it's that kind of information now, that people really want to know. And there's a lot of other things, obviously. So, I guess, generalized, there's a lot out there, I'd like to see more specifics that doctors could use.

DR. CURTIS: Dr. Jarvis has no comments? Does anybody else on the Panel have any questions or concerns they want to address to the sponsor?

DR. BRINKER: Since nobody had brought this up, I would just like to go over the thromboembolism issue. And if you look at page 5-2, under the Clinical Studies Section, which was previously referred to, Table 1. This I guess refers to the U.S. data, but its comparable results were

demonstrated in the Toronto data.

At ten years, if I'm reading this chart correctly, the thromboembolic event rate, or freedom from thromboembolic events, rather, was 80.7 percent with a 95 percent confidence interval of 72 to 89.

And in the controls, which I assumed, perhaps wrongly, were all mechanical valves. They were all tissue valves? So, none of them, presumably, had anticoagulation?

DR. HARTZ: No. There are a couple of tables further on, where a quite high percentage of these patients, especially for the mitral, were on anticoagulation and it increased over time.

DR. BRINKER: In the controls, or in the --

DR. HARTZ: The controls were other tissue valves, a different tissue valve.

DR. BRINKER: So, is there any way to -- is there any way to compare these numbers in a reasonable fashion, to suggest whether the effects of anticoagulation obviate late thromboembolism?

And by late, I think the curves, just eye-balling this, would start to differentiate at five years, and get most marked numerically at ten years. Whether this represents a difference in the anticoagulation regimen in the control, so-called controls, versus the Hancock II, or whether there is a different potential for the Hancock II to

develop thromboembolic events?

Or, whether it's just a function of the nature of reporting.

DR. ARMITAGE: I would like to start off commenting, and then I'll probably defer to Dr. David. I think in general, when you look at tissue valves, there is a built-in assumption that the singular reason, or at least one of the strong reasons to use a tissue valve, is because then you don't have to use anticoagulants.

But if you look at published data for many of the commercially-available prostheses, you find that a significant percentage, and by significant, I mean, somewhere between 30 percent and 60 percent of the patients, will be on long-term warfarin.

And there are several factors that control this, and I think that one of the factors, frankly, is just a sense of security on the part of the cardiologists or the regular follow-up physicians, who don't understand the need for it.

There is also a significant incidence of postoperative atrial fibrillation, and if you look at the STS database, the frequency with which atrial fibrillation occurs post-open heart surgery, I think it's on the order of you know, 20, 25 percent -- please correct me if I'm wrong about that.

But in those circumstances, the patients who have tissue valves may not have preoperatively had atrial fibrillation, they develop it postoperatively, and that's one of the reasons why they would be on anticoagulation.

The relevance of this to Hancock II, and to get to your question, is that, you are correct. I mean, it's very difficult to make comparisons between our Hancock II experience and these control articles, and you know, the reason being is that some of these factors that I've just mentioned, either you know, the data are not available, or they are available only in a limited way, so that you can't case-match or control for it.

We worked with the FDA to identify the best available controls, by searching the literature and coming to agreement on appropriate references, and that's what you see.

You know, your concern about the thromboembolic complication rate, I would like to have Dr. David comment on that, in general.

DR. DAVID: It's very difficult to read the publications from different institutions and come up with a conclusion as to how the numbers were arrived at.

I can tell you from experience with several thousand patients that we follow in our clinics, that the thromboembolic rate of this valve is no higher than any

stented porcine valve available.

Given the limitations for a study that we calculated these numbers, only for the first event. So there will be a few patients who had more than one event, that they're not detected here. And perhaps this might account for the difference between the Medtronic patients followed and ours. That we stopped with the first event.

Having said all this, most of our events were transient ischemic attacks, they're not strokes, in the aortic position.

In the mitral position, most events were strokes, not transient ischemic attacks. Our general policy is not to anticoagulate patients with biological valve, unless they have a medical indication for anticoagulation, such as poor ventricle function, or chronic atrial fibrillation.

But, I can't explain the difference in number, either.

DR. HARTZ: Could I comment, because the data don't really support the use -- the issue of postoperative atrial fibrillation, which is actually much higher in valve patients than the 30 percent you referred to with coronary surgery. A very common problem.

DR. DAVID: Right.

DR. HARTZ: However, in the Medtronic Study, 76 percent of patients were discharged on warfarin, at the most

recent study, 60 percent of the patients were on warfarin.

That indicates to me that most of those patients were in chronic atrial fibrillation, and it's going to get back to, again, when we do the labeling and the contraindications, indications, we have to carefully address that issue.

I think the difference in these series and the control series, is pointed out on page 44 of the FDA Summary, and I mentioned this previously.

"The number of patients in atrial fibrillation" -- I'm sorry, that's the wrong page -- it's something like 31, 45, and whatever for aortic and mitral valve replacement patients.

The number of patients who had thromboembolic episodes were mostly in those patients who had atrial fibrillation. Is what I gleaned from the data.

And that becomes of concern, because of the type of patient that we're going to conclude this valve should be used in. Not the prosthesis, but the choice to use the prosthesis.

DR. DAVID: That, really, is the clinician's decision.

DR. HARTZ: Yes.

DR. DAVID: And the patient. If a patient is in chronic atrial fibrillation, he's taking coumadin already,

why use a biological valve? Then the question of age, the risk of anticoagulation and the level that a mechanical valve requires of anticoagulation, versus a porcine valve.

Most of us clinicians believe that the level of anticoagulation required from mitral biological valve is lower than a mechanical valve. A mechanical valve is less forgiving. As a consequence, you keep a higher INR. But that decision on the part of the clinician --

DR. HARTZ: I did not notice in the Toronto Series, that incidence of atrial fibrillation that was quoted for the Medtronic Long-Term, so --

FDA Questions to the Panel

DR. CURTIS: Anyone else? All right, if we could have the sponsor step back, then?

We're going to move on now to the FDA Questions to the Panel. If we can get the first question up?

Do the data presented permit assessment of the safety and effectiveness of this device? Specifically, does the use of a mailed patient survey allow for assessment of safety and effectiveness of the long-term Toronto case study?

DR. HARTZ: I think the answer to the first part of the question is yes. The second part of the question, does the use of a mailed survey allow for assessment of

safety and effectiveness in the Toronto study?

That's a hedge, because this was not simply a mailed study. There was intensive follow-up by a nurse who did ten years of follow-up on heart valve patients. So, I don't think we should leave it in, just that it was purely a mailed survey. There was very good follow-up on the survey itself.

DR. CURTIS: All right. Any other comments, particularly, to the contrary?

DR. DOMANSKI: Well, I think the data, I actually think the data presented are not enormously strong data. It's easy to sit and take pot shots at it. I mean, you know, it's easy to do that.

I actually think -- I'm actually more persuaded by the fact that, in the end, that this valve has been out there forever, without lots of adverse events being reported, gratuitously.

I think that's, from my standpoint, far more settling than the data actually presented. In a sense, it's data presented in a negative way. So, I feel safe with it, but I don't think much of the methodology in some of those studies. In that study.

DR. HARTZ: No one has really pointed out the fact that this prosthesis is not designed for permanent use. This is a pedograft. It's easy to implant. It's not designed

for the life of a young patient. And we have not really emphasized that enough to be able to address these specific questions.

So that, when we say, long-term durability, that's almost oxymoronic in this setting. There are specific indications for patients who can't be anticoagulated, and for patients who don't need this valve for 50 years.

DR. DOMANSKI: Yes, I'm not so much -- I'm not so much referring to the durability stuff, which actually, I think was, in effect, answered for me, but rather the sort of clinical -- not clinical trial -- but the design methodology, I thought, was relatively weak.

DR. CRITTENDON: Just a point of clarification. If we accept this point about the mailed patient survey, does that obligate us in the future to allow that type of data in terms of documentation by other sponsors for acceptance of their data, in an application?

DR. CURTIS: I wouldn't think so, I mean, because of the unique way that this whole thing has come about, and we're looking at the data now. I mean, we're trying to do the best we can with some long-term follow-up, but I don't think that that has to obligate us to -- that's the only way you're going to be able to follow long-term patients in the future.

Okay. All right. So, then we have a consensus

that the data is enough for us to come to a conclusion about safety and effectiveness. Let's look at No. 2.

The sponsor wants to include information in their labeling, (Instructions for Use) about the studies performed in animals. Would this information be meaningful to the user?

Given the long history of human implantation with this device, would it be preferable to include results of the human explants and adverse event rates for structural valve deterioration, rather than information from the animal studies? Opinions.

DR. GILLIAM: I think Dr. Simmons' questions were to this point, and I think that, given the lack of convincing data, that a process is successful, at preventing calcification and problems with this, I'm not sure that we add anything to the animal data, to the labeling, that would not be construed as endorsing a process that we don't have convincing clinical data that says it's useful.

So, even if the Company did not make a claim that this process is somehow beneficial, the fact that you include the animal data in the labeling, implies that very strongly. So, I would be against putting this in, because I don't think that it adds anything necessary to the implanting physician, and those people who wish to look up the process, and learn more about it on their own, are

certainly able to go to the engineering data, and are welcome to look it up, in that arena.

DR. DOMANSKI: I would, you know, I'd really support that view. I think there is too much potential for species-specific things to permit that.

DR. CURTIS: So, we would prefer to see information about long-term human experience, particularly explants and adverse events rates for deterioration, rather than animal data, included.

DR. HARTZ: Yes.

DR. CURTIS: All right. No. 3. The sponsor wants to market the Model T505, in all the sizes listed, 21 to 29 mm, and the mitral valve in 25 to 33 mm.

Do the data presented support approval of all sizes? If not, what additional data would be required to establish the indication for sizes not approved?

We did address this directly with the sponsor before. I mean, I understand what they said, and you can't go back to 1980-whatever it is and get an echo you'd like to see now, and the long-term follow-up is good.

I don't have any problem myself with letting all the different valve sizes through. Does anybody else want to make a comment?

DR. HARTZ: I could not find anywhere in this information, nor in previous data, that there is a

heterograft in a size 21 with better hemodynamics.

That was a little bit of a surprise to me, and I think in 1996, the 19 aortic was already excluded from submission. I have no problem with the 21 aortic or any of the other sizes, for that reason.

DR. GILLIAM: With the 15 assessments, I guess I'll ask the surgeons here. I mean, would the data from 15 assessments of echo, of the mitral and the size 21 AVR, is that something that would be of, I guess, benefit to those who are implanters, to do that as a post-marketing --

And maybe I'm jumping ahead of us, but you know, is this -- it seems like 15 echos, I mean, essentially, 30 echos does not seem that hard to get, and if we're actively implanting, I think the sponsor's term was, thousands a year, I mean, it seems to be fairly easy to obtain this data pretty quickly as a post-marketing study.

Is this the kind of information FDA would like to have?

DR. CURTIS: Well, not like to have, do we need to have it? You know, because I think that's what you examine through post-marketing. Do we need to have that information?

DR. HARTZ: This is the little old lady valve, and the maximum gradient across that prosthesis in a small number was 25 mm, and unlike Dr. David, a lot of surgeons

are not going to enlarge the annulus, and we need a valve that is non-thrombogenic, in a small size, to implant in this rapidly-increasing population of little old ladies.

So, yes, we would love to have the data, but there is going to be a significant gradient. It may not be the 70 or 100 mm gradient that that little old lady presents with, but if she gets out of the hospital with a 25 mm gradient, it can function, I think. I think that's the goal with this small size valve.

DR. CRITTENDON: But, do you need -- I mean, is -- I mean I recognize that the valve is going to have the gradient, I mean, but is this the sort of information that is necessary for the implanter to have, to say that this is a safe valve, as opposed to maybe another valve where we've demanded this information, in this size, so that they have access to making a clinical decision, whether this 21 mm valve is safe, as opposed to say, some other valve?

I think most surgeons know about this. I don't think that this is information that's new. That is as an aside. The reason I put in the 21, I always hear Dr. David getting up in a national meeting saying, I never put in these valves -- but I mean, you know, at least in America, I know I've got to do it, although I regret it, and I hear his voice, but you need this valve.

DR. CURTIS: Thank you. Okay. No. 4. Does the

following Indications section adequately define an appropriate population for use, based on the data presented?

This is Indications for Use. "Hancock II bioprostheses are indicated for the replacement of pathologic or prosthetic aortic and mitral valves."

DR. HARTZ: In nonpregnant patients greater than age 60, not with renal failure, or else we have to go to contraindications. I'm not sure where to put this.

DR. CURTIS: Well, that may -- I mean, the -- it is indicate for replacing diseased heart valves, or --

DR. HARTZ: Yes.

DR. CURTIS: But in terms of those concerns, I think precautions or something, in the warning, whatever, would be appropriate. And we can do that under No. 5, but in terms of Indications, that's what it is indicated for, right?

DR. BRINKER: What do other tissue valves --

DR. CURTIS: What do they say?

DR. BRINKER: -- have as their Indications and Warnings? I don't think we could, given the nature of this, I'm not sure that we could ask for more or less than other tissue --

DR. CURTIS: It just should be comparable to another tissue valve, right?

DR. CRITTENDON: Yes, but this is all pretty

standard stuff. Every single valve has all that information in it, in the detail that I think we would accept.

DR. HARTZ: Actually, it can be used in any position, it says aortic and mitral here, I don't --

DR. CURTIS: Well, because the clinical studies were done in aortic and mitral, I would say. You can't --

DR. HARTZ: The third double valves, tricuspid, it's just that the numbers were so small, they didn't discuss that, but does this mean if this goes on Indications, that the implanter can't use it for --

DR. CURTIS: No, no, no. They'll be an off-label use. So, it's just that, you know, they've studied it for these Indications, and that's what they can get a labeling for.

All right, No. 5. Is the proposed Contraindication section appropriate? Are there any other contraindications for the use of this device?

Contraindication listed is "Use of the mitral bioprosthesis in patients with a small, hypertrophic left ventricle may be contraindicated because of the potential for perforation of the ventricular wall by the stent posts.

"Accordingly, the physician should carefully consider these potential hazards when selecting an appropriate bioprosthesis for such patients."

I mean, Contraindications are absolute

contraindications. If we can think of anything else that would fit in there, that would be appropriate, and if not, then we can move on to some of the precautions we were discussing.

DR. CRITTENDON: I think this is appropriate. I don't see anything, any reason to add anything to this.

DR. CURTIS: All right. Now, what kinds of precautions would you like to see mentioned, or -- in the labeling?

DR. CRITTENDON: Children. People with problems with calcium metabolism. I'm glossing on others now. Help me out with --

DR. HARTZ: I think that use of this prosthesis in patients in chronic trial fibrillation may lead to an excessive risk-to-benefit ratio.

DR. CURTIS: For thromboembolic --

DR. HARTZ: So, I would warn against using it in atrial fibrillations. Pregnant patients. Patients under age 60.

DR. CURTIS: Okay. Those will be all sorts of warnings and precautions that you might want to maybe think --

DR. GILLIAM: But they're not truly contraindications.

DR. CURTIS: Not, they're not contraindications.

DR. GILLIAM: They're warnings.

DR. CURTIS: Right. That's right. Or precautions.

DR. BRINKER: Does the STS have a set of recommendations as to valve use? Do they -- have they said --

DR. HARTZ: As to choosing a prosthesis?

DR. BRINKER: So, there is no guide as -- professional guideline as to the use of a tissue prosthesis, or a porcine versus -- tissue --

DR. HARTZ: Well, this is part of our training, though, in cardiac surgery, and tons and tons of our book chapter work, and I mean, the whole risk-benefits section is how we start out choosing a valve.

DR. BRINKER: What I'm asking, are there any accepted guidelines published by a peer organization?

DR. HARTZ: No.

DR. BRINKER: Okay.

DR. CRITTENDON: None that I'm aware of.

DR. STUHLMULLER: I guess as a point of clarification, Dr. Sapirstein, I mean, the FDA has labeling templates for a variety of devices, you know, is there a labeling template for heart valves, and are there generic issues that would be appropriate for the Panel members to discuss?

DR. SAPIRSTEIN: No, there isn't a template, but there are all -- well, recently, we went through the same routine with the Medtronic free-style valve, the whole question of, well, can you use that as a comparison, both with TIMMS, or use of anti-calcific material, and sizes and use in hyper --

DR. GILLIAM: This is something, sort of maybe more simple. I think, I see bioprostheses used and often in these mechanical valves, I don't believe are bioprosthesis.

And I don't think that we have to make sure that we don't somehow in our labeling, you know, in effect, imply that a mechanical prosthesis should not be used in some of these patients.

I mean, the way this is written here, it says, selecting an appropriate bioprosthesis for such patients, as opposed to saying, bioprostheses are mechanical valves.

I get the implication that bioprosthesis means specifically a tissue valve. I mean, is that --

DR. CRITTENDON: That's the common parlance. I mean, you're talking about a valve --

DR. HARTZ: And you're saying, you shouldn't say that.

DR. CURTIS: But he makes a good point. It says, the physician should consider potential hazards when selecting an appropriate bioprosthesis, or consider the use

of a mechanical valve. I mean, I don't know if --

DR. GILLIAM: Maybe that's splitting hairs, and I don't know the surgeons, what they think about it --

DR. HARTZ: Or just skip the second sentence. Skip the second sentence, completely.

DR. CURTIS: I think that might be a good solution. Any other comments on that? All right, let's go to No. 6.

At this time, the sponsor has not submitted any patient literature counseling the patient about their valve, and appropriate activity after valve implantation, such as prophylactic, antibiotic therapy, anticoagulants. Should some patient literature be developed for this valve?

I think the first question I would say is, isn't there literature out? I mean, we have all kinds of patient booklets for EP Studies and RFAs and all that. Aren't there generic booklets that cover valves?

DR. HARTZ: Everybody has their specific one that they like. There's tons.

DR. CURTIS: I wouldn't think you'd have to go ahead and develop a whole new brochure just for this one valve. I would think if you had a decent one on a bioprosthetic valve, that would be fine. A generic one. I agree. The only thing I kind of wanted to add was that, since everybody gets an I.D. card from the Company, then why

not some of this generic stuff be put on the back of that, but short of that recommendation, I agree. I think that there is plenty of stuff out there that we don't need to duplicate that.

DR. CURTIS: No. 7. Is there a need for physician training to be added to the labeling? Our surgeons are saying, no. If you're a trained cardiothoracic surgeon, you're going to be able to put this valve in.

DR. CRITTENDON: Other than the one about the orientation for left ventricular outflow tract obstruction and --

DR. CURTIS: But that's part of your training, too, isn't it?

DR. HARTZ: Yes, they better know that, or they won't pass their boards.

DR. CURTIS: Okay. Not necessary. Any other suggestions for the labeling? No. 8.

DR. CRITTENDON: Just change the word from reflux to perivalvular leak?

DR. CURTIS: Dr. David, is that -- I didn't see reflux. Does that mean inter-suture leak, that -- what does that mean? Oh, I'm sorry, I can't ask that. Sorry. We'll just change the words.

DR. STUHELMULLER: Well, actually, the sponsor will have the opportunity to address any questions raised by the

Panel at the end of their discussion, so you can get up then.

DR. CURTIS: Any other suggestions for the labeling? You mentioned the perivalvular leak rather than reflux. Anything else? Okay.

Do the data presented adequately demonstrate the safety and effectiveness of the device as labeled?

I mean, I think that actually gets into the vote, I mean, that's when we have a motion here.

Are there any other issues of safety or effectiveness not adequately covered in the labeling, which need to be addressed in further investigations before or after device approval?

I would say, no. Does anybody -- okay.

And No. 11, Do you recommend any post-marketing studies, and if so, for what purpose?

I would say, we've got more long-term data on this valve than we're ever going to see as a -- than I'm ever going to see as a Panel member here.

Okay. At this point, we'll have our second public hearing, which would mean if anybody in the audience has a burning desire to say something now, or the sponsor or the FDA wants to make any final comments before we come to a vote?

Open Public Hearing

DR. CURTIS: All right, if not, then I will ask either Dr. Hartz or Dr. Crittendon to make a -- oh, we have to -- we're going to make a motion, but first we are going to find out what motion we can make.

DR. STUHELMULLER: Panel recommendation options for premarket approval applications. The Medical Device Amendments of the Federal Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications (PMAs) that are filed with the Agency.

The PMA must stand on its own merits and the recommendation must be supported by safety and effectiveness data in the application, or by applicable publicly-available information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of intended use outweigh any probable risk.

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

when labeled, will provide clinically significant results.

The recommendation options for the vote are as follows.

Option 1. Approval. If there are no conditions attached.

Option 2. Approveable with conditions. The Panel may recommend that the PMA be found approveable, subject to specified conditions, such as physician or patient education, labeling changes, or further analysis of existing data.

Prior to voting, all of the conditions should be discussed by the Panel.

Option 3. Not approveable. The Panel may recommend that the PMA is not approveable if the data did not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective, under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each Panel member to present a brief statement outlining their reason for their vote.

DR. CURTIS: Dr. Hartz, would you like to make a motion?

DR. HARTZ: I move to approve the Medtronic Hancock Bioprosthesis Heart Valve Models T505 and T510 for

use in the United States.

DR. CURTIS: Do we have a second?

DR. GILLIAM: Second.

DR. CURTIS: Okay. So, you are recommending approval without conditions.

DR. HARTZ: Approval without conditions.

DR. CRITTENDON: I hate to disagree with my good friend and colleague, but I would like to make a motion that we approve with conditions. Is this the proper time to bring that up, or am I out of order here?

DR. CURTIS: Well --

DR. STUHMULLER: Basically, there is a motion made. It wasn't seconded, now --

DR. CURTIS: Yes, it is seconded.

DR. STUHMULLER: Oh, there was a second? I'm sorry. I didn't realize that.

DR. CURTIS: Well, since it was approve without conditions, then we'd have to vote on that.

DR. STUHMULLER: Yes, now you have to vote.

DR. GILLIAM: You can discuss --

DR. STUHMULLER: Well, you can discuss --

DR. CRITTENDON: You can bring up a discussion --

DR. GILLIAM: I mean I would like to get Crittendon's --

DR. CRITTENDON: The only thing, the two really

minor things, but I think they were important, is basically on the amount of discussion that it engendered, and that was one, just the new engineering data that we've gotten just today, or yesterday.

I know, I think the FDA feels pretty comfortable with it in terms of the official position, that they have adjudicated the argument between the two engineers, but I would just like to say, pending review of --

That one condition would be, pending review of this new engineering data, that that ought to be looked at, and if that's okay, go ahead with the review.

And then the other thing is, just in terms of labeling. I don't know if we've addressed this or not, about changing the labeling to address our concerns about thromboembolic events. And those are the only two things.

DR. DOMANSKI: One thing about the engineering data. I think the FDA is going to do that, anyway. This is a Panel recommendation. We're not approving the thing, but rather recommending its approval.

I think if they saw some problem with it -- you correct me, John, if I'm wrong -- but if they saw some problem based on the new engineering data, they simply wouldn't approve the thing.

DR. STUHMULLER: I'm going to defer that to Dr. Sapirstein.

DR. DOMANSKI: I don't see that as an issue, do you?

DR. SAPIRSTEIN: They never -- absolutely. This is a recommendation, as you say, and our approval will depend on further evaluation of the additional submissions, or information requested. You are correct.

DR. DOMANSKI: I mean, there could be other things that come in, too, that are of concern, or reassuring to the FDA.

DR. CURTIS: I would think, too, I mean, we have discussed the changes in the labeling. I'm sure that is going to happen. I don't think that necessarily has to be a condition of approval. That's something we do commonly, and don't have to list it, specifically that way.

DR. CRITTENDON: I'll withdraw.

DR. CURTIS: Okay. Any other discussion? All right. What we're going to do is we're going to go around the table and vote, and then we're going to have to go back around the table and you're going to have to tell me why you voted, so we'll start that way.

DR. Brinker?

DR. BRINKER: I vote for the motion.

DR. CRITTENDON: I vote for the motion.

DR. DOMANSKI: I vote for the motion.

DR. GILLIAM: Vote for the motion.

DR. HARTZ: Yes.

DR. SIMMONS: I agree.

DR. CURTIS: All right. The motion passes. Dr. Brinker, can you make a brief statement about why you voted that way?

DR. BRINKER: Well, I'm sure, as everybody said, including myself previously, this is a unique application in the amount of long-term follow-up of a significant number of heart valves. And I think that most of us are reasonably well-assured that this compares favorably with other bioprostheses.

And I don't see any issues that would stand in the way of making this available.

DR. CURTIS: Dr. Crittendon?

DR. CRITTENDON: I voted in the affirmative because I believe the data presented today, demonstrated that this was a safe and effective device.

DR. CURTIS: Dr. Domanski?

DR. DOMANSKI: I, too, believe that the preponderance of evidence suggests the device is safe and effective and ought to be released.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: The evidence shows that the device has been safe and effective for some time, and I support that.

DR. CURTIS: Dr. Hartz?

DR. HARTZ: Same. I believe the device is safe and effective and the process just got slowed down by a previous consideration of fraud by another sponsor.

DR. CURTIS: And Dr. Simmons?

DR. SIMMONS: I agree that the device is probably safe and effective, based on the clinical data.

DR. CURTIS: All right. I think that is going to conclude our morning session. We are going to break now. We are going to have to come back at 1:00 in order to make sure we have a Panel member quorum here, so 1:00, reconvene.

[Whereupon, at 11:33 a.m., a recess was taken until 1:00 p.m. that same day.]

A F T E R N O O N S E S S I O N (1:06 P.M.)

DR. SIMMONS: Due to some difficulties, Dr. Stuhlmuller is going to clarify some issues that have come up.

DR. STUHLMULLER: Dr. Tracy was originally scheduled to attend as a consultant who was deputize to vote. There was some question over the lunch hour whether we may or may not have had a quorum to have a vote and it was determined that we do so I just want to clarify that for the record. Also, the conflict of interest statement was read this morning and won't be read again.

DR. SIMMONS: This afternoon we are going to discuss the pre-market approval application P980050, the Medtronic Jewel AF Arrhythmia Management Device. The company will now have its presentation.

Agenda Item: Company Presentation - Premarket Approval Application P980050

DR. STANTON: Thank you very much. On behalf of Medtronic and the clinical investigators, I am very happy to be able to present the data on the Medtronic Model 7250, Jewel AF Arrhythmia Management Device. Prior to going into that, I would like to make some brief introductions. I am very pleased that we could have two of the clinical investigators here with us, Dr. Marcus Wharton from Duke University -

DR. SIMMONS: Excuse me. You have to identify yourself, your affiliation and your financial status. So each speaker that comes up has to do the same.

DR. STANTON: Sure. I am Dr. Marshall Stanton. I am vice president of medical affairs in the cardiac rhythm management division at Medtronic. I am employed by Medtronic and that is my financial conflict of interest.

All right. Our two clinical investigators that are able to attend, Dr. Marcus Wharton from Duke University and Dr. Steven Markowitz from Cornell University.

I am Marshall Stanton as I introduced myself before. I am a clinical electro physiologist. I had a practice for 10 years at Mayo Clinic and currently am vice president of medical affairs in the cardiac rhythm management division at Medtronic. Dr. Dennis Connolly is our regulatory affairs expert. Dr. Rahul Mehra is director of atrial fibrillation research. Ven Manda is the AF clinical director. Jim Johnson is the AF statistician. Cole Hannon is the study manager for the Jewel AF clinical. And Mike Hess was systems engineer for the Jewel AF.

I will start by giving a brief background on atrial fibrillation in ICD patients and then go on briefly to describe the Jewel AF system, spend the bulk of my time presenting the clinical data and briefly wrap up.

As a way of background, somewhere between 20 and 39 percent of patients who receive ICDs have a history of atrial tachyarrhythmias, atrial tachycardia, atrial flutter or atrial fibrillation at implant. An additional 3.5 percent of ICD patients develop atrial tachycardia or atrial fibrillation each

year thereafter.

Current ICDs have the ability to discriminate super-ventricular tachycardias from ventricular tachyarrhythmias. The Jewel AF incorporates an ability to discriminate super-ventricular tachycardias from ventricular tachyarrhythmias and also provide therapies for the treatment of atrial tachyarrhythmias.

Let me go now to give you an overview of the Jewel AF system. First and foremost, the Jewel AF is a ventricular ICD. It is a standard dual chamber ICD that detects and treats ventricular arrhythmias. It uses PR Logic which is present in the currently approved and marketed Gem MR and it also has atrial tachyarrhythmia detection algorithms. It has atrial tachyarrhythmias therapies and prevention algorithms as well.

Let me compare and contrast the Jewel AF with the Gem MR which is market approved. The sizes, 55 cc's volume versus 62 cc's. Maximum output per shock 27 joules delivered energy; for the Jewel AF; 35 joules delivered for the Gem DR. Both are dual chamber, are capable of dual chamber pacing. The Gem MR also has capability of rate responsive pacing. Both utilize the same PR logic algorithm for discrimination of super-ventricular and ventricular tachyarrhythmias. Additionally, the Jewel AF has the ability to detect different atrial tachyarrhythmias. They have identical therapies for treatment of ventricular tachyarrhythmias and to tachycardia pacing, cardioversion and defibrillation.

Additionally, the Jewel AF has features that allow treatment of atrial tachyarrhythmias and prevention of atrial tachyarrhythmias including anti-tachycardia pacing, 50 herz burst pacing, defibrillation, atrial rate stabilization and high-rate overdrive atrial pacing.

Let me walk you through how detection occurs in the Jewel AF. Again, first and foremost the Jewel AF is a ventricular ICD. Its main concern is whether or not there is a ventricular arrhythmia present. On a beat by beat basis, it is looking to see whether ventricular tachycardia or ventricular fibrillation are present and, if so, it delivers the appropriate therapy.

If a ventricular tachycardia is not present, then it looks to see whether an atrial arrhythmia is present. If one is present, it then starts a timer that is programmable and after the offset of the timer, the atrial therapy would be delivered.

Let me go into some more detail about the atrial detection zones. There are two different zones for atrial detection - the AF zone and the AT zone or atrial fibrillation and atrial tachycardia zones. For those of you that are not familiar with the programming of ICDs in general, these zones are programmable by the user so that the cycle length that defines the zone can be programmed.

The device uses the median P to P interval to detect an atrial tachyarrhythmia. Note that the user can program overlap of

the two zones. If the media P to P interval falls within this overlap zone, the Jewel AF then looks for regularity of the arrhythmia to determine whether it classifies it as an atrial tachycardia or as atrial fibrillation. The difference is important. Different therapies can be programmed in the AT zone and the AF zone. The thinking is that atrial tachycardias which are more regular than atrial fibrillation will be more amenable to non-shock therapies.

Note for detection to occur, 32 ventricular intervals have to occur before an atrial arrhythmia is declared to be present. The Jewel AF uses the same far-field R-wave rejection algorithm that the Gem MR uses.

Let me walk you through an example of how an episode might be detected and treated. This is just an example. On this time line is the patient's rhythm. The patient begins in sinus rhythm and again on a beat to beat basis, the Jewel AF is watching to see if a ventricular arrhythmia is present and if a ventricular arrhythmia is not present, it then is assessing for whether an atrial arrhythmia starts.

Here we see the onset of an atrial arrhythmia. And after 32 beats, ventricular beats that is, episode is declared to have started. Recall that I said that there was a programmable time that the user could program before a therapy would be delivered so in this example, I am showing that the user may have programmed in five minutes prior to the onset of the first pacing

therapy.

In this instance, if pacing therapies are unsuccessful in terminating the atrial arrhythmia, the device will wait until the sustained duration times out for the first delivery of a shock therapy before delivering a defibrillation therapy. In this instance, the user programmed 30 minutes prior to that shock delivery.

Shocks were able to terminate the arrhythmia and shortly after arrhythmia termination, the device declares that sinus rhythm is as resumed and it is the end of the episode.

In the clinical study, most patients received a two-lead system. This incorporated a lead in the atrium for pacing and sensing, a lead in the ventricle for pacing and sensing in the ventricle, and shocking coils to allow shocks between the right ventricle, the SVC for right atrium and realize that the Jewel AF like all other Medtronic defibrillators uses an active can as an electrode as well.

The difference between these two systems is where the atrial or SVC coil is located. In this instance, it is part of a lead that goes into the right ventricle and in this instance, it is part of the right atrial lead. With those two configurations, some physicians elected to place a coronary sinus lead and additional configurations that were used are details in your panel pack.

Let me go ahead and review the clinical summary right

now. I will first start off by going over the primary and secondary objectives that we had, how the study was designed, the methodology for each of the objectives, and finally the results of each of those.

The Jewel AF population was comprised of two subgroups. One group had ventricular tachyarrhythmias only. The other subgroup had in addition to ventricular tachyarrhythmias the presence of qualifying atrial tachyarrhythmias. I will give you more detail of that in a moment.

We had four primary objectives for the study. The first primary objective was to assess the relative risk of system related complications. We also sought to report and describe all adverse events. For objective one, the acceptance criteria was that the upper one-sided, 95 percent confidence bound of the relative risk of the system-related complication had to be less than three. We compared the Jewel AF clinical population with the clinical population that was used in the Gem MR study when it was approved by FDA. We looked at the populations in total and we also broke them down in each of these two study groups to those with qualifying atrial tachyarrhythmias and those who had only ventricular tachyarrhythmias.

Additionally, as I will explain in the subsequent slide, there was a subgroup of the population that had a study of atrial termination and prevention therapies on for three months versus off for three months and then crossing over. We also

assessed the system related complications in the on versus the off period.

The second primary objective was to assess the efficacy of atrial defibrillation therapy in terminating spontaneous atrial fibrillation episodes. The acceptance criteria for this was that the lower one-sided 95 percent confidence bound on the efficacy for terminating spontaneous atrial fibrillation episodes with defibrillation is greater than 50 percent.

Our third primary objective was to assess the efficacy of atrial anti-tachycardia pacing, ATP, and high frequency burst pacing, that is, non-shock therapies in terminating spontaneous atrial tachycardia episodes. The acceptance criteria for this objective was that the lower one-sided 95 percent confidence bound had to be greater than 50 percent.

Our final primary objective was to assess the sensitivity of VT and VF detection with the system's PR logic dual-chamber detection algorithm. The acceptance criteria here was that the lower one-sided 95 percent confidence bound for sensitivity of VT/VF detection is greater than 95 percent. We also had a series of secondary objectives. Please note that the study was not designed or powered to assess the statistical significance of these secondary objectives. These were items that we thought were interesting, that we wanted to prospectively collect data on.

We had six secondary study objectives. The first was

assessing the relative risk of death with the Jewel AF system, compared with patients who received the Gem MR system. The second secondary objective was assessing the change in atrial tachycardia and atrial fibrillation frequency and duration. That is, the burden of atrial arrhythmia. Third was to assess the atrial defibrillation threshold at implant and at three months post-implant.

Fourth was to assess the accuracy of detecting atrial tachyarrhythmias. Fifth, verify the sensing, pacing and detection functions of the Jewel AF system. And lastly, to monitor the pacing and sensing performance of the Model 6943 lead as used in the atrium. Please note that the Model 6943 lead is an approved lead for use in the ventricle.

Our study design. It was a multi-center, prospective study that we conducted in the United States, Europe and Canada. Patients who had both ventricular tachyarrhythmia and qualifying atrial tachyarrhythmias were randomized to an atrial prevention and termination therapies on for three months versus off for three months and then crossing over for the next three months to the off and on positions. After six months, programming of atrial therapies was at the discretion of the investigator. Patients who were in the ventricular tachyarrhythmia only group were not subjected to this randomization.

The methodology. Patients were included if they had a current accepted indication for placement of an ICD. The

ventricular tachyarrhythmia only patients were limited for each center. Patients in the ventricular tachyarrhythmia, atrial tachyarrhythmia group had to also have a current indication for an ICD, plus they had to have two documented episodes of atrial tachyarrhythmia during the year prior to implant.

For primary objective one, which was assessing the system related complications, the analysis was done using patients from the Gem MR clinical study as the historical control group. The rationale for that group being the comparison is that the Jewel AF and the Gem MR both share the identical PR Logic detection algorithm. Patients in both studies required both an atrial and a ventricular lead and a similar process and methodology for reporting and classification of system-related adverse events was used in both studies.

A complication was defined as an adverse event that resulted in an evasive intervention and an observation was classified as an adverse event which did not result in an invasive intervention.

For primary objective two, which was assessing defibrillation efficacy for atrial fibrillation, all AF episodes were classified by the investigators for appropriateness of detection. For this objective, effectiveness was based on all spontaneous, appropriately detected AF episodes that were treated with atrial defibrillation as the last therapy. The generalized estimating equation method was used to account for patient-

specific responses to atrial defibrillation outcome. For those of you not familiar with statistics, the GEE method is a standard statistical methodology that adjusts so that one patient having many episodes would not adversely weight on the whole group.

For the third objective which was assessing non-shock therapy efficacy for atrial tachycardias, all atrial tachycardia episodes were classified by the investigators for appropriateness of detection, effectiveness was then based on all spontaneous atrial tachycardia episodes that were treated with ATP only or by anti-tachycardia pacing followed by high frequency burst. Again, the GEE method was used to account for patient-specific responses.

For the fourth and final primary objective assessing the sensitivity of VT and VF detection, this was assessed based on a subgroup of the study patients who underwent 24-hour Holter recordings and also a review of all reported adverse events and all stored episodes looking for undersensed VT/VF episodes.

Let's move on to the study results. A total of 303 patients were enrolled in this study; 293 received the Jewel AF implanted. The 10 patients who did not are detailed in your panel pack.

The mean follow-up for the whole group was 7.9 months and the total cumulative follow-up for all patients in the PMA population was 2,325 months.

This table shows the patient characteristics. Please

note that for these demographic features there was no statistical difference between the group with concomitant atrial tachyarrhythmias and the ventricular tachyarrhythmia only group. The demographics are very similar to typical ICD populations seen in many studies, about 80 percent of the patients are male. The average age is 63 years. The mean injection fraction 38 percent and you can see the breakdown of primary indication for the ICD.

This table details the history of atrial tachyarrhythmias. In the group that had combined ventricular tachyarrhythmias and atrial tachyarrhythmias and atrial tachyarrhythmias, 75 percent had atrial fibrillation as their qualifying arrhythmias; 27 percent atrial flutter; 7 percent other SVTs. Note that this sums to more than 100 percent because more than one arrhythmia could have existed in a single patient.

Note also that patients in the ventricular tachyarrhythmia only group could have had a history of atrial arrhythmias; however, they did not have the qualifying two documented episodes in the prior year.

For objective one, assessment of complications, here are the results.

First, for the group as a whole, comparing the relative risk of a system-related complication with the Jewel AF compared with the Gem MR, there was no statistical difference. When we break this down to the ventricular tachyarrhythmia only group and the one with concomitant atrial arrhythmias, again, there is no

statistically significant difference in the relative risk of a system-related complication and the upper 95 percent confidence bound is listed here and this meets the predetermined acceptance criteria of less than three.

We also analyzed whether a system-related complication was any different in the time when a person was randomized to atrial prevention or termination therapies on versus off and there was no statistical difference in system-related complications with therapies intervention on versus off.

The next three slides will show Kaplan-Meier survival curves, detailing the same data that I just presented. That is, we are showing here the risk of the survival-free of a system-related complication in the Jewel AF population in yellow and the Gem MR population in orange. No statistical difference for all patients.

Then breaking down to the two subgroups, first the group with concomitant atrial tachyarrhythmias, not statistical difference and in the ventricular tachyarrhythmia only group, again no difference.

I want to discuss one complication with you in particular. This occurred in a patient who had a dislodgement of an atrial lead. This occurred 15 minutes after the completion of implant defibrillation testing. The atrial lead was a model 6940 pace sense lead. Note that this is an approved lead in the atrium. It does not have a defibrillation coil on it. It

dislodged in the immediate post-operative period and dislodged with the tip in the right ventricle. Over-sensing of bar waves and T-wave caused an inappropriate detection of an atrial fibrillation episode, 50 herz burst was delivered and this led to ventricular fibrillation. Ventricular fibrillation was immediately detected and terminated with a single shock.

Note that a feature that is built into the Jewel AF is that if a ventricular arrhythmia is detected within 32 beats after delivery of an atrial therapy, the device will automatically disable all atrial therapies. This appropriately occurred in this patient.

Let me review for you the total number of patients that had atrial episodes. There are 221 patients in the combined atrial tachyarrhythmia/ventricular tachyarrhythmia group. Of those, 58 percent had a spontaneous atrial tachycardia or atrial fibrillation episode. Seventy-four of those patients had the episode detected and treated. Most of those in the remaining patients were non-treated episodes. This could have occurred because the physician had not programmed on therapies and was just using the device for monitoring.

Let's follow on what happened to these patients who had treated episodes. These are the 74 patients with spontaneously occurred atrial arrhythmias that were treated. Twenty-five of these patients had AF episodes, atrial fibrillation episodes that were treated with shocks. Additionally, four patients had atrial

fibrillation episodes treated by shocks and also had atrial tachycardia treated with non-shock therapies. These 29 patients make up the group analyzed for atrial defibrillation efficacy, objective two that I will come to. Twenty-nine patients had atrial tachycardia treated with anti-tachycardia pacing or anti-tachycardia pacing followed by high frequency burst. Again, four patients had both shocks for AF and the non-shocks for atrial tachycardia. These 33 patients make up objective three, pacing efficacy for termination of atrial tachycardia. Sixteen other patients had a variety of other sequences.

The results for objective two, the efficacy of atrial defibrillation, as I said, 29 patients had episodes of atrial fibrillation. There were 87 total episodes of atrial fibrillation that were spontaneous and treated by defibrillation as the last therapy.

Unadjusted efficacy was 77 percent. Again, using the GEE method, the adjusted efficacy is 75 percent. This meets the acceptance criteria with a lower one-sided 95 percent confidence bound of 63 percent.

This is another way of looking at the data. What I am showing here is for each patient, how successful was atrial defibrillation for their episodes. For example, 17 patients had 100 percent efficacy for shocks terminating episodes of atrial fibrillation. Two patients had between 75 and 99 percent success, et cetera.

Objective three assessed non-shock therapies for termination of atrial tachycardia. Let me first review for you how the Jewel AF operates for delivering therapy in the atrial tachycardia zone. Up to six therapies can be programmed into the atrial tachycardia zone in the following sequence. Anti-tachycardia pacing first, and if this is unsuccessful, it can be programmed to deliver 50 Herz burst pacing second and if that is unsuccessful, it can be followed by atrial defibrillation shocks.

For this objective, let's look at what occurred with these therapies. Five hundred and twelve episodes were treated with anti-tachycardia pacing first. Success was achieved in 317 of those episodes. Of these 512, of the ones that were not successful, 131 were subsequently treated with high frequency burst pacing; 31 of those were successful.

This yields an unadjusted efficacy for anti-tachycardia pacing, following by high frequency burst therapy of 68 percent and an adjusted efficacy of 59 percent. This also meets the acceptance criteria with a lower one-sided 95 percent confidence bound of 50 percent. Analogous to what I showed you with success for defibrillation, here I am graphing the individual patients and how many had various amounts of success.

For example, seven patients had 100 percent of their atrial tachycardia episodes terminated with ATP and/or high frequency burst. Two patients at 75 to 99 percent efficacy, et cetera.

Our last primary objection was assessing VT/VF detection sensitivity. Holter analysis was performed in 49 patients with a total of 67 24-hour recordings. These 67 recordings revealed no under sensed VT/VF episodes. A total of 144 ventricular tachycardia and ventricular fibrillation episodes were appropriately detected during this monitoring. No known under sensed spontaneous ventricular episodes based on a review of all reported adverse events were seen. This yields a sensitivity of VT and VF detection of 100 percent.

I am going to move on to secondary objectives, and I want you to keep in mind that the study was not designed nor powered to necessarily meet statistical significance for these observations.

The first secondary objective was the relative risk of death. For the population as a whole, comparing the risk of death from any cause in the Jewel AF study compared to the Gem MR clinical study, there was no significant difference.

Interestingly, in looking at patients who had a ventricular tachyarrhythmia and a qualifying atrial tachyarrhythmia, the risk of death in those receiving a Jewel AF was significantly less than those who received a Gem DR.

For the patients in the ventricular tachyarrhythmia only group, there was no statistically significant difference in survival.

We also analyzed the risk of death when patients had

prevention and atrial treatment therapies on compared with off. We found no statistically significant difference in mortality with that analysis.

The next three slides will show Kaplan-Meier survival curves, and this is survival from all cause mortality, first with all patients, and we see in yellow survival of the Jewel AF, clinical patients in orange, survival of the Gem MR clinical study patients. No significant difference for the populations as a whole. For the group that had combined ventricular tachyarrhythmia and atrial tachyarrhythmia, we see statistically significant difference in survival, survival better in those who received the Jewel AF.

And in looking at the subgroup who had ventricular tachyarrhythmia only, no statistically significant survival.

For the second secondary objective, this was assessment of atrial prevention and termination therapies in the randomization period for three months with the therapies and prevention on versus off. The frequency of atrial tachyarrhythmias decreased by a mean of 50 percent reduction going from .18 to .09 episodes per day but this did not achieve statistical significance.

The duration, the total amount of time spent in tachyarrhythmia was reduced a mean of five hours per week, going from 6.2 hours per week with therapy and prevention off to 1.2 hours per week with them on. Again, this approached but did not

achieve statistical significance with the PMA population.

Objective three was looking at the atrial defibrillation threshold at implant and at three months, at implant, the atrial defibrillation threshold in a step-up to success method was 6.6 joules compared to at three months, 5.6 joules. In comparing patients who had paired data, there was no significant difference.

The fourth secondary objective was looking at atrial tachyarrhythmia detection. The positive predictive value of atrial tachyarrhythmia detection which is the true positives divided by true positive plus false positive yielded an unadjusted rate of 95 percent positive predictive value. Here is the raw data. An adjusted rate using the GEE of 93.8 percent. Secondary objective five was to assess the system's sensing and pacing function. This was performed as part of a Holter analysis study. Far-field R-wave rejection performed as designed. Atrial rate stabilization performed as designed and ventricular safety pacing performed as designed.

The last secondary objective was to look at the model 6943 lead as used in the atrium. I will show you raw data in the next few slides. The median paired differences between implant and six months for pulse width was .08 milliseconds; for pacing impedance was 41 ohms; and for P-wave amplitude was 9 millivolts. And these parameters are within the expected range for this lead.

Going over the data in more detail, these next three

slides will show you a graph of the value at implant, at one month and at six months. For P-wave amplitude, we see 2.5, 3, 2.5. For pulse-width threshold, .18, .27, .26. And for median pacing impedance, 706 ohms, 727, 747. Let me just highlight some additional study results.

This bar graph shows total number of detected atrial arrhythmia episodes. Please note that these 9,200 atrial arrhythmia episodes include many non-treated episodes. The number of episodes on the Y axis is graphed according to cycle length that it was detected at on the X axis. In yellow are arrhythmias that were detected in the AT zone, in orange, arrhythmias detected in the AF zone.

Note that 71 percent of arrhythmias were detected in the AT zone. This is significant because many atrial tachycardias are pace terminal. Additionally, we want to highlight that 146 patients received 1,072 R-wave synchronous atrial defibrillation shocks. This included both induced and spontaneous atrial episodes. All of the 1,072 atrial shocks were appropriately synchronized and did not result in ventricular proarrhythmia. This yields an observed proarrhythmic risk of shock of zero percent. Statistically estimated maximum proarrhythmic risk is 0.28 percent per shock. That represents the upper 95 percent confidence bound.

AS I mentioned earlier, the Jewel AF is primarily a ventricular ICD. Therefore, I want to briefly highlight for you

its efficacy in terminating VT and VF episodes. For the population as a whole, 63 patients had ventricular tachycardia episodes detected, a total of 875 VT episodes with overall success for termination of VT of 97.6 percent.

Fifty-seven patients had ventricular fibrillation. These are spontaneous episodes detected; 256 total episodes, all of them successfully terminated, yielding the percent success of 100 percent.

So, in conclusion, the clinical experience of the Jewel AF in patients with ventricular tachyarrhythmias with or without concomitant atrial tachyarrhythmias has demonstrated the following. The Jewel AF system is safe as measured by system-related complication free survival and survival from all causes compared to the approved Gem DR.

The Jewel AF system is effective in detecting and treating both atrial and ventricular tachyarrhythmias. The Jewel AF system can terminate 59 percent of atrial tachycardia episodes with non-shock therapies, that is, ATP and high frequency burst. Atrial defibrillation is successful in terminating 75 percent of atrial fibrillation episodes. The Jewel AF system's pacing, sensing and detection features function as expected. Atrial DFTs are stable between implant and three months.

In patients currently indicated for an ICD, the Jewel AF system is safe and effective in managing ventricular and atrial tachyarrhythmias.

Thank you, that concludes my presentation.

MR SIMMONS: Is anybody else from the company going to present? I guess we are ready for the FDA to present. The company could step back for now.

Agenda Item: FDA Presentation

DR. TERRY: Good afternoon. My name is Doris Terry. I am the primary reviewer for the PMA application, P980050.

To the circulatory system devices panel, ladies and gentlemen. The manufacturer, Medtronic, is seeking approval for the Medtronic Model 7250 Jewel AF arrhythmia management device system. Acknowledgements to the members of the FDA review team who were instrumental in completing the review of the PMA application.

The 7250 arrhythmia management device system consists of the pulse generator model 7250, the model 9961-E application software, the 6943 Sprint Lead for atrial use and other commercially available leads and accessories. The model 7250 Jewel AF detects and treats episodes of atrial and ventricular tachyarrhythmias. It is an implantable cardio defibrillator that detects and treats episodes of atrial and ventricular tachyarrhythmias and bradycardia by delivering defibrillation, cardioversion, anti-tachy pacing or bradycardia pacing. Atrial arrhythmias are detected by the model 7250 either as atrial fibrillation or atrial tachycardia by monitoring the cycle lengths and regularity of the atrial intervals.

This is the first ICD that provides therapies for both atrial and ventricular tachyarrhythmias to be considered for monitoring approval.

Preclinical tests, bench and/or animal, were performed on the components, subassemblies, application software, firmware and the finished device. The test results verify performance of the Model 7250 Jewel AMD system to specifications.

Summary of the clinical studies. As of June 30, 1998, the PMA population consisted of 303 patients enrolled; 293 actually received the model 7250. There were 221 VT/AT patients. ICD patients with documentation of at least two episodes of atrial fibrillation or atrial tachycardia and 72 VT only patients. The mean follow-up for the VT/AT patients was 8.2 plus or minus 4.8 months and 7.1 plus or minus 4.5 months with the VT only patients. Taking into account the core PMA population and the patients outside the PMA population, the implant mean ventricular DFT was 9.4 joules plus or minus 4.4 joules in 150 patients measured. The implant atrial DFT was 6.6 joules plus or minus 4.9 joules in 72 patients.

At three months, the mean atrial DFT was 5.6 joules plus or minus 3.3 joules in 15 patients.

The primary study objectives of the model 7250 Jewel AF study were to evaluate system-related complications, the effectiveness of the model 7250 in terminating atrial tachyarrhythmias and to evaluate the performance of the dual

chamber algorithm.

The secondary objectives are to estimate the relative risk of death, to estimate the change in frequency and duration of atrial tach, the mean atrial DFT and specificity of the SVT rejection rules, to verify the sensing, pacing and detection capabilities of the Model 7250 and to monitor pacing and sensing performance of the Model 5943 lead for atrial use.

For data analysis, a crude hazard rate and the Cox regression methods were used in analyzing the time to first system related complication. Generalized estimating equation, the GEE methods, were used in the analysis of episode treatment effectiveness. The results were compared to the model 7219 C and the model 7271 Gem MR populations. The comparative data presented will be those from the Gem DR.

Safety data complication-free survival. In analyzing the safety data for complication-free survival, the study requirement is met when the ratio of the upper one-sided 95 percent confidence bound for the crude hazard rate of the model 7250 versus the estimate for the crude hazard rate of the control model is less than or equal to three and when the upper one-sided 95 percent confidence bound for the relative risk model 7250 versus the control from the Cox Regression Model is less than or equal to three.

Adverse events. All events that occurred at implant prior to skin closure were classified as adverse events at

implant. System-related events that occurred post-implant and required invasive intervention were categorized as system-related complications. System-related events that occurred post-implant and did not require invasive intervention were categorized as system-related observations. The events that occurred and were not device related were called non-system-related events.

Twenty-three events occurred in 23 patients at implant; 43 system-related complications occurred in 37 patients; there were 144 systems-related observations in 101 patients; and 56 non-system-related adverse events in 39 patients.

The hazard rate complication-free survival, the crude hazard rates with the one-sided upper 95 percent confidence bound was shown. The estimated hazard rate of a system related complication for the model 7250 VT/AT patients, 230 with 23 complications is .0228. Comparative data shows the hazard rate for the complication-free survival for the model 7271 VT/AT patients 100 with 10 complications is .0428. For the 7250 VT only patients, 73 with eight complications. The estimated system-related hazard rate is .0256.

For the control VT only patient, 200 with 14 complications, the rate is .0259. All met the study requirement.

Comparison of relative risk of system-related complications for the model 7250 VT/AT patients. The relative risk was .72 with the probability of .396 with the one-sided upper 95 percent confidence bound of 1.36. The relative risk for

the VT only patients is 1.21 probability of .675 with a one-sided upper 95 percent confidence bound of 2.55.

The relative risk with the therapies programmed on versus off. The relative risk of system-related complications with the prevention and termination therapies on versus off in the VT/AT group is 1.07 with a probability of .0872 with a one-sided upper 95 percent confidence bound of 2.08.

Summary of mortality data. Twenty-six deaths: sudden cardiac four, non-sudden cardiac, 13, non-cardiac, eight and unknown, one, occurred in the PMA population.

Survival data, the Kaplan-Meier estimates for the 7250 patients, the Kaplan-Meier estimates that three months for the model 7250 VT/AT group with 189 patients followed for three months with 97.8 percent with 95 percent confidence intervals as shown. With six months, the survival for the VT/AT patients with 151 patients followed for six months is 92.9 percent. For the model 7250 VT only patients 52 followed for three months. The estimate is 98.4 percent. At six months, the estimate for the VT only patients, 42 followed, was 96.4 percent.

A comparison of overall survival of the model 7250 versus the control at three months included the following: 97.8 percent with confidence intervals as shown with a 7250 VT/AT patients and 88 percent with confidence intervals as shown for the 7271 VT/AT patients.

Episode treatment effectiveness for atrial

tachyarrhythmias. The study requirement is that the lower 95 percent confidence bound is greater than 50 percent. The atrial defibrillation, 29 patients had 87 spontaneous AF episodes; 77 percent were successfully terminated. AF episode effectiveness is 74.9 percent adjusted with GEE. Lower 95 percent confidence bound was 63 percent which met the requirement.

Episode treatment effectiveness for atrial tachyarrhythmias, for ATP and burst, 44 patients had 670 episodes. They were treated with either ATP or burst as the last therapy delivered. For ATP, 434 episodes, 65 percent, 334 of the 434 episodes, 77 percent, were successfully terminated with ATP. For burst, 236 episodes, 35 percent, 58 of the 236, 24.6 percent were successfully terminated.

Episode treatment effectiveness for ventricular and atrial tachyarrhythmias, episode treatment effectiveness for ventricular and atrial tachyarrhythmias, for spontaneous VT, 97.6 percent, for VF 100 percent. The positive predictive value for ventricular detection, 88.6 percent adjusted, 80.8 percent with 95 percent confidence intervals is shown. Positive predictive value for atrial detection, 95 percent adjusted, 93.8 percent.

Pacing, sensing and detection performance. The device which includes the features ventricular safety pacing, mode switching, far-field R-wave detection and atrial rate stabilization responded appropriately as documented by 67 Holter recordings.

Frequency and duration of atrial tachyarrhythmias. Forty-eight patients in the PMA population completed the randomized crossover assignment. There was a 50 percent reduction in the frequency of AT/AF per day and for therapies on versus off, probability .18. The average paired difference demonstrated that patients with therapies on had a reduction of five hours of reduced AT/AF burden per week. Probability .088.

The model 6943 Sprint ventricular/atrial lead was implanted in the right atrium of 96 patients in the PMA population. The patient's parameters remained relatively stable through six months.

Summary of lead-related adverse events. Seven lead-related adverse events occurred in seven patients at implant. AT post-implant there were six complications in six patients and four observations in four patients.

Conclusion. The manufacturer, Medtronic, has provided data in support of the safety and effectiveness of the Model 7250 Jewel AF AMD System.

We offer the following questions for the panel's consideration.

1. Are the clinical data adequate for evaluation of safety and effectiveness of the atrial termination and treatment therapies in the model 7250 Jewel AF?

2. Do the following indications for usage adequately define the patient population studied? Particularly emphasis

should be placed on the paragraph: the Model 7250 Jewel AF System is also designed for patients who either have or are at risk of developing atrial tachyarrhythmias but is not currently indicated for patients who do not have the VT/VF indication stated above.

3. Based on the clinical experience, should there be an additional contraindications for use of a Model 7250 Jewel AF? For example, should patients without ventricular arrhythmias be contraindicated for use with the Jewel AF ICD?

4. Several patients enrolled in the clinical study failed to meet the ventricular implant criteria and received a commercially available ICD with a higher defibrillation energy output. Should the instructions for use labeling include a warning which advises physicians that the Jewel AF may not be appropriate for patients who require greater than 27 joules of defibrillation energy?

5. Considering the accelerations with 50 Herz burst and the non-successes reported for the treatment of rhythms in the AT and AF zones with 50 Herz bursts as the last therapy delivered, are there clinical concerns and/or recommendations regarding the use of the 50 Herz burst in reducing the number of accelerations and effectively treating atrial tachyarrhythmias?

6. In one of the cases where 50 Herz bursts accelerated the atrial tachyarrhythmias episode, the atrial lead was dislodged and as a result, the manufacturer recommended the labeling as stated. Are there concerns about the labeling as

written? Is the labeling adequate?

7. Some of the model 7250 patients were programmed utilizing the device's atrial therapy sequencing feature which offers delayed atrial pacing and defibrillation shock therapies. Considering the number of non-successes for AT and AF episodes and the "failure to defibrillate" cases, could some of the failures be attributed to programming of this feature? Are there other concerns or additional programming considerations regarding delaying programming in the VT/AT population? Does the proposed labeling contain adequate information for effective programming? Also, in light of the atrial DFTs, are there considerations about programming the energy of the first atrial shock?

8. Have you other suggestions for the labeling?

Other questions include:

9. Of the 218 VT/AT patients randomized to crossover at three months with atrial therapies on or off, only 48 patients completed the assignment. The results of the data showed a 50 percent reduction in the frequency and duration of atrial tachyarrhythmias. These data are not adequately powered to be statistically meaningful. However, when the non-PMA data (data from patients in the study who are not a part of the PMA core population are considered, duration was found to be statistically significant. How do you rate the data in terms of its clinical usefulness or significance?

10. Are there concerns about the dislodgement rate of

the Model 6943 lead versus the Model 6940?

11. Are there other issues of safety or effectiveness not adequately addressed in the clinical experience or covered in the labeling which need to be addressed in further investigations before or after device approval?

Also, if time permits, would the panel please consider the future concerns for the atrial defibrillator clinical trials? Thank you.

Agenda Item: Panel Discussion

DR. SIMMONS: We will now start the panel discussion. Dr. Blinker is going to be the lead reviewer here.

DR. BLINKER: Thanks. I want to thank Marshall for his presentation which helps put into perspective some of the issues involved in this really complex set of circumstances that we are going to discuss.

Since the bottom line design of this device as far as VT/VF is concerned is predicated on a device that has a good and established record of safety and efficacy, the issues as I try to settle this out in my own mind concern whether there is excessive risk in that patient population brought about by the development of this additional capability for detecting but more importantly applying therapy for super ventricular arrhythmias. If not, whether there is an efficacy established in the detection but more importantly treatment of the super ventricular arrhythmias and as a side note, is there any reason why the ventricular lead

should not be used in the atrial position?

I guess we might start with actually that first. The dislodgement rate of 5.1 percent or so is higher than the quotes control leads and I wonder if the thought is that there is something structurally accounting for this. I know also there were a number of lead dysfunctions which in terms of helix extrusion which I honestly don't understand in view of the fact that this apparently wasn't established for this lead in the ventricular placement.

So my first questions are, does the presence of the coil affect the stability of the lead in the right atrium? And secondly, is the inability to advance the helix at least in a relatively small but significant number of these situations related to atrial placement or do people just look harder for this?

DR. SIMMONS: It might be helpful, too, if the rest of the company came back up to the table. Thanks.

MR. HANNON: My name is Cole Hannon. I am the clinical study manager for this clinical trial and therefore I am an employee of Medtronic.

I would like to first address the question about the helix extension issues. We had four atrial, 643 atrial leads that had a failure to extend the helix. Concurrently with this clinical study there was an ongoing clinical study of the 6943 in the ventricle. That has since been approved but at the time

there was some overlap of the clinical studies and there was an issue identified with the helix extension that was addressed by putting a Teflon coating over the helix to prevent crimping.

Three of our four helix extension issues were with the pre-modification leads so only one of the helix extensions occurred with the lead that had been modified to rectify this situation.

DR. BLINKER: What is your rate in the ventricular lead since the rectification of the situation of inability to extend the helix?

MR. HANNON: We have only had, the only failure to extend helix was this one in the atrium.

With regard to lead dislodgements, we have identified five lead dislodgements for a rate, as you said, of 5.2 percent. I would like to compare that to our experience with the model 6940 lead in the atrium which is a pace sense lead without the coil. That is 1.1 percent and to further put it in perspective, when the 6940 lead was being clinically investigated, that has since been approved as you are aware. The dislodgement in the Gem MR study was 4.3 percent. So furthermore, of these three dislodgements, three of the five were the first time that the investigator had used this lead with the coil on it. We are aware that the handling issues are different with this coil, and three of the five lead dislodgements were, in fact, the first time that the investigator used it and none of the investigators

had subsequent lead dislodgements.

Perhaps I would like to ask one of our investigators to come -

DR. BLINKER: Let me ask you a couple of questions about the potential and may be you will need somebody else to answer these, the potential downside of a lead dislodgement with a high frequency energy delivering coil lead. Let's suppose that the lead dislodged and fell into the ventricle and this is a two-lead system, and happened to lie in close proximity to the ventricular coil. And the patient developed V-fib. Is it possible that you would short circuit the current delivery and not successfully defibrillate the patient?

MR. HANNON: I would like to ask our system engineer to comment on that.

MR. HESS: Hi, I am Mike Hess. I work for Medtronic, as systems engineer for the project.

Yes, if the coil worked to dislodge in the ventricle and if there was insufficient displacement between the two of them, you could have too low an impedance and that could result in the short circuit in the device.

DR. BLINKER: So theoretically the dislodgement of this lead might have, might be more consequential than a lead that doesn't deliver energy.

MR. HESS: If you were to use in a more traditionalized CD an extra SPC coil perhaps to bring the DFTs down, and that was

literally connected to the can, if that lead is dislodged in the ventricle, you would have the same issue.

DR. BLINKER: But that probably won't, I mean, that would be very difficult to do it seems to me. Let me ask you the second question that bears upon this. Did you notice any decrease in atrial defibrillation thresholds between, at the atrial lead delivering the atrial lead with the high energy, with the coil and the ventricular lead in a two-lead system than you did with either a CS or a high SPC coil? In other words, is there an efficacy benefit to having a coil on the atrial lead as opposed to other traditional sites?

MR. HESS: In this study, we have not identified a difference. The DFT is using a system using the 6940 atrial lead. The mean DFT was 7.5 joules, and with the 6943 atrial lead it was 6.49. So it was lower but there was not a statistical difference between the two.

DR. BLINKER: So given all this, and I realize maybe we are much ado about nothing except for the labeling, why would one want to put this lead in as opposed to a traditional atrial lead in an SPC coil?

MR. HESS: I think that I will have some of the clinicians comment also but as you know with leads that are available right now, there are no ventricular ICD leads that are available that have two coils that can do true bipolar sensing. There are some on clinical investigation and some people feel

strong about true bipolar sensing for whatever reason. So if a person wants true bipolar sensing, then they only have one coil on that lead so they would need a second lead if they wanted to try to lower atrial DFTs and then it would be easiest for them to have that on the atrial lead. Steve, perhaps if you would comment about your experiences.

DR. MARKOWITZ: My name is Steve Markowitz. I am on faculty of Cornell University as an electro physiologist. I have no financial relationship with the sponsor other than an honorarium for this symposium.

I agree with the issue in terms of true bipolar pacing. There is indeed concern that the integrated bipolar sensing may have certain drawbacks compared to true bipolar sensing although that has not been established definitively. So it is the practice of some clinicians to use true bipolar sensing and as Dr. Stanton pointed out, that would therefore have required putting a coil lead in the atrium.

It is worth noting in addition that although you bring up a theoretical concern that had not been documented in this clinical trial and there are a number of conceivable scenarios that one could come up with although this has not been documented.

DR. BLINKER: Documentation would probably result in death so you probably don't want to document it. And you only had 96 patients that had this lead in. Let's leave this lead for

a second and get on to the other issues that I think are important. I guess I just want to, in case I get the hook here before I am done, I want to get to perhaps the only substantive thing I want to say about this and that is on your labeled indications for use, especially this second one that was sort of freestanding one, it says as a clarified that the Jewel AS system is also designed for patients who either have or are at risk of developing atrial tachyarrhythmias but is not currently indicated for patients who do not have VT/VF as stated above and I think that is true.

I would leave out the word not currently or rather currently and just put it is not indicated for patients that have VT/VF alone.

I think, and the gist of this is, I think, that this could be a very major advance the way things are going. I think atrial tachyarrhythmia therapy is very important but I don't think that this study and we can get into the ifs, ands, and buts, but this study validates a clinical benefit to the atrial arrhythmia, atrial tachyarrhythmia treatment that would justify the entire system's use for this indication alone.

I know you are probably going to say you didn't ask for that and that is good but I just, if we can clarify that, that will take away one of the FDA's questions and will further our discussion.

DR. MARKOWITZ: I think that is an excellent point, and

what we focused the presentation and the whole application is this is for the patient who has a ventricular ICD indication, a current indication as stated here. So it is not for the AF only population at all.

DR. BLINKER: Now, just as a point of interest, as long as we have that out of the way, on one of your slides, your secondary objective on relative risk of death, you point out that when you compare the Jewel AF to the Gem MR, the relative risk of death was statistically significantly decreased with the Jewel over the Gem MR in similar patient populations. That sounds terribly intriguing until you get to the bottom part where it says that if you had the atrial prevention turned off, there was no difference in the relative risk of death and, in fact, numerically it was probably higher if it was on than off so certainly if you believe in trends, and we probably don't for this way but if it trended the other way we would, you would think that there is no difference whether it is on or off unless the ability to, unless there is an improved ability to utilize the VF algorithm when you have additional super ventricular arrhythmia detection. So how do you account for those?

DR. MARKOWITZ: You raise some very important points and nice observations there. First off, I agree completely with you that I didn't want to oversell the point about the apparent reduction in death in atrial arrhythmia patients who got a Jewel AF compared to a Gem DR. This study was not designed to assess

that and as you said, we find that very intriguing as well.

Now, why was there not a difference shown in that? What I am going to do is postulate mechanistically. One hypothesis would be that the reduction of atrial fibrillation burden, the reduction of a time a person is in an atrial arrhythmia has an overall benefit for the patients. Rephrased another way, as we are learning particularly in the past year, atrial fibrillation by itself is an increased risk factor and an independent risk factor for death. If reducing the amount of time a person spends in an atrial arrhythmia has some physiologic benefit on the myocardium, then the person does not necessarily have to be in an active treatment mode at the time of death if their total arrhythmia burden has been reduced.

Let me explain a little further. It looks like Mike is getting a little antsy with my explanation but the analysis there of the on versus off is beyond just the 48 patients that were in the three month on, three month off. This was a complex analysis that was done to account for all patients when they were in versus all patients when they were not in on versus off. Does that make sense?

DR. BLINKER: Yes. And that may be true but you need a lot more evidence. Let me -

DR. MARKOWITZ: Yes, I am putting it out as a hypothesis.

DR. BLINKER: So let me ask you another question that

relates to this. After the six months, investigators had the option of programming. What was the rate of programming atrial prevent termination and again, termination is different than prevention. You have prevention algorithms so-called that are in there. I didn't see specific information as to their efficacy and I don't think you really have that but the termination algorithms I am more interested in because that is delivered therapy so the question is, what was the percentage of patients that had their termination therapies programmed on after the six month protocolization?

DR. MARKOWITZ; The calculator is out so I think you will get a number in just a minute or two.

DR. BLINKER: While he is doing that, just to keep things rolling here, you can determine atrial defib thresholds and in this mass of information, I didn't see, I assume you can program the defibrillator to the atrial defibrillation shock energy.

DR. MARKOWITZ; Yes, to be programmed up to 27 joules.

DR. BLINKER: Right. Was it typical that, was there a relationship between success of defibrillation and energy program?

MR. MANDA: Dr. Blinker, my name is Ven Manda. I am also in the AF clinical group. We looked at that particular end point and we found there was no statistically significant difference in the outcome of the therapy based on the program

time to atrial defibrillation therapies.

DR. BLINKER: Good. Did, Marshall, let me, did any of these patients, they had ventricular defibrillation thresholds retested?

DR. STANTON: That was not recommended even as part of the protocol. People may have done that as per independent centers. I don't know that we tracked that. Ven, did we track chronic ventricular DFTs if they were retested?

DR. BLINKER: What safety margin do you, I think this is important. One of the FDA questions were clearly this device is further differentiated from its predecessor by a lesser maximum energy of shock and I want to know what safety margin that you feel comfortable with and how would one express that in a labeling? Certainly the labeling of people who need more than 27 joules may not be good enough because people have different safety margins.

DR. STANTON: That is true of any maximum output. We would say the same things about a 30 or 35 joule device that anybody with a DF needing more than 35 joules is not indicated.

DR. BLINKER: So let me put it in a better way. By protocol, what was the maximum DFT that was allowed?

DR. STANTON: There were two different implant DFTs. One was meeting two successive successes at 18 joules and the other was using a binary search. You recall it could have been up-down, starting at 15? Starting at 12? Starting at 12. And

that had to meet DFT less than or equal to 18 by that method as well. So it was a nine joule safety margin.

DR. BLINKER: So do you think that it would be reasonable to put in the labeling that patients should meet these criteria?

DR. STANTON: I guess I would want labeling to be consistent across our previous devices and other devices. We are not setting a new lower limit. This is comparable to other devices that are out there for deliberate energy. We are happy to be consistent.

DR. BLINKER: Let me ask you this other question then. You gave the patient anecdotal experience of a patient who delivered a 50 herz burst in the heart fibrillated with defibrillated and then you said that notice that this defibrillation turned off atrial, does it turn it off until manually reset by a physician or does it turn it off -

DR. STANTON: Yes, it is permanently deactivated.

DR. BLINKER: Permanently until manually reset.

DR. STANTON: Reprogrammed. And I would also highlight that that was the only episode of 50 herz in the ventricle initiating a ventricular tachyarrhythmia.

DR. BLINKER: But the same algorithm would come into play if any atrial therapy was followed by a ventricular defibrillation.

DR. STANTON: A ventricular detection. Is that correct?

And, in fact, there were other instances where the ventricular, where the conduction accelerated during atrial arrhythmia therapy such that a ventricular arrhythmia was over-detected and in those instances, it is also inactivated atrial therapy.

Dr. BLINKER: What mode of therapy for this device, and I assume this can be done quite easily but maybe I am wrong. I think one of the designs for this device was a patient-activated atrial defibrillation mode and this was not pursued for whatever reason but there should be an easily accomplished physician activated atrial defibrillation entity using the device. How many patients actually had atrial defibrillation spontaneous occurring atrial fibrillation defibrillated by the physician using this device during a hospital or office visit?

DR. MANDA: There were two patients in this series who had experienced, used the patient activator. One of those patients had one episode in hospital but there was very few episodes in those two patients. In general, I think there were seven episodes in those two patients that were defibrillated using a patient activator. Because of the limited data and experience, we did not include that in the solution.

DR. BLINKER: And this is an exceedingly interesting device and we can't even hope to accomplish in one afternoon a discussion of all the potential uses of the algorithms and programmability that is very impressive so I want to give other people a chance.

DR. CRITTENDEN: I don't have much. I am just trying to learn a little bit more about this. If you recall, I am a cardiac surgeon and talking to an electro physiologist to me sometimes is like men from Mars and women from Venus. We can try and communicate but often we are not communicating.

We think that a five hour reduction in the AF burden leads to improved survival? Or is that just true and unrelated?

DR. STANTON: Very good question. Again, I don't want to over-emphasized the improved survival with the Jewel AF. We found it very intriguing and we don't have an explanation. The study was not designed to come up with an explanation. It wasn't even designed to be able to detect that.

DR. CRITTENDEN: So if this was approved you wouldn't market it in that way. Is that correct?

DR. STANTON: We are not asking for labeling based on that.

DR. CRITTENDEN: I couldn't find any mention of anti-arrhythmic therapy in these paces. Is the goal here to try to manage these patients completely with out, in a non-pharmacologic way because of pro-arrhythmia effect or mortality effect? Can you kind of elaborate on that for me?

DR. STANTON: Yes, very good question. Let me have Dr. Wharton give a clinical response and then we will give some statistics from the study on specific anti-arrhythmic.

DR. WHARTON: I don't have specific data in regard to

the frequency of use of anti-arrhythmic drugs but in this patient population given the frequency with which they have atrial fibrillation or other atrial tachyarrhythmias, I would say it is probably the rule that most of these patients are on some type of membrane stabilizing drugs, either a class one or a class three to try to decrease the overall frequency of atrial fib recurrences and that is particularly keeping in mind that one of the goals of this type of therapy is certainly to have back-up electrical therapy for treatment of atrial fibrillation episodes.

The counterpart to that, that was because the shocks can be uncomfortable for the patient, we are trying to limit how often that has to be applied so drugs are used, I think, in probably most of these cases.

DR. CRITTENDEN: Do you know if that is equally distributed? It seems to me, and again, please, educate me if I am wrong, that would kind of color how we interpret the results knowing what anti-arrhythmics in the distribution between groups. Would that not be the case?

DR. WHARTON: Are you talking in relation to the Gem MR data?

DR. CRITTENDEN : Correct.

DR. WHARTON: Except that the Gem MR data specifically that they compared it to was, where they shared the reduction, was a group with a similar density of atrial tachyarrhythmias so

again, presumptively, and I am not quoting data here, but just presumptively, similar anti-arrhythmic drug use.

MR. HANNON: To answer your initial question, we did not control for anti-arrhythmic drug usage. It was at the discretion of the investigator to keep the patient on any anti-arrhythmics he felt appropriate, he or she felt appropriate. What we do collect, however, what anti-arrhythmics they have been on, and 40 percent of the patients have been on either a class one or a class three anti-arrhythmic for rhythm control and at the same numbers, 40 percent have been on either class two or class four so either beta blockers or calcium channel blockers for weight control but 40 percent have been on anti-arrhythmics. H

DR. CRITTENDEN: And one last question that again, forgive my ignorance but is there no fear of embolic threat here? Did you guys track that at all? Is that, again, am I kind of off base with this?

DR. HANNON: We track it. Again, anti-coagulation is left up to the discretion of the investigator and we have 90 percent of the patients have been anti-coagulated. We have had three patients who have had strokes, three out of 303 so one percent. Two strokes and one TIA.

DR. CRITTENDEN: These are people who had the program on

DR. HANNON: No, not necessarily. All three of these patients were anti-coagulated. Out of the three strokes, two of

the three patients had no atrial therapies other than the implant testing and one patient had an atrial defibrillation shock six months before the stroke event.

DR. CRITTENDEN: That is all.

DR. WHARTON: If I might add just in regard to the stroke issue, clearly not addressed in the study but theoretically this type of device could hopefully decrease the risk of stroke if appropriately programmed so that you are shocking atrial fibrillation episodes for the duration is long enough to allow accrual to clot in the left atrium.

DR. STANTON: Getting back to a question quickly that Dr. Blinker had asked. At six months follow-up, 67 percent of patients had atrial termination therapies active.

DR. BLINKER: You mean after they were done with the protocolization.

DR. STANTON: Right.

DR. BLINKER: Is there a reason why the others did not?

DR. STANTON: It was up to clinician discretion. Do you have any vignettes about why you might have therapies off? Remember, some of the patients were in the VT only group and so -

DR. BLINKER: Is that true? Did the VT only group? They weren't randomized.

DR. STANTON: Oh, I am sorry. The 67 percent is the entire PMA ouplation.

DR. BRINKER: I just wanted to know what the group that

went through the process.

DR. STANTON: We will get back to you with that one.

DR. MARKOWITZ: As an investigator, there was certainly at our institution, preference to use after the six months certainly the prevention and pacing algorithms for termination. I mean, we felt comfortable but the safety felt that there was a likely benefit in reducing the AF burden. Again, this comes to philosophical issues that Dr. Wharton mentioned but we did believe that there were perceived, potential benefits of reducing the AF burden such as hemodynamic benefits and reduction in ventricular arrhythmias by reducing hemodynamic stresses in the heart so given the -

DR. BRINKER: Maybe I misunderstood you but I thought you said that you had the pacing algorithms on but did you mean also that you had the atrial defibrillation out?

DR. MARKOWITZ: That was left to the discretion of the investigator. Personally we program pacing algorithms and tended not to program defibrillation algorithms for the atrium.

DR. BRINKER: And how much of that was because you were concerned about longevity of the device and how much of it was because it was not really that well tolerated by the patients and there were recurrent AFs and stuff like that.

DR. MARKOWITZ: It was primarily the latter. We preferred to provide a non-shock therapy.

DR. DOMANSKI: You know, I just, I would like to go to

this slide that you have. You don't have to flash it up here because we have it in front of us, but the secondary objective on relative risk of death. I just want to be sure I understand this. I probably don't but if I do, it doesn't make a lot of sense. This is Jewel AF versus Gem DR. Indeed, this is, so you have got a relative risk of death and this is completely unadjusted. Is that the bottom line there? Is this adjusted for other differences?

DR. STANTON: I don't think so. That is not adjusted. That is all enrolled patients, that is not adjusted.

DR. DOMANSKI: So it is not adjusted but then if you come down and say atrial, so you don't turn on your atrial prevention or termination rhythm, therapy, so if the thing is on, you albeit not statistically significantly, appear to have increased relative risk. Is that right?

Just reading, is atrial prevention or termination therapies on or off. So if the silly thing is on, your risk appears to increase, admittedly non-statistically significantly and yet you are showing a massive reduction in relative risk of death.

I really have a problem with this table. I don't think it means anything as it is currently written because, for a couple of reasons. One is that it is unadjusted and you may have baseline differences. Secondly, there is absolutely no mechanism suggested by this certainly not prevention of atrial arrhythmias.

So that I think while in many settings atrial fibrillation is indeed a negative prognostic indicator, I don't even have to say the obvious, that is, that preventing it doesn't not necessarily mean that you are going to reduce mortality even if it is a risk factor, it may just be a marker but I don't even have to say that because here, I would suggest that this table is not useful in terms of suggesting that this device is useful.

DR. STANTON: What I would like to suggest from that table is that the Jewel AF does not increase mortality. I think that is the big take on it.

DR. DOMANSKI: I am not sure that is true.

Interestingly, well, I am not sure it is true but I am not sure I am right about this. I don't mean to be argumentative but the atrial prevention of termination of services, the relative risk is increased and you are going to say that there is yes, the P value is .61, it doesn't mean anything. I wonder what your power is to see a difference. It would be interesting to know the power. I just think -

DR. STANTON: I am going to have the statistician, Jim Johnson, comment in a few minutes. What I want to really drive home about that is that this is a secondary objective. We did not power the study to detect this. We were certainly not trying to address any mechanisms. This was an unanticipated finding.

DR. DOMANSKI: I understand.

DR. STANTON: And my only explanation which I will try

to reiterate a little bit, and this is hypothesis, I have no data to support this, but if reduction of burden, of the time that a person is AF, conveys a benefit to the myocardium such that whether you have atrial fib prevention and therapy on at the time of death or not, does not matter, you could be, you could have a benefit for your long term survival. That is pure speculation.

DR. DOMANSKI: So if it were on at other times in other words.

DR. STANTON: Right. Because the analysis down there takes into account the entire population who often, those in the randomization certainly had it on and off for certain parts and those were not randomized also had it on and off at the clinician's discretion. So it is a complex analysis that was done for that. I would like Jim to make some comments about comparability of the Gem DR and Jewel AF population and also a little bit about how the analysis was done on the lower part of that table.

DR. DOMANSKI: Incidentally, as you start, the reason for pressing this issue is not to pick at a small point. It is just if one were looking for a reason to say that this thing ought to be put in that it ought to be approved for marketing, this potentially could have been something that would have been supportive of that and I guess I am concerned that it is not supportive of that. But perhaps you could comment.

MR. JOHNSON: My name is Jim Johnson. I am the

statistician. I work for Medtronic.

To give you some idea of the analysis that went into both endpoints, when we compared the mortality to the Gem DR, we restricted it to six months because the Gem DR didn't have follow-up beyond, had very little follow-up actually in three to six month period. If anything what we noticed is there was an usually high rate of mortality in the subset of patients in the one to three month period in the Gem DR, compared to what we had in the Jewel AF.

DR. DOMANSKI: Is there any adjustment for baseline risk factors?

MR. JOHNSON: Not in the analysis that was presented because we did that and did not identify any. If anything, the two covariants that were different in the patients were body mass index and a slight difference between congestive heart failure. The P value was .09. But the only two that were, that could have an effect but we didn't include them in the model.

DR. HARTZ: Are you sure that the ejection fractions were identical in these two subgroups?

MR. JOHNSON: Which two subgroups were you talking about?

DR. HARTZ: The VT/AT and VT.

MR. JOHNSON: The VT/AT group. Yes, they were.

DR. DOMANSKI: So those things were all, this is an important point. The two covariants -

MR. JOHNSON: Body mass index and congestive heart failure.

DR. DOMANSKI: And when you plug those in, what was your relative risk in your multi-variant model?

MR. JOHNSON: It was very similar. It was 1.2

DR. DOMANSKI: It was very similar. So what we have is a difference in survival that is totally unexplained.

MR. JOHNSON: Right, I agree.

DR. BRINKER: One of the questions that the FDA asked before was, in their questions here, is why you chose the Gem DR rather than I guess the -

DR. STANTON: 7219C was the original one.

DR. BRINKER: And if, I assume you made the same comparison of relative risk of death between those two groups anyway. How different were they?

DR. STANTON: I will start and then turn it back over to Jim. The 7219 C was listed as the comparator at the onset of the study because the Gem DR was under its own clinical and was not approved. We went through the rationale for comparing the two. They are both dual chamber defibrillators, they both take two leads. They both take two leads. They both have PR logic. We thought it was a better comparator.

DR. BRINKER: But this just gives us a broader window. If that was exactly or almost the same as the Gem DR, then you have an enriched number. On the other hand, if the risk was

lower and it turned out to be relative risk of death in the Gem DR, maybe the Gem DR was a peculiar population and that is why there is such a big difference.

DR. JOHNSON: We did the analysis in your original PMA and met the objectives at that time. I don't have the numbers with me, but we didn't do the, didn't present the results comparing the Jewel AF to the 7219 C in the update primarily because we met the objective in the original PMA and just for a matter of keeping, being consistent we just decided to present the results in the panel packet with the Gem DR.

DR. DOMANSKI: The only other question I have is the numbers are really pretty small. When you go through your power calculations or at least your assumptions relative to power in this study -

MR. JOHNSON: With respect to which?

DR. DOMANSKI: The primary endpoints.

MR. JOHNSON: The system-related complication endpoint, the way we calculated the sample size was that we, the rate of system-related complications in the 7219 C subset of VT/AT patients was, the hazard rate was about 1.2 percent. Now, if we assume that was a constant hazard, at three months, that is freedom from system-related complication of approximately 96.5 percent. We said we would, it would be acceptable if we had a lower bound on the estimate from the Jewel AF of, if the survival was, freedom from complication for survival at three months was

90 percent.

DR. DOMANSKI: So it was a six percent absolute difference.

MR. JOHNSON: Right, and it comes out. Again, if you go back and determine the hazard base and submit that, we came up with a relative ratio of three.

DR. DOMANSKI: And your power to see that in this study was what?

MR. JOHNSON: Well, the sample size we came up with based upon that, with a power of 80 percent, we came up with a sample size of 70 patients. So we were well powered to meet that objective with 221, uh, 230 patients which is a subset of the VT/AT patients.

DR. GILLIAM: I have several I guess questions and concerns. I think I start by saying that I am not so sure that this is an equivalent ventricular device as we are using for ventricular defibrillation, a lead assignment that is different than you typically have used in your other device. I think with the placing the call on the atrial lead and using that in that manner, alters at least in some way and I would ask, I wonder if Dr. Wharton would like to comment whether, is it possible that we have not gotten enough data to compare that this particular type of VF protection? You would only have 96 people so I don't think you would have enough data to really to see a particular big problem but I don't want to walk away saying we have demonstrated

there is no difference between this device and the Gem DR.

DR. STANTON: I am not sure I quite understand your question.

DR. GILLIAM: Essentially we have the atrial lead, the lead that is moved with the coil in the atrial lead as opposed to either a two-coil system or an SPC lead or even a device with shock, a ventricular lead. So I am just concerned that, do we have enough data or is the people who have implanted this, have you seen enough defibrillation threshold testing to know at what level of confidence you have that you are going to reliably defibrillate people from VF with this device with the altered lead configuration.

DR. STANTON: Just from a theoretical construct, first off I don't think it is that different from an SPC, RV type coil so I don't see that much concern just from a practical point of view and I think the data is sufficient to say that it is safe and consistent with other data as well from other types of studies.

I think it is a good question, and one of the things that we have done in the past is we have done a lot of modeling of ventricular defibrillation looking at what are the differences between having coils in a lot of different positions and I would like to ask Rahul Mehra, one of our senior scientists to comment on that.

DR. MEHRA; Again, I am Rahul Mehra and I am an employee

of Medtronic. As Dr. Marshall Stanton pointed out, we have done a lot of theoretical modeling and have shown no difference in terms of the position of the SVC lead, whether it is high SVC, middle SVC or low, sort of mid between the SVC and the right atrium.

Concurrent with that, there was a recent abstract presented by Dr. Michael Gold. In fact, I was reading it on my way in. It was just going to be presented at Berlin which is a clinical study where they prospectively looked at the effect of very low SVC positioned slash RA to high SVC position using campos SVC to RV as a defibrillation vector and found no difference in ventricular DFTs. So I think the modeling and the clinical data support that it is not a big difference.

DR. GILLIAM: To that end, I guess the next question would be, if you were using a two-coil system, is there, and I guess a single regular pace sense atrial electrode, is there any advantage or disadvantage for your atrial defibrillation threshold testing? I tried to really get a handle on your atrial defibrillation threshold testing and I can't say that I have an appreciation that I saw the advantage maybe of this particular new lead system demonstrated anywhere.

MR. HANNON: If I understand your question, you asking about the atrial defibrillation thresholds with the 6940 pacing lead versus the 43 with the coil in the atrium?

DR. GILLIAM: That is right.

MR. HANNON: There was not a significant difference. The DFTs with the 6940, the pace sense lead in the atrium, the mean DFT was 7.5 joules plus or minus 5.6 and with the 43 lead in the atrium with the coil, the mean DFT was lower, 6.9 compared to 7.5 with the standard deviation of 5.5 so there is no statistical difference between the two thresholds.

DR. GILLIAM: I would like the sponsor to comment on, I am looking at the FDA page 4-22. This is an intentional treat analysis looking specifically at device explants. It concerns the 10 patients not implanted with the model and eight of ten of the patients there were explants with several, several with device failures. Specifically I am concerned that there were essentially almost six cases in which there was some type of short circuit or low resistance in the transistor occurring one after death in device explant, one showing, I would just like some idea. This seems like an awfully large number of device failures early on. I mean, given that we have not had this device out there very long. The six mechanical failures of the device.

MR. HESS: Two of the failures were related to a design issue that was discovered during the clinical. And a subsequent design change was made to prevent that probability from occurring. Two of the short circuits occurred in the pocket, and they were related to a lead insulation damage delivery to the active can. One of those was a lead which was being used over

from a, it was a replacement situation so the lead wasw about four years old with a new implant and the other case there, the insulation was damaged by the suture tie-down and there was a breach there in the pocket and that caused device damage.

Of the remaining two, one of them involved delivery on a previously untested electro-configuration that you can have up to three coils in the heart plus the active can. In the hospital setting they undelivered a 27-joule delivery using all four electrodes and they had never done a test shot previously and the impedance was too low in that whole composite system and that resulted in a short circuit. We generally recommend you do a test charge on any pathway you are going to use before you deliver a full energy charge.

And then in the last case was a short circuit where we were not able to conclusively determine the cause of the short circuit. The damage to the device when this happens is quite extensive.

DR. GILLIAM: To that end, I noticed that you have and this is something that I have seen out there, a .2 joule, a high voltage discharge to measure the high voltage lead impedance. Are you saying perhaps something to that level would have perhaps detected an in-circuit short circuit that would have led to maybe the higher voltage? My experience has been often that some short circuits to that degree, a small amount of current, delivered even if you were to go up to even a joule of energy delivered may

not pick up that type of short circuit until you get to the higher voltages.

MR. HESS: If they had done the .2 joule monophasic test charge, that would have reported back a very low impedance. In fact, when they did a similar test at the explant of that device using just the three coils, the impedance measured by our DSD was, I believe, 22 ohms. So 22 ohms in conjunction with the can would be less than 22 ohms so that would put us below the recommended lower end for what a safe defibrillation impedance would be.

DR. GILLIAM: Just a few more questions concerning looking at your system complications again, particularly the lead, I think we have already touched on the lead dislodgements. I sort of echo that that seems to be an awfully high number of atrial lead dislodgements, out of 96 to have five percent, particularly since I am assuming these are all by a very skilled operators and particularly, it seems quite high and I will give your operator experience but that is something that we certainly would have to approach in labeling because there must be some magic that they have learned if they have done it once. I don't think anyone who implants an atrial lead says I really didn't do a good job on this one and are surprised when it is dislodged. I would like to understand from the implanters what did they learn.

DR. STANTON: I will ask Dr. Wharton to address that in one second. I will just reemphasize that certainly compared to