U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

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CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

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88TH MEETING

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FRIDAY
APRIL 30, 1999

The meeting took place in the Jack Masur Auditorium, National Institutes of Health, Bethesda, MD, at 8:30 a.m., Milton Packer MD, Chairperson, presiding.

PRESENT:

Milton Packer, M.D., Chairperson
Joan C. Standaert, Exec. Secy.
John DiMarco, M.D., Member
Thomas Graboys, M.D., Consumer Representative
JoAnn Lindenfeld, M.D., Member
Lemuel Moye', M.D., Ph.D., Member

PRESENT: (cont.)

Ileana Piña, M.D., Member
Dan Roden, M.D.C.M., Member
Udho Thadani, M.D. FRCP, Member
A. John Camm, M.D., Guest Expert
Craig Pratt, M.D., Guest Expert
Jeremy Ruskin, M.D., Guest Expert
Robert Fenichel, M.D., FTIA Representative
Robert Temple, M.D., FTIA Representative

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:56 a.m.)

DR. PACKER: Can I have everyone take their seats. I would like to apologize. For some reason my own notes indicated the meeting was going to start at 9:00 so I really am very, very sorry that we are starting late. It is entirely my misreading of my own schedule.

Joan, do we have any special conflict of interest issues for this morning?

MS. STANDAERT: The following announcement addresses the interest of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of SCD at this meeting.

Since the issues to be discussed by the committee will not have a unique impact on any particular firm or product, but rather may have wide spread implications with respect to an entire class of products, in accordance with 18 U.S.C. 208 each participant has been granted a general matters waiver which permits them to participate in today's

discussion.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12, A30, Parklawn Building.

In the event that these discussions include any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. That completes the conflict of interest statement.

I would also like to make an announcement on behalf of our transcriber who has asked that all participants address the microphone directly because there appears to be quite a bit of feedback from the roof here and she has difficulty hearing. Thank you.

DR. PACKER: Thank you very much, Joan.

Is there any public comment this morning? Okay. There being none, we will proceed with the topic for this morning. Actually there is no NDA for this morning. We are discussing general issues related to the evaluation of antiarrhythmic drugs in patients with an ICD.

The ICD is actually used in this case as a way of measuring antiarrhythmic drug efficacy. There have been a number of studies and a significant amount of information of relatively recent vintage pertaining to this. Therefore, it was felt that putting all this information together and trying to develop some sense of consensus or guidance would be useful.

With that in mind, we'll have actually five presentations by invited guests and experts. Also by one member of the committee. The idea is to develop an interchange and to reach some sense of what we may be doing or what direction we should go.

The intent of this morning is to take a brief break but to complete these proceedings before lunch. Lunch perhaps would start around 1:00. We may

adjourn about that time and hopefully we'll meet that deadline. With no further ado, we will ask John Camm to come to us and introduce the topic for this morning's session. John.

DR. CAMM: Thank you very much, Milton. I would like to take this opportunity to thank Ray Lipicky and Craig Pratt for setting up this meeting today. I don't know what the protocol is but I would also like to thank the members of the cardio-renal advisory board for staying to listen to this series of presentations.

As Milton already mentioned to you, we are going to address the issue of ICD endpoints as applied to clinical trials predominately pharmaceutical agents.

My particular interest in this area was born from a wish on the part of the European Society of Cardiology Working Group in cardiac arrhythmias to design a trial using an ICD supported population to explore the antiarrhythmic interaction between beta-blockers and amiodorone.

The notion was a simple trial design, at

least in theory, with a factorial design between amiodorone and beta-blockade and their respective placebos, acute testing in a population fitted with an ICD prior to the start of the trial. Then acute testing followed by long-term follow-up.

So far so good. The issue that tantalized us was what endpoint could we use in this trial in order to access the antiarrhythmic activity of these two component drugs. We know, of course, that there were other trials underway which were exploring antiarrhythmic efficacy drugs of other types using models of this kind of trial. But we are unsure about the feasibility and the reality and the probity of using the endpoints that other investigators have decided to apply to their trials.

I think it's germane in this very brief introduction to demonstrate to you that there are basically three trial designs in which ICD may play a part. This is the traditional design in which the ICD is merely tested against another therapy. For some years, as you recall, we had a concept of hypothetical or projected mortality which was developed such that

patients fitted with ICD's could act as their own controls in such a way that the value of the ICD could be compared against the hypothetical patient who would not have had the ICD.

However, after a good deal of debate in the cardiological arena, it was rapidly decided that the concept of hypothetical mortality was a dubious probity. Instead the all-cause mortality endpoint was encouraged for all trials of this nature. I've listed a few of the trials that you are very familiar with which have now been completed of this particular design. This includes trials of so-called secondary prevention and primary prevention.

Indeed, the so successful have been these three trials in secondary prevention, AVID, CASH, and CIDS, all of which show to a degree, and certainly together, support the fact that the ICD appears to be better than other conventional NDA antiarrhythmic therapies. It is, I think, unlikely there will be other large-scale mortality trials for this design.

We know that there are still a few such trials underway, but they are generally smaller trials

and unlikely to produce any further data except in support of this general conclusion that the ICD is better than current antiarrhythmic therapy for the management of patients with life-threatening ventricular arrhythmia.

However, there is a second circumstance in which ICD's may play a part in a clinical trial of a pharmaceutical agent against another active control agent or against placebo. This kind of trial will involve patients at high risk to sudden cardiac death but it may not involve patients who have already suffered from life-threatening ventricular arrhythmias that may include patients who have a high risk of suffering in the future from ventricular arrhythmia.

In this kind of trial a drug is compared against a placebo or another active comparator. This trial is not a trial of ICD efficacy. The ICD is simply in place in various patients and may range from merely an instrument which will perturb the general mortality endpoint signal to one in which the device may be used to contribute to the mortality signal or to other endpoints within the trial.

In many CHF trials that are currently underway, patients with an ICD may be enrolled unless specifically excluded by protocol. That might end up at the present time with a smattering of ICD patients on one or the other or both sides of the equation. In some trials there are large numbers of ICD patients. I draw to your attention the CASCADE trial in which this was the case.

Such may be the case in future trials of pharmaceutical agents for the indication of congestive heart failure treatment. In such trials thus far the major endpoint has been all-cause mortality but composite endpoints have been developed to include not only all-cause mortality but also a variety of events of a therapeutic nature which have been provided by the implantable cardioverter-defibrillator.

I mentioned to you the example of CASCADE. You will recall this very clever acronym which stood for Cardiac Arrest in Seattle: Conventional versus Amiodorone Drug Evaluation which was reported in a number of papers. The particular paper I allude to is that by Dolack in 1994. The basic population was 228

patients with high risk of recurrence of out-of-hospital cardiac arrest.

The endpoints in this study were composite. They included cardiac death, resuscitative ventricular fibrillation, and ICD shock of an appropriate type defined by its association with syncope.

The basic trial result was that empiric amiodorone when compared against programmed stimulation guided class I drug therapy was successful with a 9 percent recurrence of the endpoint versus 23 percent.

Within this trial there were a large number of patients with implantable cardioverter-defibrillators, 105 in all. Here are the results for those patients alone expressed in terms of the composite endpoint of shock-free survival. The patients were obviously still alive and they had not received a shock from the device. You can see that using this composite endpoint, a result very similar to the result of the trial as a whole was achieved.

Except I think you will notice that the

actual numbers are substantially different with endpoints amounting to about 12 percent on the amiodorone side and about 58 percent or so on the class I side.

The third trial design is the design which I think presents to us the greatest challenge at the present time. In this trial the ICD is on both sides of the randomization and all patients within the trial a fitted with an ICD. The design of the trial is two-fold or the purpose of the trial could be of two types. Firstly, to explore the antiarrhythmic efficacy of a therapy for a patient who suffers arrhythmias despite or because of the presence of an ICD.

On the other hand, the trial which stimulated my first consideration was a trial where the ICD was not specifically relevant to the therapy of the patient but it did provide at least in theory, and more of this later, a safety net which would allow ethically a trial of an active therapy against a placebo therapy in patients with life-threatening ventricular arrhythmia.

In trials of this nature, the ICD acts as a passive monitor and an active therapy. It is the interaction between these two roles that deserves particular attention this morning.

I know that there are four trials which have been conducted of antiarrhythmic drugs using trial designs of this nature. Later in the morning some of the results from these trials will be discussed in a generic fashion. In other words, not attributed specifically to one or the other of these drugs. I think that all four of the trials are now completed, although I have not seen official reports or peer review reports on any of these agents.

My last slide in this introduction recalls for you that we are reentering a phase of argument that has gone before. NASPE issued a policy statement in 1993 which discussed in large part the standardized reporting of ICD patient outcome. At that time their concern was with trials of ICD therapy. Today we must face the same arguments to consider trials utilizing the implantable as a protection on the one hand and as an instrument or monitor on the other.

Thank you very much.

DR. PACKER: John, we'll just pause for some brief questions from anyone on the committee on any of the issues that you brought up.

Yes, Ileana.

DR. PINA: John, how would you classify a study such as MUS or the CABG patch trials that are going on right now which, I guess, you would call them primary prevention because none of those have had an event.

DR. CAMM: In the cardiological arrhythmilogical community these are casually known as primary prevent trials and there are a large bevy of these trials. They are of the design I that I put up on the screen. These trials are largely still proceeding, although three have been reported, MADIT and CABG patch and, more recently, MUS.

DR. PACKER: I guess they would be design I but primary prevent design I as opposed to secondary prevention design I. Udho?

DR. THADANI: John, in your trial design II one of the concerns always is there is a

proarrhythmic effect of drugs. If you look at your second all-causes, fine, but when you look at the shock-free survival, how much you are really driven in the absence of the placebo group to be absolutely sure that the results are not artifactual, that it might favor a drug when another drug is actually making it worse. That's point one.

Point two also is some of the ICD patients, if you just put at random for trial III, for example, they might have nonsustained VT but they tolerate it. The fact that VT was more than 30 seconds of algorithm at the moment of trial, how do you get around that? There's no logical way unless one of the issues that each of the II and III trials is compared to all-cause mortality. I was just wondering if you would comment on that.

DR. CAMM: Well, with respect to your second point about nonsustained ventricular arrhythmia that might trigger the device, we agree that is one of the complexities of using this instrument as a trial monitor because it also intervenes and perturbs and points signals. A large part of the presentation this

morning will, in fact, consider that in detail.

With respect to your first point, could you just quickly remind me?

DR. THADANI: Proarrhythmic effect of drugs when you just evaluate in the endpoint of the shock free.

DR. CAMM: Yes. I admit that in my second design I did admit the potential for having an active comparator rather than a placebo. Under such situations I think in general terms we are faced with the predicament that you raised. I don't think it is specifically greater in this particular form of trial except that proarrhythmia is also a consequence of an ICD and, therefore, adds another dimension to be considered. That, again, will be considered later this morning.

DR. MOYE: I wonder if you could briefly speak for the sensitivities and specificity of the ICD?

DR. CAMM: Again, we will discuss that as part of the program this morning. I would rather than anticipate the contribution of others in that regard.

DR. PACKER: JoAnn.

DR. LINDENFELD: We may get into this later again, too, but could you just discuss for me the relative incidence of serious bradyarrhythmias and the validity of that as an endpoint and how we would measure that particularly as we talk more about people with heart failure.

DR. CAMM: Yes. I am going to mention this particular point in my second presentation, but I was not going to talk specifically about the incidence of bradyarrhythmia. That has been variously estimated in ICD populations from approximately 15 percent to 50 percent. Because this depends on how you define bradyarrhythmia and the significance of that bradyarrhythmia.

Undoubtedly it is relevant because it is certainly again modifies electrophysiologic substrates and will modify the response of an antiarrhythmic therapy with may, for example, be particularly effective or ineffective or proarrhythmic or antiarrhythmic at particular rates. It is very relevant when you seek to extrapolate the results in

a trial supported by an ICD to a population that might not be so supportive.

So it is certainly a very relevant question within the terms of the generalized ability of results flowing from ICD supported trials to populations at large.

DR. PACKER: John.

DR. DiMARCO: John, you may be talking about this later but maybe you can give us a hint. If you are looking at drugs, either comparing a drug to placebo or comparing two drugs, do you think the device has to be kept standard? In other words, do you have to have a single capability or a single set of capabilities in the device and does the programming of the device have to be relatively standard in the population?

DR. CAMM: Indeed I will be discussing this later. Essentially my story line is that in the first place devices were nonprogrammable and, therefore, this issue did not arise as they are becoming increasingly programmable and some form of standardization should be contemplated for a variety

of reasons that I will discuss later.

DR. PACKER: It sounds like we are very anxious to go forward and do the other presentations. I just have one question. I guess design III theoretically in a sort of crazy way could be used as a monitor, not only for antiarrhythmic interventions but for proarrhythmic interventions. I don't know if that is something you'll be bringing up.

DR. CAMM: I believe it will be a fundamental part of the presentation.

DR. PACKER: Why don't we move forward. Sounds like that's what we all want to do.

DR. PRATT: Well, first of all, before I begin, my thanks to Bob Fenichel and Ray Lipicky for organizing this. Good morning to Dr. Temple and the committee.

My task will be to sort of review some of the designs that have actually been done and we're going to be talking about design type III. There are a number of trials. I'm just going to go over some general principles here and differences between four trials that have already been completed. As John

said, now three have been analyzed. One actually probably never will be analyzed as the data has been accumulated. All these trials have some primary ICD endpoint. It could be one of many kinds and I'll talk about that a little bit.

Secondly, the sample sizes have been in this range based upon some estimated placebo event rates. The duration of the trials has primarily been at a year and some at six months. One might argue this is long or not long enough to really appropriately evaluate both efforts and safety of an antiarrhythmic drug.

Notice the estimated placebo event rate. That is how often the investigators estimated that there will be a discharge within a year. That's quite a range. Needless to say the people that estimated this might have presumed a sample size here and the people of this a sample size here and that might be true.

There's a lot of other issues that have been different in the trials. One of them you have actually heard presented here had stratified

randomization by ejection fraction. One of the trials actually was smart enough to think that they might need an interim analysis to adjust for sample size; that is, if their ICD discharge rate and the way that they defined it was not adequate if they would go ahead and they would change the sample size.

The degree of prespecified ICD interrogation is an interesting feature and I think you're going to hear a lot about that today. Some people have done this with just an investigator analysis of whether or not there was an ICD shock if the investigators analyzed the appropriateness of that shock. Others had a simple committee or a group of experts that looked at all the ICD interrogations and made their own independent guided decision regarding that.

The definition of primary endpoint, we'll come back to this after I show you a couple of clinical trials. I think there are some important issues here. One can talk about time to first appropriate ICD shock, appropriate for VT or VF.

One can talk about total shocks. I guess

a patient doesn't really care whether it's appropriate or not. That still bothers the person.

Then one needs to ask whether you're talking about the tiered therapy; that is, the tachycardia/antitachycardia pacing or you are just talking about simply the number of shocks for VT/VF.

One of these trials was smart enough to think that this might be a good way to explore a dose range of their drug. Of course, that does have implications for their sample size. There have been a number of these trials that have not only entered people when they have their new ICD put in at a time when they might be presumed to have a higher event rate but when they came back to have a new battery installed in a generator. At that time one might wonder about the frequency of those events. Different trials have tried to estimate that by having required a ICD discharge within three to six months but some have not.

The degree to which there is in-hospital testing and the appropriateness of the follow-up testing varies greatly between these trials. That

might be of some interest. Also, the timing of the efficacy evaluation. Interestingly some of these are typical randomization intention to treat. Some of them have a required waiting of X number of half lives prior to the counting of primary endpoint.

My goal is not to talk about drugs. My goal is only to talk about the trials so you see that we're going to talk about antiarrhythmic drugs, not individual files. So that's antiarrhythmic drug.

This first trial is one that took patients that had an ICD implanted for VT/VF or cardiac arrest. The ICD had to have adequate electrogram recording capability, although different devices were allowed. The design was 12 length randomized parallel placebo controlled design.

This primary endpoint is time to first appropriate ICD intervention. It's quite different than the second trial in that they count shocks for VT/VF or tiered pacing for VT/VF. This is a composite endpoint that does not include death but includes an independent committee that looks at the appropriateness of these shocks or pacing

intervention.

The kinds of patients, these are patients that basically have low ejection fractions, some clinical heart failure, mostly male, and already on a variety of other antiarrhythmic drugs. In both these trials sustained VT is about two-thirds of the patients and VF one-third. Here it's more like three-quarters and one-quarter. There is primarily patients that have had VT. Here is one thing that you can do. You can just look at the defibrillation threshold of these drugs. That's one thing that is very worthwhile.

Here is the primary endpoint. Remember, this endpoint here is timed to first appropriate ICD intervention for VT/VF whether it be pacing or whether it be shock. We can see that there was pretty much a wash here. The one year estimate of event rate was pretty on target here. It was about 60 percent of the patients that had an event. There was no difference between these two groups.

Now, when one looked at other things like total shocks, the antiarrhythmic drug had less total

shocks than placebo. There was a longer time to the first ICD intervention in general, but when one looked at the endpoint that they picked as the primary endpoint, that was the result that they got.

Here is a second trial. It does have a significant number of differences. In the first place, patients had to have either a new ICD or generator replacement within three months with evidence of a shock within three months. Sample size was larger.

Primary endpoint this time is quite different. Timed to first all-cause shock. Any shock but not tiered pacing. We have no information in this trial about pace termination. It's all all-cause shock. Stratified randomization by ejection fraction and the same kind of analysis that was done in the first trial.

When we look at the characteristics here, these patients have higher ejection fractions but otherwise were patients with little or no congestive heart failure and they looked pretty much like the previous group, four-fifths male and a lot of patients

with coronary artery disease. A majority having presented with symptomatic or invisible sustained VT rather than aborted sudden death.

Here was this result. This result is quite different. First of all, this drug does beat placebo for this primary endpoint but this is all-cause shock. This could be due to VT/VF. It could be due to a shock for atrial fibrillation and nonsustained VT. It does not include the tiered pacing events. At one year the event rate is actually smaller even on placebo of about 40 percent but it's accumulated by almost half with the antiarrhythmic drug.

If you want to look at something that is closer, albeit not the same as the first trial, this is shocks for VT/VF. Again, this is as judged by the investigator, not by a central committee or death. I must say death in these trials makes them about -- if you make a composite endpoint of ICD plus death, it's only about 10 percent of the events.

Here is another way of looking at it. It would be nice to be shock free if you had one of these

devices and antiarrhythmic drug over the one year period reduced from almost 4 to 1.5 shocks over that interval in the average patient if you think that's a more important way of looking at this.

So let's go back to this now and just talk about some of the specific differences. We've talked about the fact that sample size varies and the placebo event rate is varied greatly. I think the people who are in this trial, which is a trial that an agency has not evaluated, probably overestimated a placebo event rate.

They also had an interim look and they were allowed, if they wanted to, to change their sample size. This may or may not be something important. This is certainly something that could be done to make sure that you have enough events in your sample size.

This is going to be a very important issue at the prespecified SCD interrogation. I think you're going to see this as probably pretty important and needs more attention by the people that are planning these trials. I think here will be the crux of a lot

of discussion today.

First of all, if the ICD discharge is appropriate for VT/VF they argue, and it will be argued today either yea or nay, that this is a reasonable surrogate for mortality. So one might have a composite endpoint of appropriate ICD shock for VT/VF plus death as being a reasonable composite endpoint. Other people might argue that any time the device goes off, that's pretty troublesome to the patient and all-cause shock is the most important endpoint.

Mostly importantly I think that it's possible that tiered therapy with pacing might be a very important element. If not taken in consideration, patients may have a proarrhythmic effect in their antiarrhythmic drug and they may get paced out of that proarrhythmic effect and that would not show up in the primary endpoint.

Finally, I think that when you hear Dan Roden's talk, you are going to realize that even if ICD shocks are reduced, the qualitative information of those shocks is very important, for instance, if this

is an IKR blocker. There is more polymorphic VT shocks in the ICD group with antiarrhythmic drug than placebo. Event though the total shocks are reduced, it may be hiding a very potentially lethal proarrhythmic effect.

So all these issues, the devils and the details here, and that's what we're here for, to talk about those details. Clearly, this would be a reasonable place to explore in a very sick and high-risk population a dose responsive drug if you have enough money and enough time and enough patience with ICD's.

I think the other thing is that the event rates may be quite different in these kinds of patients. These patients may not behave the same. I think that would have to be considered when one is analyzing this kind of information. Certainly making a very vigorous attempt to make all the in-hospital testing and follow-up testing of the devices uniform and ideally making the devices self-uniform with adequate interrogation capacity and the ability to obtain and store these electrograms is an ideal

situation. In the real world that's no so easy.

This is an important issue. One of the two trials you saw today started counting endpoints after five half lives of the drug and there was not a typical at randomization and intention to treat evaluation. So with all those sort of preliminary remarks, I'm giving you a feeling for what this data looks like. I'll turn it over to Dan Roden to talk a little bit about more detail of this kind of interrogation.

DR. PACKER: Before we do that, let's just pause for questions from the committee if they are any. Bob.

DR. TEMPLE: In the ones that use predominantly appropriate shock endpoints, would they also include appropriate pacing endpoints? Sometimes that's the response.

DR. PRATT: Well, that's what I was saying. In fact, one of the trials here even though the primary endpoint looks tremendous, it does not include the ATP pacing. In fact, there is no information about that.

DR. TEMPLE: Even if the pacing was for sustained VT?

DR. PRATT: Correct. And one would think that there would certainly be more information to be gained to look at that. In the trial they combine both. The ATP pacing made up almost half the composite endpoint. That's why the event rate in the first trial appearing to be less general, there was no all-cause shock. In fact, a higher event rate of one year.

DR. PACKER: And maybe we just clarify for those of us who are not electrophysiologists. I was trying to ask Dan this question but I think it may be more general and important. There are some devices that have ATP capability and some that do not. All devices have ATP. How does the device decide whether to shock or pace?

DR. DiMARCO: It's programmed. You choose.

DR. PACKER: So for each individual patient, you dial in what criteria need to be met for pacing and which criteria need to be met for shock.

You could dial in parameters that would preferentially induce pacing as opposed to shock?

DR. DiMARCO: Usually. I mean, typically you can set up varied zones. Your top zone is usually a shock zone. Then if you choose to have a second zone, and this would depend on what arrhythmia you expect the patient to have, you can set up zones below the top zone within which your first response may be antitachycardia pacing, it may be low-energy shock, or it may just be a shock again at a different rate, if you will, with a different duration of arrhythmia. You have a lot of flexibility which makes it very complex.

DR. PRATT: And you also can't standardize it. I mean, I think that's the important part. Milton.

DR. DiMARCO: Yes. The zones are determined by rate or cycle length.

DR. PACKER: Oh, you can do a pacing.

DR. DiMARCO: One of the things that Dan will probably get into is the duration for a response can also be set so you may choose a slow arrhythmia to

let it go on for a certain period of time before you intervene, where in a very fast arrhythmia you wouldn't want to do that.

DR. PACKER: The reason that you would prefer pacing is that it is more pleasant.

DR. DiMARCO: It's usually asymptomatic.

DR. PRATT: But that does that other level of complexity. Milton, when I had mentioned that one should try to have some kind of standardization of the times of ICD reprogramming, it doesn't mean you can standardize the programming. It just means that you standardize the time.

DR. PACKER: Udho.

DR. THADANI: Craig, one of the problems sometimes with ATP is you can actually induce. Say patient is going into VT and you pace them. They will go into malignant VT. So not only is pacing useful but it could also generate arrhythmias. This algorithm might count like the drug induced arrhythmias, at least in our lab, to test the patient before they use the pacing because there might be actually induction of V. fib. in these patients

triggering that. That's point one. That's one comment I think you should keep in mind. I don't know how you get around it.

DR. PRATT: Let me make one comment about that. I think these protocols can at least standardize the time of testing and mandate testing at some intervals.

DR. THADANI: But could it vary, say, you test them in the lab, make changes, and next time pacing actually could produce -- you have to pace them pretty fast. That would be one issue. The other issue is I've seen patients at least who arrest every two years. There are patients who have arrested repeatedly who might be on IV amion or whatever.

There are patients who have out-of-hospital cardiac arrest. For some reason they don't have a device and they come back after five years and yet do not have an implant but maybe a small micro infarct. Should you try to randomize those patients?

Also, the same issue with patients who are only inducible in the cath. lab. but don't have necessarily spontaneous cardiac arrest because they

have nonsustained VT. Does randomization ever take that into account because that could have an influence if there is an imbalance just for that.

DR. PRATT: The only stratified randomization that I've seen is for ejection fraction with the belief that there might be a difference in antiarrhythmic drug performance and preserved functioning and lower function. You hope the randomization takes care of a lot of this issue.

I will tell you that it's very few patients that enter these trials that have only inducible arrhythmia. Most of these people had a spontaneous arrhythmia.

DR. THADANI: But given the frequency of 35 and 75 with a sample size of 150 you might run into that hassle if you don't have a very large sample size.

DR. PRATT: Absolutely. It gets back to the fact if you pick only new implants, you know now from a couple clinical trials your event rate will be 50 or 60 percent depending on what endpoint you pick. If you pick old implants, it does goes down.

DR. PACKER: JoAnn and then John.

DR. LINDENFELD: I was wondering if you could educate us a little bit about how these studies are stratified by additional drug therapy. You didn't mention that and maybe there's a standard way but if you look at total mortality --

DR. PRATT: Randomization.

DR. LINDENFELD: Just randomization?

DR. PRATT: That's it. The underlying therapy is pretty stable. I didn't spend a lot of time on it today because, again, we are not really talking about, you know, specific issues like that. About 30 or 40 percent around a beta-blocker. Fifty or 60 percent of these people are on ACE inhibitors. They are typical LV dysfunction, post MI, multiple MI population.

DR. PACKER: John.

DR. DiMARCO: Craig, the event rates in the secondary prevention trials aren't that much different than the primary prevention trials. In fact, sometimes they go higher. Do you think both populations would be appropriate for a drug trial? In

other words, someone has an indication for an ICD, gets an ICD for primary prevention, say, on MADIT criteria. Would that person be a candidate with an inducible rather than spontaneous arrhythmia?

DR. PRATT: Well, I guess it depends on the question you are trying to answer. I mean, it's hard for me to imagine that the event rates are exactly the same. I haven't really thought about it that much. Clearly the idea of testing a drug in that situation seems equally valid. You're only going to be limited by the event rate, a really appropriate shock for VT TDF. If that's really 50 percent or near, that's pretty good.

DR. DiMARCO: And then if you're talking about secondary or primary prevention, do you think every drug needs a study with a SCD hep type design where there's a placebo group, a drug group, and a device group to see whether it is relative to the device alone?

DR. PRATT: I would kind of like to defer that to the end. Let's hear them all. It's a great

question.

DR. PACKER: Just one comment. It would seem that based on having nothing to do with the device but having a lot to do with the way this committee has considered outcome measures before. All endpoints in trials of design III should include death as one of a composite.

In other words, to ignore death as an important outcome and just take ICD shocks would seem to be similar to using, for example, hospitalization or nonfatal myocardial infarction as an endpoint without considering outcomes that are clearly worse than the outcome that is being specified. My sense is there's been at least one trial that didn't do that.

DR. PRATT: But not as its primary endpoint. Correct? The two I showed today, one of them did have it as primary endpoint. I think in general, John didn't mention it, but he set up a workshop at the European Congress a year and a half ago where we certainly all agreed that made the most sense. It would be more difficult to interpret it without it.

Obviously you would still have the death information. It makes up about 10 percent of one of these composite endpoints. But obviously if you are dead, you can't have a discharge and I think the analogies are perfect. I think that's the way the agency has seen this. When people have come to talk to them about these designs, they have encouraged them with that primary endpoint. I know that Bob and Ray did.

DR. PACKER: I suppose a clinical and statistical basis. The criminal court says that it's bad to be dead. Second is that its competing risks. That is, if you're dead, you can't have the shock.

DR. TEMPLE: I don't think one should be absolute on that question. That's fine when the deaths are only 10 percent of the endpoint. It doesn't matter. You can throw them in and nothing happens. But if you had a situation where the nonarrhythmic deaths were a very large majority of it, you would want to know whether that was increased certainly but you might not necessarily make it part of the endpoint. I think that needs further*

discussion.

DR. PACKER: This is a really interesting topic because there are all sorts of -- for example, the roll of anticoagulation in diseases where the number of involved events is going to be a very small number of the outcomes, that lots of other bad things happen and involved events is only one of them. If you included all the bad things, you would overwhelm any treatment effect on the involved events. I think that is the point which you're making.

DR. TEMPLE: I think one doesn't want to be absolute. You certainly want to see if events are going the wrong way or something weird is happening. That's not the same as including it in the endpoint.

DR. PACKER: Right.

DR. TEMPLE: It's a different issue.

DR. PACKER: In this patient population --

DR. TEMPLE: It seems okay.

DR. PACKER: -- I think it's more appropriate to include and one would be curious why the rationale for excluding death. In other words, I think this is a disease where there is a lot more

reason to include death than not to.

DR. TEMPLE: In here you are also specifically worried about some of the drugs making some of the other causes get worse like increasing the rate of death due to progressive heart failure. That's a good case. I'm not saying you wouldn't often want to do that but not absolutely. I mean, I think that could be something one would discuss.

DR. PRATT: But one can certainly mask an occasionally lethal proarrhythmic effect by this ICD endpoint. In a small number of patients it may arrhythmia worse and couldn't be defibrillated.

DR. TEMPLE: Actually, I have a question about that. Wouldn't the committee looking at the appropriate discharges and things be able to say, oh, this was torsade and maybe you can't do that from the lead you have. I don't know. Could they be able to tell whether it was a likely proarrhythmic event?

DR. PRATT: It's a great segue to the next talk. Perhaps you could introduce the speaker.

DR. PACKER: Well, JoAnn. One more question.

DR. LINDENFELD: Brief question. How do you differentiate from studies. Several shocks for the same episode? Does that count as three shocks or one?

DR. PRATT: Well, there are many other endpoints and Dan will talk about them. One could count every shock. One could count shocks only at certain intervals but obviously these have been timed to first appropriate shock so the counting of all the shocks is a different issue. Certainly for the patient lots of shocks aren't fun.

DR. PACKER: Dan.

DR. RODEN: I want to thank Craig for inviting me to talk. It will become clear that the reason that I'm talking is that we conducted an analysis in one of the trials he presented to actually address the specific question of proarrhythmia. He asked me to present some actual electrograms to sort of put this in more of a concrete context for those of you who don't think about these things every day. It gives me a chance to show some pretty pictures.

Here are some electrograms. I never know

whether it's a good thing to be talking before or after John Camm but I know that it's a bad thing to be talking both before and after him because he may have some of the same messages to tell you.

This is what the ICD is supposed to do. This is a patient who is having something. I'm not sure what this rhythm is. They have run a very fast tachycardia shock here that is ineffective but they feel it obviously. More tachycardia, another shock that's effective and restores quality sinus rhythm.

All the electrograms with one exception that I'll show you are from one vendor. I'm sorry. They just make prettier pictures than other vendors. It's a device that I'm sort of more used to. The other thing you should be aware of is that you don't see P waves on these electrograms. These are highly filtered. They are different from electrocardiograms. You actually don't see a QT interval. Each of these spikes is a ventricular complex but what it would look like on the surface is actually something we don't have a good handle on.

This is as good as it gets for therapy but

it does raise the question that JoAnn asked. Does this count as a good thing or a bad thing because this patient got two shocks.

I'm particularly fond of this slide. This is a patient who had amiodorone pulmonary toxicity; got a defibrillator; had recurrent rapid ventricular tachycardia with shocks; got quinidine which slowed down the tachycardia cycling but made his tachycardia events much less frequent.

One of the things that people who take care of patients with defibrillators will be aware of but may not be immediately apparent to everyone else is the way in which a shock is now treated compared to the way in which an episode of sustained ventricular tachycardia might have been treated 10 or 15 years ago.

A patient with an episode of sustained ventricular tachycardia, even if it's well tolerated, will end up in an emergency room, will end up getting semiemergently cardioverted, and, as likely as not, will end up getting admitted to the hospital to rule out myocardia infarction.

This sort of gets to be a recurrent problem and a recurrent burden to the arrhythmia and the general cardiology communities.

The ability to just be able to interrogate the patient's defibrillator at a routine clinic where they say, "Oh, look. Two months ago you had an episode of tachycardia that was terminated by the device and you went about your ordinary daily business," that's an advantage that I think can't be addressed necessarily directly in terms of a morbidity trial or a mortality trial. There are quality of life issues that the defibrillator does fix.

The reason I like this slide in particular is this is exactly what happened to this man. He came in February and we interrogated his device and said, "Oh, look. You had an episode of sustained VT. Good thing you had the defibrillator because otherwise you would have ruined your day." The day that he would have ruined would have been his family's Christmas. This event occurred at 11:30 on Christmas morning. I really think that's a real tangible benefit to this patient.

This is sinus rhythm and then the onset of something followed by the onset of sustained monomorphic ventricular tachycardia. A single episode of antitachycardia pacing restores normal rhythm. Now, you could make the argument maybe if this had been left for 30 seconds he would have spontaneously terminated or not. The fact is, this is an episode of which he was totally unaware. This is as good as it gets it think.

You talk about shocks for all causes. I mean, there is a rare cause of shocks that we would prefer not to have to count and that's shocks for lead malfunction. This is a patient who is actually having sinus rhythm but they have a lead fracture so they have a lot of electrical noise and this is the shock effect. That probably has not much to do with whether they are on the drug or placebo but it may have something to do with whether they got the ICD in the first place in a MADIT type design.

This is a problem that has been alluded to already. I'm not sure how much of a problem it is or not. The patient has irregular fast tachycardia which

is atrial fibrillation. The little dots indicate the times at which the defibrillator has finally decided that the rate is fast enough to require a shock.

This is what we're talking about before, Milton. Once you dial in the rate, no matter how the patient gets to that rate, they get a shock. There are ways of programming or monitoring defibrillators to ask the question, for example, did this rate start suddenly or did it start gradually. This is an episode of gradual onset as opposed to sudden onset. The shock is delivered here and, of course, does nothing.

Craig alluded to the idea before that, you know, if you're a patient and you got a shock for this, then that is just as bad as getting a shock for VT or VF. Maybe a composite endpoint that includes shocks for atrial fibrillation is not great from the patient's point of view.

Udho alluded to this. This is atrial fibrillation. A shock is delivered. This is very rapid sustained monomorphic tachycardia. A second shock is delivered to rescue the patient.

This is an issue because most defibrillators will cycle through five or six episodes. If this goes on, will deliver five or six shocks. If normal rhythm is not detected, the device will turn itself off with the assumption that it is treating noise or some undefibrillatable rhythm. It is conceivable that you could get five shocks for atrial fibrillation. The sixth one would then trigger the ventricular tachycardia which the device would then decide to ignore.

So there is a potential, although I don't think I have seen a case. Jeremy may have something. There is certainly a potential that will have cases of defibrillator induced death. I haven't seen one and I don't know of one. I know of other kinds of defibrillator induced death which Jeremy may have a word to say about because there are occasional device malfunctions that can cause mortality.

The question that I was asked to address is what can we learn from analysis and intracardia electrograms. I think you get the flavor already that there are complex analysis issues. Yes?

DR. TEMPLE: Just one thing about the previous slide. I understood that you can train these things to recognize both rate and form. If someone has fibrillation, maybe you could train it not to identify that complex or look at the URS or something.

DR. RODEN: I think you're looking at a movable feast right now. There are devices that are dual chamber, for example, that will be able to tell us what is going on in the atrium and what is going on in the ventricle at the same time. So, for example, that might be a way of detecting atrial defibrillation. The philosophy underlying the design of those devices is that they will err on the side of assuming that the rhythm is ventricular and treat it.

DR. TEMPLE: So most of them just respond to rate?

DR. RODEN: At this point I think it's fair to say that most of the devices respond to rate but there is a lot of work going on in terms of trying to do discrimination but the discrimination is going to be difficult in terms of, for example -- I don't have a good example with me but ventricular

tachycardia is not always dead regular and certainly polymorphic ventricular tachycardia can be very irregular.

That was the first one I showed you. If you are in ICD or an ICD manufacturer, the last thing you want to do is not treat a rhythm that might be a lethal ventricular arrhythmia.

DR. DiMARCO: And it gets very complex because in the population who gets these things, a very large percentage of them have Y complexes to start with or will widen them in the presence of a faster rhythm so that your morphology characteristics are okay but they are often unreliable. Even if you have a two-chamber device, you never want to miss the F arising out of AF. If somebody goes into AF and has AF, well, then if they develop VT, you want to be able to shock that so it's very complex.

DR. RODEN: The slide that I didn't put in because I thought it would get too messy, and it still ended up too messy, occasionally you actually have electrograms that look absolutely identical during VT and sinus rhythm. We are convinced for other reasons

that it's VT. Even the morphology of these guys here can't be used as a good detector.

DR. THADANI: What happens with a patient who is (indiscernible) and he gets a tachycardia with sinus? Would the device still fire?

DR. RODEN: The device generally fires because of rate unless there is some other -- some devices now have onset criteria that you can use but I don't use those.

I think you already get the flavor that in trials like this it's not just a matter of sort of looking at and counting the number of shocks and saying this is what happens because there are issues of the diagnosis of nonventricular arrhythmias that the device may sense. That comes obviously in all flavors including sinus tachycardia.

Then there is a theoretical issue, and I think it is a theoretical issue at this point, of ventriculary arrhythmias that don't get detected. There's a variety of reasons that could happen, not just running out of episodes but device malfunctions. There are causes for that.

I'll come back to this issue in one second. Think about the things that the drugs might do. They might modify VT/VF frequency. That's obviously what we would like to see. They might make ventricular tachycardia slower and easier to pace terminate. If a trial uses total events as it's endpoint, you won't find that but that would be a very, very desirable thing for the patient's point of view. I showed you the Christmas day slide, I think. It sort of speaks as eloquently as it can for that sort of issue.

Obviously devices may modify the frequency of events such as atrial fibrillation. Then drugs might modify the mechanisms of tachycardia that remodify defibrillation and efficacy. Craig already alluded to that.

The reason that I'm standing here is that we did an analysis of one of the databases looking at the question of whether we could detect drug induced torsade during long-term treatment in patients with ICD's. That's what I'm going to sort of talk a little bit about.

One of the questions is how do you diagnose torsade at the best of times. The best of times you get a faxed ECG. This is a person who has a very long QT interval particularly long after a pause. That's rhythm strip No. 1 on the 21st of August. Here is rhythm strip No. 2 on the 21st of August one minute later bearing a polymorphic tachycardia.

That is pretty suspicious. I would like to see the onset of a tachycardia to see if it is pause-dependent and we just don't have that from these rhythm strips. I would end up saying this is probably torsade, at least by a sort of preset criteria that many trials use.

In fact, this patient had an ICD. This is an ICD case of a different kind of device. You can see that they had an episode of tachycardia. It stops, a pause, a sinus beat, and then the tachycardia starts up again. This is a intracardiac electrogram. It is filtered differently. This presumably corresponds to this part here and somewhere up here. Actually, I see the onset here and this is an episode

of torsade. You can only make that diagnosis with certainty from the intracardiac electrogram.

Another issue that comes up in terms of thinking about this, here is a patient who is having ventricular fibrillation. You will notice that the electrograms are very, very variable and there is a lot of what appears to be noise but that is fibrillatory activity. They got a shock and normal rhythm is restored.

The difficulty here is that I'm not certain how this rhythm started. It may have started as torsade and generated to VF but I can't say that because I don't see the onset of the tachycardia. When you see an event like this during an analysis like the one I presented to you, we just can't make head or tail of what to do with that.

DR. TEMPLE: Why is it that you don't see the onset?

DR. RODEN: Because of the device that was used in this particular trial by in large. Most of the devices had limited recording capability. That's programmable. You can say you wanted to remember more

of an episode, less of an episode. Some of the devices now we'll remember started the episode which is actually pretty convenient. You would see this and you would also see a strip that might be two minutes before recording the start of the device. The trial that I'm going to present to you didn't use those kinds of devices.

DR. DiMARCO: But, Dan, isn't this probably single dropout here because you have such a long detect time?

DR. RODEN: Well, that's actually the problem. I was presuming that somebody was going to ask the question why this person has 24 seconds of ventricular fibrillation before they get a shock. actually, John, I think there's a shock right there.

DR. DiMARCO: Oh, really?

DR. RODEN: Here is another problem if you are looking for torsade. This is a Holter monitor in a patient who has palpitations as their symptom. This is a pretty typical episode of torsade. This patient happens to have an ICD. This is what the ICD looks like. This is pause-dependent. There's a pause, a

sinus beat, and one more tachycardia. This is what we would expect torsade to look like; pause-dependent, polymorphic tachycardia labeled conveniently enough VF but that's not what it is.

This is a person who actually has shocks on their Holter monitor. This is marked five minutes before the actual events up to nine minutes before of events like this. Even way before they had actually a shock, they were having echocardiograms that were typically torsade.

This is what happens with the shock so the times are about right, a typical episode. The intracardiac electrogram looks like you would expect it to look, pause-dependent. I'm not sure how this starts exactly. This is clearly pause-dependent. This is a sinus beat and this is probably initiation of the torsade. Not very quick at the beginning but then speeds up. The shock right here restores normal rhythm. So no secrets which drug this is, I'm afraid.

So the analysis goal in our study was to look at the incidence of -- I guess I should say at the beginning that obviously the intent here is to

study the phenomena enough. Not necessarily this particular drug but to ask the question can we detect torsade occurring during long-term therapy.

What we decided to do is to compare the incidence of pause-dependent, polymorphic VT in these 174 patients randomized, half randomized to drug, half randomized to placebo.

We looked at 623 electrograms in 133 patients who had electrograms that were recorded. There's a group of about 40 that had no events at all. Of those electrograms we saw the onset of 411 and those were the ones we started with. We don't know how many of the other 200 or so might have been torsade. 327 of those were monomorphic VT. We're not so interested in them anymore. 72 were polymorphic VT. Then there's a whole sort of little smattering of others.

I must tell you that many of the patients in whom we didn't see the onset actually had ongoing atrial fibrillation as a result of their shocks it seemed to me. So there were a lot more supraventriculary arrhythmias or atrial fibrillation

that appear on this thing here.

So let me just say a word about the patterns of onset. Jeremy has published on this. This is sinus rhythm with nonpause-dependent monomorphic VT. This is sinus rhythm with pause-dependent monomorphic VT. There's a break here because this would have been on the next line down. I didn't want to do that for the slide.

This is nonpause-dependent polymorphic VT and this is pause-dependent polymorphic VT. This is the guy we're looking for because this is what we decided that has the electrogram characteristics of torsade.

Then to just complicate life a little bit, here is a patient with monomorphic VT and no pause. Here's the same patient with the same monomorphic VT but they have a positive onset. I think you already get the flavor that you need to sort of be looking at each electrogram and thinking about each different patient as opposed to sort of adding numbers up.

What we did was we found 20 polymorphic VT events, pause-dependent polymorphic VT events. The

way we found them was by electrograms in five cases. Then there were five cases -- remember, this is the trial that looked at patients between day one for the first five half lives. Didn't count events but there were events of torsade during the first three days of therapy in the five patients.

Many of those for a variety of reasons didn't actually have electrograms which is frustrating for a torsadesophile like me to not see all those electrograms. One of those patients was actually a patient at our center so I'll take the credit for that as well.

We have a total of 20 events where we have pause-dependent polymorphic VT. Fifteen of them are on electrograms and five of them are patients who actually had torsade monitored from days one to three.

In these 15 electrograms the first thing we did was we went back and looked at the case report forms for all of them to see whether, in fact, those are patients who had actual real-life torsade that had been missed on a surface electrogram. Notice I'm using the term positive polymorphic VT as opposed to

torsade. Out of those case report forms we actually found three further episodes of torsade where surface ECG documented the arrhythmia. I'll talk about those in a second.

So basically we have cases that arose early within the first three days and we have cases that arose late. So 15 on drug and five on placebo. Of the early cases there were the five early torsade cases. Those were all on drug. There are 10 cases that occurred late during therapy and five on placebo.

We have to remember we had eight cases of torsade and there are seven of them on this drug which is not a surprise, I guess. There's one in the placebo arm and this is a patient who was on placebo and on day 62 was withdrawn from the study and started on amiodorone and on day 64 had clear cut torsade. That's an intention to treat analysis as appropriate.

So the torsades occurred mostly, again, five of them occurred early, the same five here, and two of them occurred late. One I told you about on placebo and these two on drug. The way they are detected is the patients coming to the hospital

because of a shock. They are monitored and they have further events that are recorded on the electrocardiogram, one on day eight, one on day 289.

The QT's are not very important, I think, for this analysis. Not surprisingly the QT's -- actually there was a point. The QT is long here but interestingly the QT is quite long in the placebo treated patients as well. I think this is just a manifestation of how sick this population is because I think QT prolongation occurs amount patients with advanced heart failure. I think that is what we're seeing here. This is a population with pretty advanced heart disease.

That's really what I want to say at this point. Just to summarize, I hope I've given you the sense -- I think I've given you the sense that an analysis of these electrograms is not something that should be undertaken lightly. There are a lot of nuances to try to interpret the electrograms themselves and put them in the context for these kinds of trials. Nuances like quality of life, like whether something is terminated by antitachycardia pacing or

not, whether things are detected appropriately. The sorts of things that we already talked about.

I think one of the most interesting results of this analysis that I've presented to you actually is the fact that we still have five cases of pause-dependent polymorphic ventricular tachycardia in patients who were treated with placebo.

Given that, it's very, very difficult to say that we have an increased incidence of episodes of torsade, or strikingly increased incidence of episodes of torsade on drug. I think that what you could say is that the phenomenon occurs with both.

I guess the conclusion that I have is that the patterns of VT/VF onset are very interesting for those of us who are interested in mechanisms. In terms of interpreting these large trials, they are probably less important than other outcomes such as a reduction in the number of shocks, perhaps a reduction in the number of events, and perhaps a reduction in the total number of shocks, issues that we are going to come back to later this morning. That's all I want to say for now.

DR. TEMPLE: Well, that's pretty interesting. I hesitate to call the results shocking but one might. What do you make of the apparent torsade, although you didn't call it that, in people not known to be on a drug that causes it and what does that mean? Does that mean people who are sick commonly die of that mechanism?

DR. RODEN: Yes.

DR. TEMPLE: Or is that just --

DR. RODEN: I would defer actually to JoAnn and Ileana and Milton. There is certainly a flavor in the heart failure/arrhythmia literature. It's hard to believe that there is such a thing, but there is such a thing which suggests that patients with advanced heart failure have alterdine channel regulation that, in fact, predisposes them to arrhythmias that may be mechanistically not dissimilar from torsade.

Those are a lot of words. I'm sorry to sort of qualify it that way. Not only might arrhythmias that patients get in those situations be morphologically similar, pause-dependent and

polymorphic, but they actually may share some underlying mechanisms. That's why I picked the conclusion.

DR. TEMPLE: I don't know if it's been discussed here or not. Probably not. One of the phenomena we observed with nofepradil was that apart from the torsade associated with inappropriate combinations, there were these mysterious ones almost as frequent in number where the only underlying thing was heart failure and frequently the presence of digoxin but, of course, that could be the heart failure.

DR. RODEN: We have a much more elaborate theory with regard to digoxin that actually implicates intracellular calcium overload as a final common pathway which would implicate digoxin in these kinds of arrhythmias or would indicate heart failure in these kinds of arrhythmias.

DR. TEMPLE: Okay. So it may actually have been interactive. But one of the points that a consultant to the company made was that there is a literature that says that heart failure alone is

associated with torsade.

DR. RODEN: No. There is theoretical literature that suggest that mechanisms like that may cause arrhythmias that look like that. The arrhythmias I showed you, the real live torsade with the really long QT intervals and the pause-dependence, that doesn't occur in heart failure, the really long QT intervals.

One of the things that we haven't done is gone back and looked at things like coupling intervals to see whether we can sort that out or not. I'm not sure what conclusion we would draw. We are certainly going to do that.

DR. TEMPLE: I may have been misusing the term. What they had was polymorphic VT. I don't know that the QT was very prolonged. It might have been just a little prolonged but it was identified that way. One could say, however, that if you had a question about a drug, this method did detect an increase because of the population substrate there was plenty in the placebo controlled group too. It's hard to think how you would do that. I mean, I'm not sure

how one could make use of that exactly but it does sound like one could.

DR. RODEN: Let me just put this in context. I'm glad you asked me that question. This is the dofetilide trial. The overall result is a total wash. The number of events is identical in the two groups. One interpretation is that dofetilide doesn't change the incidence of arrhythmias but what it does is it makes them look different. An arrhythmia that would have been nonpause-dependent monomorphic on drug is now pause-dependent polymorphic. That's one possibility.

Another possibility is that it's antiarrhythmic and that it's balanced by a proarrhythmic effect obviously. I don't think you can make that interpretation from these data.

DR. TEMPLE: Actually, I was thinking of drugs that weren't intended as antiarrhythmic but are intended as antihistamines. It's still hard to think how do you do this exactly.

DR. PACKER: Based on all this you've done on using electrograms in either high risk or heart

failure populations or sudden death populations, what percentage of patients who have pause-dependent polymorphic VT have no clinical event? In other words, of all of the events how many of them are clinically apparent?

I know that some of them. For example, you showed three cases where you went back. There was no clinical data reported but there happened to be a surface cardiogram that actually confirmed the event. Of course, the fact that there was a surface cardiogram was a fortunate accident. There might not have been a surface cardiogram at the time.

One is getting the impression that these patients are actually having these events a lot. A lot of them, maybe even 90 percent of them, are self-terminating. That may be true as a result of the disease. It may be exacerbated by a drug or there may be a disease/drug interaction. These are really common. What we've been picking up in clinical trials, which are primarily clinically apparent because they are symptomatic, is not just the tip of the iceberg but it's the extreme tip of the iceberg.

DR. RODEN: Well, the events that are detected by the device and not treated, the self-terminating events have to be of a certain duration. Again, that's programmable what duration one might expect to see. We're going to have a discussion. At least, I think one of the questions that we're going to talk about is whether nonsustained VT events are things that are worth tracking, in which case reprogramming devices to detect more of them is one approach.

We are coming back to the idea of ventriculary arrhythmias as predictors of mortality events in patients with advanced heart disease, which I guess is not a new concept. Again, the question is what if people with very, very frequent events are at more risk than people with rare events because it's a stochastic process.

The more frequent events you have, the more likely it is that you'll have one that happens to trigger VT or VF that is sustained and lethal. That's always been my understanding of why frequent PDC's are a bad thing in the wrong population. I think we are

seeing the tip of the tip of an iceberg that we know is there.

DR. PACKER: The only reason is that in many of the discussions that have taken place where patients were given drugs that could cause torsade, the committee is always asked, "How do you know how many torsades could have occurred and you didn't pick them up?" Of course, the sponsor says, "We don't know. We didn't pick them up."

What you are indicating is, yes, you can pick up a lot more episodes than are clinically apparent. But that raises the question are they things that are worth picking up because you are no longer talking about clinical outcome. You are talking about a correlate of the clinical outcome.

DR. RODEN: I haven't shown you episodes of torsade that go on for two or three or four minutes and then self-determinate. That happens. That is well described. Even if you had an event that was that long, it's not necessarily a mortality event. But it's an event that might cause syncope or it might cause a car accident or that sort of thing.

DR. TEMPLE: But one of the things that was always odd was that torsade was a VT that you managed to get to the emergency room with. A lot of VT's you don't get that opportunity. It obviously can come and go. At the same time, torsade inducers like d-sotalol sometimes show no torsade at all and just show an excess of death which we presume was a torsade mechanism, although it's hard to know for sure.

DR. PINA: Dan, do you think that in these ongoing trials like SCD hep, for example -- and I keep pointing to SCD hep because we're involved with SCD hep -- since a proportion of the patients are going to get ICD's, and it is primary prevention as we said, would we have the opportunity to scan the electrograms and look for what I suspect as you do, Milton, how many patients have these off and on?

Now, we are seeing this in patients waiting for hearts but, of course, some of the ones in the hospital are already on ionotrope so you have introduced an arrhythmic agent. We are seeing these spontaneously, you know. They make me very nervous every time I see them and you never know if it's the

drug that you're giving them or is it the disease itself that's doing it.

DR. RODEN: I presume that somebody is going to look at the electrograms.

DR. THADANI: Dan, yesterday in the presentation I asked this question because they had three innovations with some of the ICD stuff and they did not really have much evidence of torsade. At least, they didn't have the data. The question is really are you right calling it torsade just because it is very dependent? You have to have a QT prolongation in the torsade. I have seen the T waves look really peaked in the class I arrhythmics.

DR. RODEN: Let me be explicit.

DR. THADANI: So it could be polymorphic VT.

DR. RODEN: I use the term torsade to apply to pause-dependent polymorphic VT associated with these QT deformities that you are talking about. That's why I've made the distinction, although I obviously haven't done a very good job of it, between typical torsade de pointes and pause-dependent

polymorphic VT.

I think when you look at electrograms all you can do is look for that phenomenon. I'll just leave it at that. The conclusion I think that we come to is that the phenomenon of pause-dependent polymorphic VT does occur in patients treated with placebo. It occurs with at least equal frequency and possible increased frequency with that particular drug during long-term treatment. How many of those were actually typical torsade and how many of those reflected the underlying severity of the disease.

DR. THADANI: Maybe that's the placebo. That's why the incidence is high. If you look at the classic torsade it may not be. Other thing is now we are using more and more beta-blockers which also reduces your heart rate. And if a patient on beta-blocker and something else, you might get a pulse. It might be more complicated than what you are --

DR. RODEN: No. Of course. And the nofepradil data said there was an underlying brady arrhythmia issue. The beta-blocker probably -- I don't want to get into this too much but beta-blockers

while they slow the rate probably have an anti-torsade effect in general.

DR. PACKER: John and then JoAnn.

DR. DiMARCO: Dan, do you want to comment on the type of electrogram you want to analyze? Fortunately I think we're out of the interval log. Do you think we should record -- you know, you were showing one manufacturer's type of electrogram. There are other types of things that look more like a cardiogram. Which do you think is the best for this purpose?

DR. RODEN: Oh, I think probably the ones that make some assessment of at least low QT interval that one might believe in are probably more desirable. Obviously the manufacturer that we used here was sort of first to the post with the intracardiac electrograms. That was the one that was used in this particular trial.

DR. LINDENFELD: Dan, were most of the episodes paused-dependent polymorphic VT, were they associated with other clinical events or not? Do you know that?

DR. RODEN: I don't know the answer to that. Most of them were patients who came back for their routine three monthly visit, had their interrogation, and they said, "Oh, look. You had an episode." I take that back because when they had a shock they were seen, particularly if it was the first shock and then they were interrogated.

DR. THADANI: Then also the treatment other than beta-blocker for torsade at least is basic. There are more of these devices than you would think to pace them out. Is there a duration to see if the torsade expires when the pacing kicks off or would it kick off within the third or fourth beat of the onset of the VT?

DR. RODEN: They are two different kinds of pacing. One is anti-bradycardia pacing. That will be highly effective in treating or preventing further episodes. In fact, in some of these patients, at least the patients that we took care of at our place, that was, in fact, the treatment.

The second thing is whether antitacycardia pacing can terminate episodes of torsade. This is

probably the one time when one could prove that because in general once you put a pacemaker into someone who is having recurrent episodes, you don't have anymore episodes. I must say I would have to go back and look and see whether these particular events were terminated by antitachycardia pacing. I presume that this tachycardia could, like many other tachycardias, be terminated by antitachycardia pacing. Often it self-terminates so it might be difficult to determine.

DR. PACKER: Okay. Why don't we go on to the next presentation. Gee, I hope you give us some answers soon. I'm beginning to get the impression this is sort of like the Heysenberg uncertainty principle. For those of us who were mildly depressed before are becoming increasingly depressed as the day goes on. We are looking hopefully for some good news.

DR. CAMM: The word Heysenberg has been very high in the minds of all of those wrestling with this problem. Our recognized goal, though we are trying to bring gifts to you today, those gifts may be poison chalices.

Obviously I'm going to say a little about what has already been said because there's an essential overlap in presentations. My purpose at this point is trying to give the committee an appreciation of what the potential endpoints might be in an ICD supported trial and how those endpoints may be effected by the details of the trial design, by the programming of the device, and by the kind of treatment that a patient is taking.

I need to restate from the outset that the trial of design III could be undertaken for two specific reasons. One of which is to identify complimentary drug therapy to patients who are fitted with an ICD for life-threatening arrhythmia. The other is to explore the antiarrhythmic effect of the drug with an intention to extrapolate that antiarrhythmic effect out with the realm of patients who are fitted with an ICD. I think it is that second potential purpose for the design of trials of this type that presents the greater problem.

So if we consider an ICD discharge taking place during a trial, we have to wonder whether we

should try and prevent this by excluding all patients from including in the trial if they have an ICD. This has been certainly a policy which has been followed in trials of heart failure patients with heart failure drugs where the number of patients with an ICD was anticipated to be very small.

Other trials have included such patients and when discharges have occurred, they have censored the patient from further continuation in the trial. They may or may not have counted the ICD discharge or therapy as an event depending on what endpoints or outcome parameters were being logged in the trial.

In some trials, for example, these events have been counted as the equivalent of a resuscitated cardiac arrest. Sometimes the endpoint is counted and added to a composite endpoint which includes all-cause mortality. Sometimes any ICD intervention is added to a mortality endpoint. Sometimes and increasingly the notion is to restrict the endpoint which is added to a composite including mortality for those ventricular tachycardias that might fairly be thought of or most appropriately thought of as a potential surrogate for

death itself. In other words, fast ventricular tachyarrhythmias.

This issue has been covered just recently by Dan because I wanted to just remind you about the complicated events which surround or precede mortality from ventricular arrhythmia. These data are from the papers Bayes de Luna, Kumel and LeClerg. They looked at more than 100 patients who were wearing ambulatory recorders when they died. They documented a variety of ways in which they died.

For example, they found some patients who seemed to go straight from sinus rhythm with some ventricular ectopy into rhythms which could be described as ventricular fibrillation. They described such great patients as having primary ventricular fibrillation. They had other patients who seemed to develop rhythms equivalent to torsade as defined by Dan, pause-dependent, long QT intervals, relatively slow polymorphic ventricular tachyarrhythmias accelerating into much faster ventricular arrhythmias. Even in these ambulatory patients this constituted 13 percent of the group.

Finally, they described what in their experience in these ambulatory patients was by far the most common method of mortality in which sinus rhythm was interrupted by a fast monomorphic ventricular tachycardia which after some time degenerated into ventricular fibrillation which was the rhythm that killed them.

Of interest, and since you were already discussing device-based diagnoses, recent information with dual chamber devices suggest that a number of patients who are fitted with these dual chamber devices have atrial fibrillation as an initiating arrhythmia and that atrial fibrillation converts to ventricular fibrillation which is then attended to or not by the implanted device.

Now, I want to take you back some years to the idea of hypothetical mortality which was an issue first "invented" by Michel Mirowski. On the left is a representation of a graph which appears in Mirowski's paper in 1983. He plotted the actual mortality of the cohort under examination. He plotted their sudden death mortality.

Since all his patients had ICD's, he was also able to construct a mortality which he described here as an expected mortality. What he meant by that was if the patient's ICD had not discharged and kept that patient alive, they would have died. Therefore, he constructed a hypothetical mortality for a group whose actual mortality is portrayed here.

It's important to realize that in 1983 we were largely dealing with implantable devices which came from the factory preset for a single rate of intervention. It had virtually no programmability. So an event was only one event, a discharge, which occurred at a single rate that was not variable. It was easy to see how Mirowski, his colleagues, and many like them could see this as an appropriate surrogate for mortality.

But there was considerable disconcert about whether this could be regarded as a surrogate for mortality and there were at that stage further develop. Rich Fogoros, for example, in 1990 took this a stage further. He said that we don't need to call to include all discharges or therapeutic interventions

from a device as an expected mortality or hypothetical death. We could adjust or recalculate the survival according to whether the shock or therapy was "appropriate."

For example -- and here I apologize. I've mislabeled these two curves -- he could change the crude expected mortality, or predicted survival as it is labeled here, to a recalculated value which included only appropriate shocks and compare that to the actual mortality in the group.

We also had another small cadre of patients in this particular presentation who were described as controlled patients; that is, patients who did not have a device whose actual mortality was plotted on these same axis. It is, I suppose, no accident that the controlled mortality is closer to the recalculated predicted mortality than to the crude recalculated mortality.

Now, what might constitute an appropriate shock? What might turn a therapy into something that is equivalent to a mortal episode? Well, originally symptomatic criteria were used. Does the patient have

syncope or no syncope? Other groups varied this and became less demanding. Was the patient lightheaded or did they have any form of hypotensive symptoms. Others went on to say, well, any symptoms associated with the shock at least would sort out those who have sinus tachycardia from those who have an arrhythmia worthy of treatment.

When electrograms or logs of events became available in implantable cardioverter-defibrillators and when programmability became available, it became possible to define specific interventions for specific tachycardias and call them appropriate, i.e., closer to a surrogate for mortality and not others. For example, a higher rate or a longer duration of an arrhythmia. In some reports an appropriate shock was merely defined as one that could not be demonstrated to be inappropriate.

In this series of patients reported from Germany, we can explore the value of syncope as indicating the appropriateness of an ICD shocks. Bansch and colleagues reported in this rather recent publication that patients with syncope had a discharge

frequency that gave a lower projected mortality than those who had any ventricular tachycardia or fibrillation.

They found that syncope occurred at a median heart rate frequency of 240 beats per minute with almost all tachycardias causing syncope were greater than 180 beats per minute and that only very rarely did slow tachycardias cause syncope.

This is an example of an electrogram demonstrating the way in which the device ought to work and the kind of information that we can obtain from electrograms to help us refine the classification of the event treated by the device. We are already well attuned to looking at these electrograms so I don't have to point out very much.

This is obviously a slow rhythm. You see the electrogram shape enter in the slow rhythm and this is the equivalent of sinus rhythm. You see the faster rhythm. You see the electrogram shape during the faster rhythm in this case is different to that sinus rhythm. This is not always the case. You can see with this particular electrogram derived from the

particular electrodes in use, the width of the electrogram during the ventricular arrhythmia is actually if anything narrower than that sinus rhythm.

But with more modern devices, different electrode arrays are being used and morphological criteria and width criteria can certainly be employed to refine the diagnosis. Certainly atrial events plus ventricular events can be used to refine the diagnosis.

In this instance, tachycardia is recognized. The response by the device is antitachycardia pacing. As you can see in this instance, a slower rhythm is restored with the same electrogram characteristics as previously. This is interpreted as the restoration of sinus rhythm.

Now, let us return to the issue of hypothetical survival and consider if there is any characteristic other than ventricular tachycardia or "ventricular fibrillation" that would bring us close to a surrogate for mortality.

These are data available from the German group in Muenster published by Bocker in 1993. The

curves are at the top sudden death. The solid line arrhythmia related death. Not all of them specifically due to an arrhythmia at the point or including some arrhythmias that produce a rather lingering mortality.

Below that is cardiac mortality. The bottom, any interventions recognized and/or treated by an implantable device. There is an intermediate line which is labeled as fast VT or VF. For this purpose the Germans selected the rate which they had identified as the median rate for syncope in their population and that rate was 240 beats per minute or a cycle length of less than 250 milliseconds.

So they suggested that the benefit for the device could be more fairly estimated by taking a rate of 240 beats per minute, i.e., this line, than by taking the rate of any ventricular tachycardia or ventricular fibrillation, i.e., this line. This particular shaded area represented what they believed was the use of the benefit of the device.

Of course, there is no particular single rate that we could identify that reliably separates

those who would have lived from those who would have died had the defibrillator not been in place. I think what we can say is that the faster the rate that we choose, the more likely it will be associated with hypotension, with syncope, and probably with death. We can also perhaps say that the more likely it would pick up and identify ventricular fibrillation proarrhythmia. Therefore, we could say, I think, that would be more specific but perhaps certainly less sensitive.

We go to the other side of the equation, of course, and we reduce the rate that we take as the rate which will separate those who would have lived from those who would have died. We are going to achieve a less specific but more sensitive measure and we are going to pick up, I think, more atrial fibrillation proarrhythmia by moving the line downwards.

There is very little evidence in the literature for us to select any specific rate, but what there is is a history of this rate being selected in a number of publications.

I should say whilst I'm on that slide that it is important to consider the issue of when patients are censored from the trial because, for example, these patients, who are actually dying, are clearly censored by their death. These patients who are receiving perhaps trivial logging of arrhythmia or asymptomatic termination of arrhythmia should almost certainly not be removed or censored from the trial.

Often in many trial designs those patients who have sustained an arrhythmia, which is regarded as a primary outcome event, are also regarded as reaching an endpoint if not by protocol design, then certainly by the practice of the trial where the patients are then withdrawn from the trial or given alternative medications, so on and so forth.

Now, the time to withdraw the patients from the trial is obviously critical because if we have a high frequency of time to first events early in the trial, then obviously we will effect the reliability of endpoints related to mortality because the patients are merely not there. They have reached an endpoint, or part of a component endpoint, and they

don't go on through the trial to potentially suffer from any mortality.

As we heard earlier, the reverse is true, of course. If they are dead, they certainly don't suffer any of the events that would contribute to the other composite of the endpoint. In other words, the fast arrhythmias.

The most serious problem in my view is how these patients leave the trial either by protocol driven withdrawals or censorship, or the practicalities of managing these patients when they are withdrawn because they stop taking trial agents and start taking other agents.

As we heard, several trials have considered enrolling patients after the implantation of the device, but some have not started to countervent until late after the implantation at some stage when the drug has reached a steady state. It's well known that events commonly occur in the first month following the implantation of the device and much more commonly in the first week following the implantation of the device.

In part, this was related to the trauma of device implantation and because of the destablizing effect of the repeated testing of defibrillation specials and so on. It is certainly greater in patients who have had thoracotomies than it is for patients who have had nonthoracotomies leads implantations.

But it is not only that because we can see that those patients who have shocks within the first week and the first month also have far more frequent recurrences of shocks as we notice here on the follow-up of this particular group of patients. You can also see that atrial fibrillation and sinus tachycardia is relatively uncommon in this first one but it doubles and such like in the second one. The likelihood of other arrhythmias entering the fray becomes more important.

I think it is very critical for all of us to appreciate that the ICD is not a passive monitor in this circumstance. You cannot simply put it in and have it log events and assume that it is doing nothing to influence the likelihood that those events will or

will not occur.

One example that you raised with me earlier of a bradycardia support pacing being an important potential modulator of the frequency of attacks or the likelihood or arrhythmic events is another possibility and it is a frequently observed possibility.

In this particular circumstance of ventricular tachycardia is present. It has a cycle length of 360 milliseconds. It attracts a burst of antitachycardia pacing from the device. This is not successfully converting the patient to sinus rhythm. You can see that another tachycardia of a different morphology is present.

We can see that the rate of this tachycardia is faster than the rate of this tachycardia, in this case alternating between 302.70 or thereabouts in its first few beats. Not fast enough to now enter this category of less than 250 milliseconds that I was talking about, but there are certainly examples of that also.

But the important point is that the

antitachycardia pacing mode converts a relatively benign arrhythmia that could have terminated spontaneously perhaps, or could have responded to a shock into an arrhythmia which is faster. It may be much more difficult to terminate by pacing or by a shock. It might convert an endpoint that we have defined in terms of a specific rate into another endpoint within the trial.

How often does this happen? Well, a couple of small series, 42 patients, 14 with antitachycardia pacing off, 28 with it on. Of those 15 patients used their antitachycardia pacing and nine of those 15 had an acceleration to fast ventricular tachycardia or ventricular fibrillation. That's none out of 42 patients with a device, 28 of whom had antitachycardia pacing program on.

There's another series of 176 episodes. 166 invoked antitachycardia pacing. They were successful in the vast majority but in 11 it was not. Five had simply failed, but in six there was an acceleration and defibrillation. If our trial was looking at defibrillation as its endpoint, we would

log an event here which might not have happened if the particular program for antitachycardia pacing had been made, for example, better such that it terminated the tachycardia.

Here are three series in which both the acceleration rate per patient is identified and the acceleration rate per VT episode. The acceleration per VT episode is gratifyingly pretty small, 46 percent. But, of course, in our trials we are looking at the way in which patients respond to our trial. You see that the figures are rather alarmingly high in terms of acceleration to faster rhythms so 20 to 43 percent in these three particular series.

This is an example of where an arrhythmia which perhaps does not deserve an intervention by the device, which does not deserve logged as an endpoint or outcome parameter in our trial, is converted to an output event by antitachycardia pacing. For example, here we have atrial fibrillation recognized by irregularity, lapidity, treated by two bursts of antitachycardia pacing. By the first burst probably it has converted to a ventricular tachyrhythmia and it

certainly has by the end of the second burst.

Another example on this slide shows a proarrhythmia which is induced by random pacing or inappropriate pacing by the bradycardia element of the ICD where a ventricular tachyrhythmia is the result. Another proarrhythmic artifactual endpoint but not from our drug necessarily but from the device that supports the trial and monitors the trial.

We have seen an example of noise causing the activation and intervention by device. Here is a straight supraventricular tachycardia inducing an antitachycardia pacing event and the second such event and converting the supraventricular tachycardia with one specific morphology into what is now called the ventricular tachycardia with another cycle length and another morphology which in the end invites a shock and the shock in the end produces a rhythm not fully defined but with a rate less than the VT trigger rate.

If we look in this series of 29 patients who suffered 194 tachycardias, there were 74 ventricular tachycardias but there were 24 episodes of atrial fibrillation. There were 30 episodes of

supraventricular tachycardia. There were six electrical problems. There were four oversensing of T waves.

There were three vents; that is, interventions by the device that could not be categorized. We had a total of 194 tachycardias. Of those 101 electrograms. Then the 74 of these were due to ventricular tachycardia that would have interested us as being an endpoint of the trial.

We did give a little consideration earlier to whether devices should be programmed in some standardized fashion. I think my comment in small print at the bottom of the slide is probably correct, that it is unlikely that specific clinical trial programming will be ethically appropriate. However, it might be possible to make certain changes suited to the trial and/or to obtain some uniformity of programming.

The classical way of programming a device might be to select certain zones of rate which might be further qualified by other possible diagnostic parameters like stability of rate, or regularity of

rate, or by electrogram widths, or by sudden onset, and so on and so forth. But essentially different zones of rate which different therapies were delivered.

From a clinical perspective the idea generally is to make a diagnosis quickly and activate an intervention as quickly as possible.

From a trial design, of course, it might be best for us to have the device only respond to the fastest of arrhythmias that is closest to out definition of mortality and then to wait for a fairly long time to make increasingly sure that the arrhythmia was not going to be nonsustained. That, of course, is ethnically quite inappropriate. We're not going to get that far, but we might at least be able to consider reserving one of these zones perhaps at one of the highest rate cutoffs for an early discharge which we would use, for example, as a component in the composite of trial endpoint.

We have to ask in the so-called ICD protected trials whether there is any substantial evidence that the ICD will actually protect. It must

be admitted that there is considerable evidence that it might not in some circumstances. The therapy might increase the defibrillation threshold and render the device incapable of defibrillating the patient.

The therapy may render the tachyrhythmia incessant such that if it is terminated by the device, it will only promptly start again. The therapy may provoke a new arrhythmia, an arrhythmia in this instance not amenable to the therapy that is being programmed in the device.

I'm not talking now about the pharmaceutical therapy that we are testing. Heart failure may change the substrate, may change the circumstances in which the tachycardia occurs, may change the implications of the tachycardia. The therapy may prevent tachycardia recognition by making it slower by changing the slue rate of the electrograms, and so on and so forth.

The therapy may provoke much more frequent arrhythmias. I think that we have to give a resounding no to the question that we can guarantee protection from proarrhythmia. That is not to say

that the majority of proarrhythmia might not be well suited for by the device. There is a level of uncertainty in this.

This simply illustrates the point of the rise of the defibrillation threshold. In this case, with amiodorone and with older generation of devices. There is a lot of controlicy about this and probably today this isn't much of a quint but I think it's important that we recognize that antiarrhythmic drugs will change the characteristics of ventricular tachycardia and fibrillation which may make them either harder or easier for the device to deal with.

We should also ask whether we can use ICD data to refine death classification. This has been well explored by several groups of investigators. We have heard part of this this morning from Dan Roden already. This refers to an analysis made by Craig Pratt and published in 1996 in a cohort of patients with defibrillators.

It is very convenient if we have a situation in which we have at the time of death a sudden tachycardia which we could see on electrograms

and we have this very convincing log, but it's not like that all the time. The ICD could well have been buried with the patient. The ICD memory could certainly have been erased before you can get at it. The terminal event might not be recorded. The ICD might have been programmed off and the arrhythmias that you do note may merely have been bystanders in a process that had nothing to do with the arrhythmia causing the death.

Finally, I want to remind you that in coming to some composite endpoint we do have some, I think, very significant difficulties. On the one hand, we have a range of mortalities that might be considered relevant to our trial. By in large I think all-cause mortality is the most relevant for the trials from the point of view of the primary endpoint, although other classic occasions of mortality perhaps aided and abetted by the device in terms of its logging ability of electrograms could be useful in our mechanistic appreciation of the trial results.

On the other hand, we also have an infinite variation of ICD endpoints that we can choose

from to add to the composite. The problem, however, is that the ICD endpoint may vastly outweigh the mortal endpoint. On the other hand, what mortality signal there is, and it may be a real signal, may be adverse whereas the signal for the reduction in shocks may be favorable. We have to wrestle with how to handle such a result.

I think I cannot bring to you a list of any firm recommendations or conclusions about how to handle all of this. I do think one of two points deserve further discussion. I think all-cause mortality should be included in the primary composite endpoint of a defibrillated, protected, and monitored trial. Also, we should consider the inclusion of a high rate ICD shock rate endpoint and this could be considered as contributing as a surrogate for mortality.

Certainly if there is an issue of removing the patient from the trial and treating this as an endpoint rather than an outcome parameter, the rate should be as high as possible and our certainty that this is a death equivalent as sure as we can be.