We obviously do not want to disregard interventions and logged events at lower heart rates. On the other hand, we certainly do not wish to use them as endpoints in the trial because the ready removal of such patients from the trial will degrade the power of the trial in the sense that patients persisting in the trial will be too few to allow the mortal contribution to the endpoint to be fully appreciated or securely appreciated.

I think ICD supported trials are valuable. They are a neat idea. They are not, however, as easy as we once thought they might be. We have to bear in mind that our cozy, comfortable view that they may protect our patients from proarrhythmia in particular is not necessarily true. Thank you.

DR. PACKER: Thank you very much, John. Questions from the committee? We may all be shocked.

DR. THADANI: I have a question. Although your rate is important, there are some patients who tolerate the slow rate when they are supine. That's where when they stand up they get syncope. That might be again a tricky issue. Your last comment is very

valid because you don't want to lose those, you know, the guys that come in with a heart rate of 140 which is not yet threshold for 240. Yet, they go to 150, they stand up and they pass out on you because the pressure just dropped by itself.

DR. CAMM: I fully understand that.

DR. THADANI: When you interrogate them in the supine position when they are sleeping, you may not count it. That's a dilemma.

DR. CAMM: I think that the whole ballpark is full of dilemmas and I acknowledge that is very much one of them.

DR. TEMPLE: You didn't actually read the last item on your last slide. What sort of evidence of safety did you have in mind?

DR. CAMM: I had in mind that you know something about whether the drug effects the defibrillation threshold in particular. I think you need some information probably about what effect it will have on heart rate and how that will interact with the device. Some idea of what it will do to the tachycardia rate, whether it will render fibrillation

still identifiable by the devices that you use.

I think the only one of those concepts that I think is firmly understood at the moment is the defibrillation threshold. I don't know that there are a lot of drugs out there that do much adversely to defibrillation. The one that we came to think of as potentially being a disaster in that regard is amiodorone. Even that is controversial with biphasic shock devices of the new order.

DR. TEMPLE: Actually, that leads to my other question which is that among the trials that have been carried out so far, I guess they would be of your design III which is to use the effect from these patients as a predictor of how we do in patients who didn't have defibrillators. Have there been any that appeared to adversely affect survival apart from whatever effects they had on surrogates for survival?

DR. CAMM: I'm not treated to the results, Bob, but Craig I know has seen two sets of results. I haven't seen any.

DR. TEMPLE: Okay. I guess dofetilide was something of a watch on survival and maybe that's

because it --

DR. CAMM: Yes. I'm aware of that sort of headline but I don't know the details.

DR. DiMARCO: John, can I ask you just two questions. One, for your heart rate VT's or arrhythmias you said the first shock should be 35 Joules. Do you think that's important or do you think you could just set it with a 10 Joule safety margin like we clinically did?

DR. CAMM: Oh, I have absolutely -- on the left could be any detail at all. I didn't mean to offer that as a prescription. On the right it was purely nominal. I think, yes, you could -- I think we are going to be forced into using the devices in a clinical mode. To stray very far from that I think would be inappropriate.

The question, however, is if we can seek some standardization within the trial, that I think is just about possible. But to suggest any trial specific programmation such as let's wait only for fast arrhythmias and let's wait a long time to make sure that they are equivalent at death, I think is, of

course, not possible.

DR. DiMARCO: Do you think you could program some type of duration, say, like in your lower VT zone could you set in a 30 second delay?

DR. CAMM: Yes.

DR. DiMARCO: Because one of the problems with ATP accelerating arrhythmias is it accelerates these things after a few beats. I think that may be a major problem. But if you programmed in a 30 second delay, some of them may still stop but it might well be a good way to do it.

DR. CAMM: Yes. I think that would be very helpful if one could eliminate device interventions for unnecessary arrythmia by extending the duration of the lowest ends.

DR. PACKER: I just wanted to clarify your response to John's question. You could if you decide to only use very high rate VT/VF program all devices only to recognize that or leave the programming of the device to the investigator and only count those.

DR. CAMM: Yes.

DR. PACKER: The former has more appeal

than the latter, but the former is unethical?

DR. CAMM: Yes. I think it is. That's the problem.

DR. PACKER: The reason it is unethical is because it just wouldn't be accepted by the community or because you would genuinely put people at risk if you did that?

DR. CAMM: Well, I think one could genuinely put people at risk by allowing the ventricular tachyarrthymias to degenerate to ventricular fibrillation to increase, for example, the ischemic insult consequent upon the fast arrhythmia and so on. I think there would be many voices raised against doing that. I agree, it's very attractive to do that.

If you come to the other side and say, well, let's just count them, that's fine provided you don't use the time to the first event of that nature as a reason to abandon the patient in the trial. Once you do that because the numbers shrink quickly as the trial goes by and your opportunity to count more significant events whether it's farce effective

arrhythmia or death becomes less and less secure.

DR. PACKER: And you could ethnically say that although it might be uncomfortable for the patient to undergo these interventions that, in fact, you could make the statement that the patient remains in the trial, has all of their data collected as long as they are alive regardless of what happens even if they experience a high rate VT/VF.

DR. CAMM: Indeed, you can. Yes. I would like to see that happen but it's inevitable, I think, in many of those instances the trial medication may be abandoned and the new medication introduced. Not necessarily, of course, but it would happen in a logical fashion.

DR. THADANI: Another issue comes up, sir. You have very early incidents of 25 percent within a week of inserting ICD. Yet, unless patients are having recurring VT, that's really unusual. You say it could be the device which is doing it. Is it true also with the percutaneous devices?

DR. CAMM: It's in part true but it's not as big an effect as the effect that I've shown you on

that slide. I showed the effect both in terms of the events during the first month and then to show that there was more do it than simply cracking the chest or causing destablization from defibrillation testing.

I showed you that if you followed those patients up in the months that followed, their event rate was very much greater. My implication was that we want to recruit patients as early as possible following the implantation of the device in order to maximize the opportunity to see the drug effect.

DR. THADANI: Although it could be artifactual because your discharge rate is so high, you might to wait for two weeks before you start the trial.

DR. CAMM: Yes. If we still had the situation which I demonstrated on the slide. I was seeking to explain that was no longer the case with nonthoracotomies leads.

DR. TEMPLE: I guess one implication of one of your suggestions is that if you only counted events that occurred after a very rapid rate as mortality endpoints, you could have a hierarchical

series of endpoints where perhaps the main one being actual data plus these rapid event rates and that would be sort of a lower estimate of your benefit. Then you could look at the others in addition and observe whatever skepticism one wanted associated with those endpoints.

DR. CAMM: That's very much the position that I take.

DR. PACKER: Okay. Why don't we do this. Today is different than most days because there is the possibility of a continued interaction and, in fact, there is the desire for a continued interaction between the presenters and the committee during the A&A which would not necessarily be typical for the sponsor's presentation. I get the impression that Jeremy is going to try to summarize.

What we'll do is take a break now for 10 or 15 minutes, bring Jeremy back and use Jeremy's presentation as a segue into the questions and encourage all of the presenters to help us through the questions and to attempt to provide some answers. We'll take a 10, 15 minute break.

(Whereupon, at 11:10 a.m. a recess until 11:29 a.m.)

DR. PACKER: If we can have everyone take their seats. We are getting really depressed up here.

DR. RUSKIN: Well, I would like to thank Ray Lipicky and Bob Fenichel and Craig Pratt for inviting me to participate.

Having watched this field since the early '80s and having expected a somewhat different outcome to these trials, not the results of the trials but their interpretability, I am humbled by everybody's experience. I am not going to answer the questions obviously but I'll put my head on the block up front I suppose as a way of avoiding repeating what everybody else has said which is in large part what I'll end up doing.

Let me just say that I think at the present time I can't imagine a situation in which an ICD trial alone will constitute the basis for a sudden death or arrhythmic death claim. I think that it will end up being part of a package of studies that may be useful in a number of respects. Unlike what was hoped

perhaps 10 or 15 years ago, I don't see these trials as standing alone as a substitute for a mortality trial.

I'm going to just make some general comments about the devices and some of the issues that have been raised by previous speakers and then spend one minute talking a bit about future technology because if you think it's complicated now, wait until you see what we're going to be dealing with in about two or three years.

The number of devices being implanted worldwide is really quite extraordinary. It will exceed 70,000 worldwide in 1999 and will exceed 100,000 new implants by 2002. The population of patients with ICD's is becoming quite large and they are accessible. Certainly in addition to gaining protection from these devices, they serve as a useful resource in terms of clinical research. The question is how to do that safely, ethically, and productively.

DR. PACKER: Jeremy, was that cumulative or annual?

DR. RUSKIN: No. Those are new implants.

DR. PACKER: Those are new implants.

DR. RUSKIN: New implants. In excess of 70,000 worldwide this year and in excess of 100,000 worldwide in 2002.

As has been alluded to by several people including Udho, who made this point quite early on, the use of ICD's is largely dependent upon substrate so that since we're using endpoints here of shocks for arrhythmias, knowing which patients are entered into the trials becomes critically important.

These are old data from our cardiac arrest survivor series in which you see the frequency of ICD shocks for VT or VF as a function of left ventricular ejection fraction. You can see that patients with impaired ventricular function use their ICD's for appropriate reasons twice as often as patients with well preserved LV function. In fact, most of the survival benefit is in this subset. We also found out from uncontrolled observations years ago and those observations have been confirmed by the AVID subset analyses based on EF at 40 or 35.

This is important obviously in terms of

patient selection because when you do small studies, it's entirely possible that one could have an unbalanced randomization. I would be in favor when the trials are relatively small in size of limiting enlargement for this subset of patients although one could argue that point.

The other is that the presenting arrhythmia is a very powerful determinative of ICD utilization. Here these are data from the AVID trial showing you ICD shock rates, cumulative shock rates at three months, one year, two and three years as a function of the presenting arrhythmia, the clinical arrhythmia.

You can see that people with ventricular tachycardia use their devices far more frequently than people in whom VF is the primary or initial presenting arrhythmia. Again, this may be very important in small trials with regard to patient selection.

So in selecting subsets of patients for drug trials, the etiology of the heart disease, and in particular the degree of LV dysfunction I think are very important. The ICD systems, which have also been

discussed by several people, are important. To the extent to which these can be used in a uniform way, the trials will be easier to interpret.

First and foremost it is important to know now that about 30 percent of ICD's being implanted worldwide are dual chamber devices. Although I have some concerns about overuse of these devices, when they are in the fact is that they provide a much higher level of discriminatory power with regard to separating supraventricular from ventricular arrhythmias than do single chamber devices.

The detection algorithms differ among different devices. Again, their sensitivity and specificity varies. The lead configuration that is used to looking at electrograms, and John DiMarco got at this question a little earlier, can also be important because the earlier devices had only bipolar local electrograms from the rate sensing lead to look at.

Some of the newer devices allow you to use far field signals between a right ventricular coil or a right atrial coil and an active pulse generator

electrode that gives you something that looks a lot more like a surface ECG and one's ability to discriminate supraventricular from ventricular arrhythmias may differ.

In addition, the experience of the investigator in programming these devices may have an important impact on shock rates.

What about endpoints? Well, I agree very much with what John Camm said in his talk which is that I think one has to use a broad range of endpoints here and that one cannot simply rely on a single gold standard. Time to first shock I don't think is going to be an acceptable or adequate surrogate for anything.

In using these devices to test drugs, it's going to be important to look at a whole host of variables including all ICD discharges; shocks for ventricular fibrillation, or fast VT as John detailed for you; antitachycardia pacing or shocks for slower VT; atrial fibrillation events, something that we are getting much better at diagnosing particularly with dual chamber systems; the whole issue of potential

proarrhythmic effect which is a very complex issue. I'll come back to it in a minute; and defibrillation energy requirements.

This is a real life example of one of the ways in which you can be led astray by looking just at shock rates. These are composite Kaplan Meier curves from two different mortality trials, both of them primary prevention trials in which the ICD was tested against conventional therapy to determine whether it would reduce all-cause mortality in two high-risk subsets of patients.

The first trial is the MADIT trial which, as you know, comprised patients with LV dysfunction and nonsustained ventricular tachycardia who had inducible sustained VT at ET study that was not suppressed with procainamide. They were randomized either to an ICD or to conventional therapy which was about 70 percent of the time amiodorone. This trial was markedly positive with a 54 percent reduction in all-cause mortality in the defibrillated group at about 18 months. This was a sequential design and the study was rather small by the time that the boundary

was crossed.

This is another trial that was designed for prophylaxis and it's the CABG patch trial. It was carried out in patients with coronary artery disease and comparable degrees of LV dysfunction to the MADIT population. This was a group of EF less than 36 percent who also had a positive signal average ECG. I think they required frequent VPP's on Holter.

This was a group thought to be a very high risk for sudden death and half of them got ICD's and the other half didn't. You can see that the mortality curves here were absolutely superimposable. In fact, the mortality rate in both groups was fairly close to what was seen in the ICD population in MADIT.

Yet, if you look at the shock rates in the two studies, you see a very different picture and that is they look the same. These are ICD shock rates in MADIT and ICD shock rates in CABG patch. At a year you can see that 50 percent of patients in both trials had been treated by the defibrillator.

Now, obviously the controlled group in these studies answers the question with regard to a

mortality benefit. But if you had used these two populations, the ICD recipients in these two populations to carry out a drug study, you might have been very seriously mislead. For example, in the MADIT trial a reduction in shock rate. The shock rate here, in fact, reflected a real endpoint that translated into a mortality benefit. So if a drug reduced that shock rate significantly, one might have been close to being on target in terms of a clinically important effect.

In CABG patch you saw that there was no difference between the drug treated group and the device treated group; that is, conventional therapy and device. Yet, there was a very high shock rate in the device population.

A reduction in shock rate in this group couldn't have offered any mortality benefit. Not only would you have missed the target, you would have missed the barn all together in this particular situation.

Much of this is dealt with by having intracardiac electrograms and knowing a lot about the

circumstances in which the shocks occur. I think the important point is that we have to be very careful about using time defer shock as a soul method of evaluating efficacy.

What about all-cause mortality? Well, this is, I think, a critical issue. It was raised by Milton and also by Bob Temple. I think the critical points have been made, and that is that it is possible to die from a variety of mechanisms. We are dealing with competing risks all the time. Not only in this population but in all populations with heart disease.

The modes of death, or the mechanisms of death in people with ICD's don't only involve ventricular tachycardia fibrillation but they may involve ischemia, heart failure death, bradyarrhythmias, and EM dissociation, and perhaps proarrhythmia.

It's not difficult to imagine a circumstance in which a composite endpoint of ICD shocks or time defer shock plus mortality might look very favorable for a drug that had an antiarrhythmic effect under some circumstances and reduced the

frequency of shocks, but increased mortality by this mechanism or this mechanism or this mechanism.

I think both Bob and Milton got at this point, and that is you could miss a very significant adverse effect of the drug with that kind of design.

Clearly one has to look very closely at mortality and perhaps both in a composite way and separately to get a clear sense of whether or not you could be reassured by what a drug is doing or whether you ought to be worried about it.

What about proarrhythmia? Well, I think this issue was addressed very incisively by John Camm. I just want to offer one slightly different perspective, or perhaps a real life example, in which one might have gotten into serious trouble using ICD's to assess the potential adverse effects of an anti arrhythmic drug.

It gets to the question of ethics. The issue is is it ethical to use devices to evaluate drugs for proarrhythmia? Now, it might be fine if the drug is an antihistamine. But I'm not sure that it's always fine if the drug is really a potent sodium

channel blocker or does other things that may have consequences that the device cannot deal with.

These are data from the CAST trial. I suspect these are familiar to most people in the room. Let me just take you through some of it to remind you of the fact that if you look at nonfatal ischemic events in the past. There were far fewer on active drug than there were on placebo.

Interestingly, and as you all know, there were far more sudden cardiac deaths and cardiac arrests on active drugs than there were on placebo. There were also quite a few more nonsudden deaths and arrests. That is, fatal myocardial infarction or myocardial infarction with cariogenic shock on drug than there were on placebo.

In fact, if you add these columns up you come up with almost an identical number suggesting that these drugs were converting nonfatal ischemic events to either fatal arrhythmic events or fatal pump dysfunction events. If you did this study in an ICD population, it is possible, but not known with certainty that the ICD might have saved these

patients. It is very unlikely that it would have done anything for these patients.

In fact, one third of the excess mortality in CAST was nonarrhythmic. In that circumstance the device would not have been protected. It's not at all clear to me that CAST would have been an ethical trial were we to do it today in an ICD population.

What about cost and quality of life? In the AVID trial it is clear that the ICD is a very expensive therapy. Certainly a lot more expensive than drug therapy. It's a lot more effective, too, but there is a price to be paid for it. We all know that patients with ICD's get rehospitalized for a variety of reasons, device related and sometimes drug related.

In this particular instance what you are looking at is time to rehospitalization in AVID. You can see that there is a statistically significant increase in hospitalization rate in the ICD group compared to the antiarrhythmic drug group.

Well, would an intervention that improved this so that it moved the ICD curve down to here be

useful separate and apart from a mortality benefit? The answer is sure, it might be if it reduced morbidity and cut costs and did so with an acceptable mortality profile. That might be another reason perhaps to look for an indication. This is very similar to what you saw in one of John Camm's slides.

This is an example of a very problematic clinical situation in which a patient with atrial fibrillation has a rapid ventricular response that exceeds the rate cutoff of the device. This is detected as VT. There is a burst of pacing here. It converts the atrial fibrillation to ventricular tachycardia, delivers another burst of pacing which is ineffective. If VT continues, it is redetected. Another burst of pacing, the VT continues, and we then get to an initial shock which converts the patient back to atrial fibrillation. This is normal device function. It's a clinical problem that happens and it is one in which perhaps an antiarrhythmic is one of the commonest indications for antiarrhythmic drug therapy. If you had a drug which in this situation completely prevented this sequence of events, that

would be a real benefit provided it did so without any evidence of significant proarrhythmia or an adverse effect on mortality.

I think everybody has agreed that antiarrhythmic drugs that can prevent this kind of event and do so reliably are important agents to add to our armamentarium. This endpoint is obviously a very useful endpoint. The difficulty is knowing how often we really are measuring this as opposed to other things. I think other speakers have addressed that at great length.

Just a couple of words about lesser endpoints. We've talked a lot about monomorphic ventricular tachycardia and antitachycardia pacing for that problem. That is a lesser painless intervention for perhaps a less significant endpoint.

This is an example of a patient who was in sinus rhythm and had a very short burst of ventricular tachycardia. This is a device that has a hair trigger for responding to VT within about 10 or 12 beats. There's a burst of pacing and the patient's rhythm reverts to sinus.

This event in this particular patient occurs 10 to 30 times a month. This is always the response. Does a drug that prevents this constitute a real benefit? I don't know. It certainly doesn't to this patient that I can see but there are circumstances in which it might to patients in whom the ATP is not highly effective.

I think again we have to be very cautious about evaluating the impact of drugs on lesser events and knowing the clinical settings in which they occur. I think a drug that only improved a situation in this kind of patient and did not have a similarly favorable effect on fast VT and VF would not hold a lot of interest.

The other point that I want to make is that when you use ADP as an endpoint in your trials, you really have to be very careful about looking at the distribution of events over time and over patients because we all have patients who do this 30 times a month and there are some people who do it 300 times a month. If you have a drug that shuts off those 300 events in a couple of patients, it can have a

profoundly favorable appearance in a trial but may turn out not to be very clinically relevant in a broad population of patients. Again, patient selection and distribution of events are very important and they complicate this enormously.

I think that at least for me the limitations of ICD endpoints are that clearly we are asking them to be a surrogate for arrhythmic death. I think right now they probably can't be. The reasons for that have been elucidated clearly by other speakers.

The rate cutoff of 240 beats per minute I think is as logical as any one that I can think of and it makes sense to use. The truth is that it remains arbitrary and it may overestimate or underestimate the benefit of devices.

Finally, drug efficacy may vary with substrates so, again, we need to know what populations we're talking about. Most important, I think, the duration of drug benefit may differ significantly from that of the ICD. If we use only time to first shock, we may be very seriously misled.

I think it's important that patients not be censored and dropped from studies and that they be followed for as long as possible. Certainly if there is any hope of using these kinds of studies to substitute from mortality trials, that is absolutely necessary because even a 12-month study is very, very short in the life of a patient who ought to be around for five or 10 years. Those are patients in whom the substrate is changing.

The one thing about ICD's is they don't care very much about changes in substrate. They tend usually to keep working until end stage heart failure has developed. But drugs do change with changing substrates. If you add a little ischemia or some ventricular dilatation or more hypertrophy, a drug may go from antiarrhythmic to proarrhythmic. A drug that is beneficial at three months may not be beneficial at two years.

I am finished with my general comments. I want to just say a few words about where the future of this technology is heading because I think it holds a lot of promise. But also perhaps the makings of a

lot more conferences like this with perhaps fewer answers about appropriate endpoints.

The reason that we're able to do the kinds of studies that we are now doing with ICD's is that patients can get small pectoral systems with simple lead systems that can be implanted in the EP labs rather than in operating rooms. The reason for that primarily are changes in capacitor size that have allowed manufacturers to create their own capacitors and downsize devices tremendously.

There will be in the near future ceramic capacitors that have much higher capacity for energy storage than aluminum capacitors and that will cut device size probably by another 50 percent over the next five to 10 years allowing not only smaller devices but inclusion of other technologies into pectoral systems that will dramatically enhance the complexity and the diagnostic and therapeutic power of these systems. And that's really the only comment I wanted to make about this.

The other area of great interest and excitement is that of biosensors; that is, physiologic

sensors that will give us tremendous amounts of diagnostic information primarily, I think, with regard to hemodynamics, but also electrical information and QT interval being one of those that will be used to assess patient status and will be very powerful tools for evaluating the impact of the variety of pharmacologic interventions, not necessarily antiarrhythmic.

We are now dealing with dual chamber pacing almost as a rule, as you know, and dual chamber defibrillators comprise about 30 percent of ICD implants worldwide and that number is increasing. Pacing is now involving to three and four chamber pacing in patients with heart failure, although mortality benefit is clearly not established there.

We have, or will have very shortly, access to hemodynamic sensors and perhaps in the future metabolic sensors. The technology for incorporating drug delivery systems within these implantable devices is already here. What isn't here is a logical way to use them, or the knowledge of which drugs to use and under what circumstances. But the technology to do it

is already here.

The areas in which these devices are likely to be applied include not only the treatment of ventriculary arrhythmias but certainly the treatment of atrial fibrillation. This has already happened with atrial defibrillators and a variety of pacing technologies that are being used to attempt to prevent atrial fibrillation. They will certainly be used in congestive heart failure and in ischemia as well.

I think the one area perhaps over the next couple of years where you will see the most data will be in this combined population. Most of the patients with congestive heart failure, but also those with AF.

It is important to emphasize that these two are fellow travelers and this is a unique opportunity, I think, to get information about both of these problems with regard both to understanding the physiology better, understanding pharmacological inventions better, and providing therapies that may actually prolong life.

What is happening is that you will, in fact within a year, be seeing merging of ICD and

pacemaker platforms so that what we will be using will be arrhythmia controlled devices. Not pacemakers or defibrillator, but rather arrhythmia controlled devices capable of three or four chamber pacing and dual chamber defibrillation equipped with very sophisticated long life physiologic sensors and perhaps three or four years down the pike with drug infusion systems.

The diagnostic power of these systems is extraordinary and they will provide us with not just intracardiac electrograms but hemodynamic data as well presented in a format that will allow us to follow the status of patients over days to weeks or months. These devices will communicate seamlessly with patients and physicians both by warning systems and headless telemetric systems. So we will have access to án extraordinary amount of not only therapeutic power, but I think perhaps equally exciting diagnostic power.

Certainly the heart failure experts on this panel I'm sure know more about this than I do. But certainly the opportunity to evaluate the impact

of pharmacologic interventions on the course of congestive heart failure will be a major aspect of these technologies in the future. I think it will begin to extend to other areas as well.

This discussion about endpoints perhaps couldn't come too soon. It will not solve any problems or provide any gold standards. If there is one thing I can tell you with certainty, this is just the beginning.

DR. TEMPLE: I presume they are going to have satellite linkages with appropriate consultants.

DR. PACKER: I can only comment that there used to be a time when something was wrong with your automobile, you would go to a mechanic who would use his or her judgment to diagnose the problem. Now your car is hooked up to a device that reads the computer in the automobile and makes all sorts of diagnostic evaluations similar to the pattern that you have described here.

The problem, of course, is sometimes the major reason for visiting the mechanic is that the computer isn't working very well. I happen to have

such an automobile and I spend more time trying to correct the computer communications than fixing any real problem with my automobile.

DR. RUSKIN: Well, it's certainly an appropriate caution. I think one of the remarkable things about these technologies has been the reliability of the systems. The level of accuracy and the robustness of the algorithms and the precision with which the microprocessors function is really nothing short of dazzling.

The major weak links in these systems have been the lead systems; the lead factors and insulation breaks and so on. The fact is that technology, I think, is a lot smarter than we the physicians who are using it right now. That's my take on it. I think we are the ones who probably need the tuneups, not the devices.

DR. PACKER: You can just imagine that you come in and interrogate the device and you tell the patient, "You know, you don't know this but you had an episode of septic shock four weeks ago. It was asymptomatic and didn't require therapy just in case

you wanted to know."

DR. RUSKIN: Well, I think in terms of the ability to use physiologic sensors, Milt, you may well be a decade or less from now telling patients that they were close to having pulmonary edema and that you aborted that based on information that you got or treated long before they ever had any symptoms. That's entirely possible if not probable.

DR. TEMPLE: That's the implanted dobutamine infusion, I suppose.

DR. RUSKIN: Well, I was just talking about diagnostics, Bob. I hadn't gone that far.

DR. TEMPLE: That's the next group.

DR. RUSKIN: I was just thinking about a change in the lasix prescription.

DR. PACKER: Okay. Any specific questions to Jeremy?

DR. TEMPLE: The study that basically can never be done without the implanted defibrillator, I think, is one in which people have a history of life-threatening arrhythmias. You can do studies on people who are at risk but it has become very difficult to do

and always was difficult to do, the so-called life-threatening arrhythmia trial. We had a lot of drugs labeled without ever having a proper trial in those settings.

I guess one question is even though no one wants to make final judgments is how plausible is a trial in that population? I guess one question is who would get the drug instead of the defibrillator. Leaving that question aside, if one took as an endpoint death with rates of over 240, how plausible does that seem for that special case which can't really be studied any other way? You can do comparative trials. That seems like the one way you can actually get a treatment/no treatment answer that's safe enough to do.

DR. RUSKIN: I think that's right. I think that's the most logical conclusion from today's discussion is what you've articulated. I think that the hope that those trials would actually substitute for mortality trials and allow one to perhaps approve a drug for a reduction in arrhythmic death is not going to happen. But in terms of reducing the

frequency of life-threatening ventricular arrhythmias in an appropriate population, I think what you have articulated is the right way to do that.

DR. TEMPLE: So you don't think preventing rates over 240 reflects a -- well, you obviously do think it reflects a likely survival advantage but that would not lead you to think one could claim that?

DR. RUSKIN: Yes.

DR. PACKER: Can we just have clarification of that, Jeremy? Again, if a sponsor were -- I just want to hit this on the head. If a sponsor were to come in with a trial with high-risk patients, say, sudden death survivors who had all received a device, the drug suppressed the combined endpoint of a debt and high rate VT/VF over 240 with 90 percent of the events being nonfatal as opposed to deaths, and the P value was robust and the data were internally consistent and no serious questions were raised about whether that was actually what was found in the trial, you would not feel comfortable -- I hope I'm phrasing this correctly -- you would not feel comfortable indicating that represented a drug

benefit?

DR. RUSKIN: No. I would be very comfortable saying it represented a drug benefit. What I would be uncomfortable saying is that you could label this drug as reducing mortality in patients with life-threatening ventriculary arrhythmias.

DR. PACKER: I see.

DR. DiMARCO: The labelling would only apply to people with defibrillators. And, you know, in my mind you would have to have the two groups where you would have significant better survival in the drug plus defibrillator group and ICD. That survival would have to be good enough that you could then anticipate a drug only study. Right now the evidence is the defibrillator beats every drug it's been looked at against. You wouldn't want a truly life-threatening arrhythmias a drug only recommendation.

DR. PACKER: So then in the example that we just spoke about, one, if I understand correctly, you would not provide a mortality claim for the drug. That's one. You might provide a drug benefit claim for the drug but only in conjunction with the use of

a device. John, that's the modifier that you added.

DR. DiMARCO: In this particular situation.

DR. PACKER: Of that were the case, one would almost be implying that the drug didn't have so much an impact on the disease process, although it may have, but it was really used as a way of suppressing a function of the device which is definitely unpleasant and potentially dangerous.

I don't want to over read this but I'm trying to figure out whether the nature of the claim because it would be put in on people already receiving an ICD. John, I take your point very seriously. You are calling this adjunctive therapy, (1) because of the patient population studied, and (2) because of the need for adjunctive therapy in the first place.

The patient benefit is more likely to be described as an ICD adjunct. That could be just the prevention of symptomatic shocks. That would be the primary thrust of the claim as opposed to a claim that was more linked to the prevention of a process related to the underlying disease. I hope I'm describing that

accurately.

DR. RUSKIN: I think it would have to be taken in the context of the whole picture of the drug. For example, if it was a drug that had a salutory effect on ATP events as well so that it reduced the frequency of slower monomorphic VT but had this very favorable effect that you described on fast VT and VF and the mortality went in the right direction, then I think you could say a lot more about the drug.

For example, you might use it with a lot more comfort in patients with slower VT's in whom you don't want to use a device. Or you might say to a patient who doesn't want a defibrillator that, "This drug has a extraordinary profile.

It doesn't look quite as good as a defibrillator but it's the best pharmacologic agent we've got and these are the data." I take a lot of comfort in that. The question I think where it gets really dicey is where you start to claim equivalence to a defibrillator in terms of prevention or death. That gets very difficult.

DR. PACKER: My understanding is that the

design we're talking about would never allow you to get there.

DR. RUSKIN: Right. Never. I don't think it would allow you to make a mortality claim. The other area where it might be helpful would be a drug that had some efficacy and atrial fibrillation. If you saw those kind of data and you had some efficacy in AF, that would be a wonderful surplus.

DR. TEMPLE: There are a number of circumstances. My presumption is not everybody wants an implanted device. One doesn't like to think about cost in this but it seems likely that everybody who's at risk of sudden death is going to actually get one. One possible claim that someone might seek is for use in patients at risk of sudden death to be defined when they don't want, can't tolerate, whatever, a defibrillator. That raises the question of whether this kind of data would support that kind of use and whether, you said, if the prevented answer is death is sort of a minor consideration in some ways.

Of course, the other implication is that in parts of the world where defibrillators are not

everybody's expectation, these kind of data could be considered pretty important. You would still say that until you actually have shown mortality improvement, you would still be uncomfortable actually saying anything about it even though one might expect a favorable result.

DR. PACKER: So that the only claim that they would get would be a claim for the patient population studied as opposed to the extrapolated claim?

DR. TEMPLE: No. I didn't hear that. For example, maybe you shouldn't say this specifically. What about for people who don't want an implanted defibrillator? Wouldn't this be a basis for a claimed -- I mean, would this or would this not be a basis for saying this is a reasonable thing to do in people at risk of sudden death because of whoever can't get a defibrillator?

DR. RUSKIN: Yes. I think it would with the kind of uniformly positive profile that Milton described. I think it would.

DR. RODEN: But if you had a drug with

that kind of uniformly positive profile in an ICD trial, the logical next step for a sponsor would be to go ahead and do the known ICD based trial. They would be comfortable with that in certain parts of the world perhaps or in certain other populations to do that. That would, it would seem to me, provide very important data to support such a trial.

DR. TEMPLE: That's a tricky question though. For example, it's going to be very hard to beat the ICD and it's going to be hard to even match it. If you do a direct comparison you'll lose.

DR. PACKER: He's not saying do a direct comparison.

DR. TEMPLE: You do the placebo control.

DR. PACKER: John, you can step up and say anything at any point in time because this is really the purpose. Can you just clarify this? If a sponsor intending to do a large scale trial in a geographical area in which ICD is not uniformly available or utilized says based on a uniformly positive profile in an ICD trial -- I want to make it as clean as possible because clearly most databases will not be as clean as

this -- would you allow the claim that in addition to an adjunct to ICD therapy, which is what John was saying before, that the drug could be used where an ICD was deemed to be undesirable or not feasible?

DR. RUSKIN: Yes. I think I would.

DR. FENICHEL: Well, there is a problem here in sequence it seems to me. If the intended claim is that the drug be used in people who don't want ICD's, and one believes for various reasons that have been described that efficacy in that population can only be uncertainly derived from a trial in the ICD population, then it might be not only incompletely effective but, in fact, unwise for a sponsor to begin with the credibility increasing, although not establishing effort of the ICD trial because once there's a very strong impression that the drug will indeed be effective in this ICD rejecting population, if that impression may be so strong, although not perfect, that trial is no longer ethical.

Necessary but no longer ethical. The sponsor might have shot himself in the foot and it may be if that is, indeed, the intended target population,

the thing to do is to go after it.

In the case of an unproved therapy in a population rejecting ICD's abenicio, there's no ethical problem in doing a placebo controlled trial.

DR. PACKER: Yes, Bob.

DR. TEMPLE: Well, there could be. The history with these drugs is that a lot of them make arrhythmias worse. This would provide some assurance that the drug you are putting in the trial didn't do that. I guess maybe I didn't understand what Jeremy was saying.

What I was asking was wouldn't the data we just described, as Milton said, bullet proof, perfect, wonderful data showing a reduction in unequivocally nasty arrhythmic events that are reversed by the defibrillator and a satisfactory endpoint on death plus those events, could that support use in a population of this drug in a population of patients who didn't have implanted defibrillators and couldn't get them because that's the best therapy without further data?

DR. TEMPLE: Now, that might or might not

lead to a survival claim but that might still support that use. When this all turned up 10 or 15 years ago, that was clearly the plan. We thought this would be a way to pass drugs for life-threatening arrhythmias in an ethical way that would lead to a conclusion that would say, yes, it's a good thing without doing the placebo controlled trial that everybody thought would never be done and, in fact, never was done in people with life-threatening arrhythmias.

DR. PACKER: Bob, could I just take the offer to your question and ask Jeremy to clarify an answer to a previous question.

DR. RUSKIN: I feel like I'm back on the committee.

DR. PACKER: You said you wouldn't give the mortality claim but you would describe a drug benefit. Can you tell us what the wording would sound like? Because if you could tell us what the wording would sound like, it would then help Bob get from where he is to where he wants to go. Can you take a stab at it?

DR. RUSKIN: I'm not sure that I can give

you labeling right now but let me see if I can clarify my response a bit. Bob asked a very specific question about whether or not one could justifiably extend the results of this perfect looking drug within an ICD trial to benefit in the same population who would not be candidates for the defibrillator for whatever reason.

I think you could word it like that with appropriate caveats. One of the caveats would be that equivalence or comparable degree of mortality protection to the ICD has not been demonstrated with this drug. Essentially every other element that you need in place for protection is there. That is, there is reduction in life-threatening events. There is reduction in slower VT events. There's no evidence of proarrhythmia. There's a favorable mortality trend. All of those things fit and atrial fibrillation goes away.

That would be the context in which I would describe. I can't give you the precise wording. I think it would have to contain a caveat, though, that this study had not established the drug as a

substitute for the defibrillator in all candidates, but that's not what I heard Bob say.

DR. TEMPLE: No. Right. It would just be that, well, there is more than one flavor of this. It could say that it looks like it's useful and prevents the nasty events. It could also go further and say this appears likely to correspond to a survival benefit but that has not been specifically tested. Don't think for a minute this is as good as having your own laboratory.

DR. FENICHEL: Yes. Well, this is a classic situation of a second line therapy. Isn't it? At best it would come out synthesizing all the data which says that we never found anything as good as ICD. It says. "Look, if you can't take ICD's, if you re allergic to devices or if you don't want people cutting you or whatever your reason, or you can't afford it or whatever, this is a second line therapy."

DR. PACKER: I'm still confused. Is the indication -- I understand that, Jeremy, you don't necessarily want to go there but I still want to know is the nonmortality component of the indication the

suppression of the arrhythmia that triggered the device or the suppression of the operation of the device?

DR. RUSKIN: It's the former.

DR. PACKER: It's the former.

DR. DiMARCO: Don't we already have sort of in a compressed form the indication? If you look at intravenous amiodorone my interpretation, or my memory of the data is it decreased the frequency of arrhythmia events in several different measures, but the long-term survival at whatever measure you looked at was unaffected so that it was thought that it was clinically reasonable to decrease the frequency of events even though competing therapies and the disease process didn't affect overall mortality or didn't show a change in mortality.

DR. TEMPLE: That's true. The only life-threatening arrhythmia setting where there has ever been any study is short term while people are monitored so they didn't have any planted defibrillator but they had defibrillator access from outside. There aren't any long-term studies of that

kind. There are high-risk patients but not people who are known to have frequent nasty arrhythmias.

Yes, you are right. We concluded there it was useful to suppress the events. The hope would be in implanted defibrillators that you could get closer to actually establishing mortality benefit because you're not in the laboratory so you would really be preventing things that are reasonable surrogates for that.

DR. PACKER: Okay. Please, I would like to invite all of the guests to jump up at anytime. Many of the issues that we have just been discussing in the last few minutes, in fact, are dealt with in questions No. 1 and 2. I think we can reach consensus on one and two very quickly. In fact, my sense is that we could probably go through all the questions fairly rapidly because there has been a discussion on all the issues except for No. 7.

The first question is to support approval for symptomatic claim that a new drug therapy reduces the frequency of ICD shocks. It's not just the frequency of ICD shocks that Jeremy has clarified.

It's the suppression of the arrhythmia that the ICD shocks represent.

DR. FENICHEL: No. No. Wait. Because that's the mortality, the required mortality claim. The symptomatic claim is the patients feel better and they can have lots and lots of arrhythmias not suppressed or even more arrhythmias presumably. This is a pure symptom claim for patients who are walking around with one of these boxes.

DR. PACKER: As I understand it, there are three levels of claims that are being discussed. One is a mortality claim, self-evident. Two is a suppression of lethal arrhythmias which is not equivalent to a mortality claim but is considered to be clinically very relevant and represents a prevention of IDC shock which has a benefit other than through prevention of a uncomfortable symptomatic event.

Then there is the prevention of the ICD shock which itself can be viewed as benefit because the shock delivered by the device is unpleasant. Am I correct, sir?

DR. FENICHEL: That's right. This question deliberately dealt with the last one.

DR. PACKER: It's only the last one.

DR. FENICHEL: Patients feel better because they're not getting zapped.

DR. PACKER: Okay. So if a sponsor were to come in -- as I understand now question 1 which I didn't understand before -- could a sponsor come in I suppose is really what the question is. What would be the basis for a sponsor's claim only for level three? That is, for the suppression of ICD shocks? Could someone do that?

DR. FENICHEL: The spirit of the question is exactly the spirit with which we've approached other symptomatic claims, which is that it is okay in congestive heart failure for a drug to make one feel better even if as with prosecramen, for example, it makes one lives shorter and the key message was the patient has to know that that's the bargain.

Perhaps if the mortality cost were sufficiently high, then we might decide no, it doesn't matter if the patient says he knows that. That cost

is prohibitive. We will not approve a drug that is where the symptomatic benefits associated with that cost in mortality.

The question here is given that one might have a symptomatic claim, we should perceive that as a benefit. How much of the cost side in terms of the true mortality or mortality quasi equivalent that has been discussed on and off during this morning, how much of that must be understood and to what extent must it go in the right direction? That was the spirit of the question.

DR. PACKER: Does it not presume that the committee as well as the experts agree that a level III claim per se is achievable? You are presuming that it is. You are presuming that the prevention of shocks in itself is good and many of the experts have suggested that might be. But a level III claim has to be viewed as being somewhat disappointing to a sponsor that might have been pursuing at a minimum a level II claim.

In other words, when the sponsor did their trials, they weren't shooting for mortality. They

were going for a level II claim which is the suppression of lethal arrhythmias which have they not been sought would have reasonably been associated with a bad outcome. They missed that because if they had hit that, they would be asking for it.

DR. FENICHEL: Well, I suppose that's true that is a nicer claim but there is nothing wrong with the claim that here is a adjunct. I mean, it's carbadopa. It's paramtenine. It's something that comes in to deal with the specific gap in the discerning capability of this device which is that this device does just fine with lethal arrhythmias but we couldn't figure out a way to design its algorithm to avoid picking up on this peculiar version of atrial fib.

Well, this stuff does nothing to the device's response or, indeed, for the patient's generation of serious arrhythmias. The only effect it has is this peculiar version of atrial fib. is suppressed and, therefore, the patient feels a lot better because he's not getting zapped all the time. That's a perfectly good claim. It's not as good as

some you can make up.

DR. PACKER: Tom.

DR. GRABOYS: I may be missing something. I'm just not clear. Also it sounds a little cavalier to be talking about separating these three. I don't really understand how we can do that. The population that Jeremy underscored is precisely that benefits of EF less than 40 percent is precisely the group that is going to be prone to proarrhythmia.

I don't know how we can allow a pharmaceutical company to come here with a drug that may make the patient feel better transiently but is associated with an understandable enhanced mortality. What have I missed here?

DR. TEMPLE: I believe that for someone on a defibrillator any enhancement of mortality, even if you reduce the total number of shocks, would be largely considered unacceptable. A second part of Bob's question is how much assurance would you need if it didn't increase mortality? I mean, people on defibrillators have pretty -- well, if it's just for arrhythmia they have very low annual mortalities so

you're going to need a fair number of patients to know that it's not doubled.

If the only benefit is decreasing the number of shocks, one question is, well, how many people do you have to have to be sure that you're not making something else worse and we are going to have to come to grips with that. We might need 4,000 or 5,000 patients to be reasonably sure. I don't know.

DR. FENICHEL: I would assume that in this programming, and I would like Jeremy to speak to this, that this tradeoff is made all the time. As one increases the sensitivity and makes the device more of a hair-trigger device, patients feel worse and live longer and that decision must be made all the time. I don't think this is so exotic.

DR. RUSKIN: I'm having trouble understanding why anybody would have any interest in a claim for a drug that reduced shocks without reducing the arrhythmic events that cause the shocks. I mean, it strikes me as -- I agree with Tom completely. It's just logically inconsistent.

The only way a drug could do that would be

by perhaps converting sustained VT to nonsustained VT or just making the VT slower. It's unlikely that you would find a drug that would do that and have a powerful impact on time to all-cause shocks and not have some favorable impact on the underlying arrhythmia. If that were the case, that indication would hold no interest for me as a clinician. I don't see why you would want to even consider it.

DR. TEMPLE: I'm surprised to hear that because five years ago this was widely talked about. That is, reducing partly to maintain battery life. That was one reason it was given. Maybe that's all irrelevant now because the batteries are better. In the past it was. The idea was that being shocked is bad. If you're driving a car it can make you lose control and having spurious unnecessary shocks was all by itself a bad thing.

If you added amiodorone or something like that at a lose dose and could reduce the number of shock events by 50 percent, even if you didn't change survival, which is not easy to do to change survivals since everybody is protected, that would have been

considered a benefit.

DR. RUSKIN: I couldn't agree more. I am not arguing that point.

DR. TEMPLE: That's the answer to your question.

DR. RUSKIN: No. I guess I'm hearing something different from Milton then. What I heard was a drug that actually decreased ICD shocks but that didn't have a demonstrated improvement in arrhythmia frequency. I don't see how you could get that.

DR. TEMPLE: Well, for someone --

DR. RUSKIN: One, I don't know how you could get there in the first place and, two, if you did, why would you have any interest in such an agent?

DR. TEMPLE: Bob gave an example. It might be decrease the likelihood of having sinus tachycardia sufficient to trigger the thing. Let's just take a trivial benefit. Nonetheless, despite programming the thing so it wouldn't respond to that was leading people to have shock events.

Let's put the question in its most naked form. That is obviously not a survival benefit. It's

not going to tell you to use the drug in a unprotected population but it decreases the number of shock events materially without apparent cause. Wouldn't that be reasonable?

DR. RUSKIN: In that particular case it wouldn't because that's just not a clinical problem. I mean, that's a problem that was dealt with by reasonably sophisticated programming so it's not a clinical reality. The reality is that shocks occur because of atrial fibrillation and ventricular tachycardia and ventricular fibrillation.

Those are the reasons that are amenable to any sort of therapy. The others are lead discontinuities and fractures. I think to have an agent that will have a clinically relevant important impact on shock frequency, it will have to effect atrial fibrillation, ventricular tachycardia, ventricular fibrillation, or all three.

DR. TEMPLE: Okay. So any drug that could ever pass any test would probably have a favorable effect on results.

DR. RUSKIN: I would think so. Even

though it wouldn't affect survival in someone with a defibrillator.

DR. PACKER: Essentially the concept would be that if level III, my hypothetical level III, were considered to be the only claim that the sponsor could make because they hadn't shown level II, that it is likely to be a lot of discussion as to why level III was achieved asymptomatic reduction in shocks but level II wasn't enough to raise concerns about the safety. In other words, was there a reduction in some kind of an event but an increase in another kind of event.

DR. TEMPLE: I think what we're hearing is that the only way to achieve level III is to either reduce true ventricular arrhythmias of some kind. Maybe not the greater than 140 ones but at least the others or atrial fibrillation. People would generally not argue that it's good to do those things.

DR. DiMARCO: I think we shouldn't underestimate the problem that comes up with arrhythmia frequency even in people with defibrillators. If you look at AVID where there was

specific rules that you were supposed to have had several shocks before you could have an antiarrhythmic drug I believe was about a 22 percent crossover to drug. Even in a study where there was a prohibition and you had to call the center to get permission to use a drug, you did that.

We see the people often present with flurries and if you look at the AVID registry there were 4,500 people with eligible arrhythmias. Only 1,000 ended up in the trial. The two most common reasons were physician refusal and patient refusal. I don't think all of that was because people just believed that the defibrillator was better.

I think a lot of it was because physicians were unwilling because of arrhythmia frequencies that they detected in people to commit somebody to just a defibrillator from the start. They were already on a drug to suppress things and, therefore, they couldn't be randomized to device only. It's not an uncommon problem.

DR. TEMPLE: The implication of that is that level III benefit would be highly worthwhile.

DR. RUSKIN: Just another comment. I agree with what John says. In fact, across the board about 50 percent of defibrillator recipients are on antiarrhythmic drugs precisely for the reason that everybody here has articulated. The way that they do that, the way they achieve that efficacy is by arrhythmia suppression.

DR. PACKER: Bob, maybe the best way in trying to synthesize it, level III is a perfectly reasonable claim in association with level II. Pursuit of level III without the evidence for level II raises too many questions and inconsistencies.

DR. TEMPLE: Remind me what level II means.

DR. PACKER: It's arrhythmia suppression without mortality. It's arrhythmia suppression represented by a shock. In other words, the suppression of the high-rate VT or VF. No mortality claim.

DR. TEMPLE: But not necessarily high rate. You get zapped by your defibrillator even if you're not at 240. There's usually a built-in lower

response rate. If I understand, you could not have a -- as I understand it, the plausible effect, although not necessarily one that anybody is going to stave, mortality would be found if you reduced high-level arrhythmias that elicited shocks and mortality and won on that. That might have implications for people who wouldn't take defibrillators and so on.

A lesser degree of effectiveness would be that you prevent what appear to be appropriate shocks but not these death surrogate shocks, if you like. Ones where you are not sure what the consequence would have been. It might have been nonsustained. It might have been a lot of things. It seems probable from everything that anybody has said that the reduction of discharges would occur because you suppress those things plus atrial events. Maybe the distinction isn't all that helpful because nobody can quite imagine how to achieve level III without achieving level II.

DR. PACKER: I think that's a point. If you showed level III but didn't show level II, people would ask all sorts of questions about the integrity

and internal consistency of the data.

DR. CAMM: I'm sure that you are quite right that level II and level III go hand in hand. One is mechanistic explanation of the other so to speak. I'm sure you would expect them to run together in order to justify the claim.

We had a preliminary conversation earlier about whether or not one would have to demonstrate that there was no loss of life associated with achieving this level II or level III claim. We have a slight difference of opinion between the two Bob's with Bob Fenichel telling us that we could perhaps accept a little extra mortality but let's give patients their freedom. Bob Temple is telling us it wouldn't be very much if at all.

I wonder if we need to now consider how helpful the surrogate mortality endpoint of shocks for very fast tachycardias would be in helping us come to some comfort level about whether or not mortality was going to be adversely affected in the face of improved symptomatology.

DR. PACKER: John, let me just ask a

question and ask you to clarify. Jeremy, I think, made the point that there are mortality issues related to drug therapy which are not related to sudden death which I guess would not be dealt with in a proposal to use as that surrogate based on arrhythmias.

DR. CAMM: Yes. I understand that. I'm assuming that we are looking at mortality to a degree.

DR. PACKER: The second, which is the biggest problem of all is what Bob Fenichel I think is driving at in question No. 1, is that the number of lethal events is likely to be sufficiently small but the confidence intervals will be very wide both for sudden and nonsudden events if one could even clearly distinguish between the two. Consequently, you would be left in the final analysis with a high degree of uncertainty. I don't think it would be a problem if there was a mortality reduction which was highly comforting, although not statistically significant.

I think what we're concerned about is that we are more likely than not to find mortality rates in the two treatment arms which are precisely on top of each other if not numerically slightly adverse in the

drug group but with so few events over the period of observation that the competence intervals will led one to believe that no reasonable conclusion could be made. That problem is unavoidable.

DR. CAMM: I understand every point you've made and agree with it right down the line. All I'm asking is would it be helpful to ask the data about the mortality shocks to increase the level of comfort about the claim to level II and III.

DR. TEMPLE: I'm sure it would. One of the other things you could do to give yourself comfort is to make sure there are enough people with bad heart disease and not just arrhythmia problems in it. I mean, the unnerving figures generally show that there is plenty of opportunities to see if, in effect, it was a three-fold increase. Even in a relatively low-risk population you might well be able to see it if it were that magnitude. The trouble is how will you rule out a 30 percent increase when the rates are very low. Part of it is to try to figure out what you're most worried about which I would think exacerbation of heart failure is a big candidate and make sure there

is a reasonable number of people with defibrillators who also have fairly advanced heart failure for one thing. Technically speaking, you'll have enough events to help foresee something. Second, you are addressing the area of probably greatest concern other than proarrhythmia. That one you ought to be able to see.

DR. DiMARCO: Bob, could you envision an antiarrhythmic drug coming in with just an ICD trial? I mean, I think that from what you've just said and my own feelings would be that almost any antiarrhythmic drug is going to have to have a heart failure population or some high-risk primary prevention trial that is placebo controlled to also give us an idea in that population. It's hard for me to imagine a drug coming in just with this secondary prevention ICD group.

DR. TEMPLE: I could imagine a drug, for example, with some torsade potential that people would say, "I don't think I want to study this as a primary prevention drug. I want the protection of a defibrillator there. I think in that setting we will

actually net out with a considerable advantage. The few cases where I might make things worse will be protected, but the many cases I'll suppress I won't."

I don't know. I can imagine that. The goal would be to use it only in people protected with the defibrillator for two reasons. First of all, the arrhythmia suppression potential may be of much more importance than in populations likely to have arrhythmias. The proarrhythmic potential may be less important than in the primary prevention situation where you are preventing fewer events and provoking more events. As someone said earlier, the risks and benefits could be highly population dependent. I can imagine it but it would be a little odd.

DR. CAMM: Milton, I think it's important in this context to appreciate the rate at which ICD implantation is increasing. We are still dealing with a highly unpenetrated market and a highly undeveloped market. If industry projects that, we won't be implanting 100,000 units per annum in the United States, but within a few years from now it will be 400,000 or 500,000 units. This represents a very

significant patient cohort. An adjunctive therapy for that cohort will, I'm sure, form a reasonable basis for claims to this agency.

DR. PACKER: Okay. We have covered to a significant degree many of the issues surrounding 1 and 2, I think, to the degree that we have addressed all of the issues in 1 and 2. I'm not certain that we have answered all the issues but I think we have addressed all the issues.

DR. FENICHEL: Well, answers per se were not really expected. The short preamble uses the word "suggest" some of the topics, etcetera. I think the questions should be taken in that spirit.

DR. PACKER: Okay. Let's move on to No. 3. I think this has already been addressed as well. Is it plausible that ICD patients could be recruited as patients in trials of a noncardiovascular drug, for example, an antihistamine, as an ethical means of coping with the suspicion that the drug was proarrhythmic? Now, it was referred to briefly that it may be a crazy idea. Dan, what do you think?

DR. RODEN: Well, you know, the problem is

a different one from the problem of arrhythmias in patients with heart failure or patients with ongoing arrhythmias. I think, first of all, the ethics of giving a drug with the expressed goal of seeing whether that drug is proarrhythmic are dubious in my mind, No. 1.

No. 2, I think the event rates for some of those drugs are relatively low. While you could enrich those event rates by studying them in patients with heart failure and what not, I think the reassurance that you would get from such a trial would be almost negligible.

In other words, if I wanted to know whether my antihistamine has a risk of 1 in 100,000 of being proarrhythmic, I think doing a trial in a large cohort of patients with heart failure and not seeing anything wouldn't reassure the others.

DR. FENICHEL: Let me explain the spirit of the question. My idea was that we commonly tell people with drugs -- actually, we in the division work through intermediaries. We tell people in other divisions to tell people coming forward with

antihistamines or antibiotics or antinflammatory drugs and so forth that the thing to do is to give mega doses of this somewhat suspect drug to your healthy volunteers and see if the QT prolongation or whatever other phenomena you think you've detected really get significant.

The answer commonly is, "Well, they are healthy but they are not that healthy." These people are destructible and so you can't give these mega doses. We know what doses we want to give to achieve histamine blockade or whatever.

The idea behind the question is that these people with structural heart disease, with everything else, who have been given these devices because they are at much greater risk than the general population of sudden death nevertheless are in their way the healthiest possible volunteers.

The spirit of the question was isn't this the population in whom to try out -- might this not be the population in whom to try out something like that. I think it's a pretty wild idea too. I was not saying this is a sure thing. I wanted people more expert

than I to speculate upon it.

DR. RODEN: Well, I guess there is conceptually probably not much difference between giving very, very large doses of the drug to normal volunteers and giving largest or normal doses of that same drug to a group that for some reason happened to be particularly sensitive, or you think might be sensitive. The kind of result that you might see is similar in both trials.

I guess the heart failure group has the virtue that they might be more susceptible to arrhythmias. My answer is not very different from --

DR. FENICHEL: The claimed virtue was not that they might be more susceptible. I'm willing to say that they might be equally susceptible. The point is that if they get the toxic effect they are protected.

DR. RODEN: I understand what you're saying. You would do the mega trials with normal volunteers under some monitored condition anyway. I guess the discussion is not very different from the old discussion we were having this morning, and that

is if you did this and if you saw such and such a result, what might you do. I guess the answer is I would love to see the result and then I might be able to think more rationally about what I would do.

DR. DiMARCO: Yes. I think that John Camm outlined it. Even though we say they are protected, it's not an absolute thing and there are bad things that could happen. I think you would have to design the consent form. You know, if you had a drug that was effective in gram negative sepsis in people with defibrillators, that would be a nice population but, boy, I would hate to see any many centers you would have to have to try to evaluate that.

For a no benefit trial or a minimal benefit trial to expose someone, which even with a defibrillator would have a substantial mortality risk on purpose would be hard for me to design.

DR. TEMPLE: I think the assumption is you have already -- you don't do this as your first trial. You have already done trials and you push the dose a little bit and you haven't seen any QT prolongation or

anything much but your animal data makes you worried and now you want to do something to really pin it down before you launch it on a large population in the U.S.

I think the question really asks can you think of these people for some circumstances as normal volunteers even though they have an underlying disease and invite them to participate in a study that you are applying adequate protections to because they can probably do it somewhat more safely than other people.

DR. PACKER: And be paid?

DR. TEMPLE: Uh?

DR. PACKER: And be paid?

DR. TEMPLE: In the way that normal volunteers are.

DR. PACKER: They are usually paid.

DR. TEMPLE: Some. It can't be excessive.

DR. PACKER: You could have a whole long four-day ethical conference on that.

DR. RODEN: Right. Bob, I think just to sort of be concrete for second, if you wanted to, for example, decide whether ordinary doses of terfinidine without metabolic inhibitors cause arrhythmias in

patients with heart failure. Just like high doses of terfinidine or high concentrations might cause arrhythmia in volunteers, then you might do such a study. I think the numbers required might be enormous and the ethics required we've already touched on.

DR. TEMPLE: Well, the ethics there actually are more straight forward because those people have an interest in the answer to that question. There are people with heart failure you might want to use an antihistamine.

DR. RODEN: I understand that but you can always make that argument about many drugs. You can make that argument about a drug that has efficacy (indiscernible) and more susceptible to that too. When it comes time for them to have that drug, they may not be in a position to sort of discuss it with you.

I still think the likelihood that you get useful information is small and the efficacies are large, which is not to say somebody might not want to try it.

DR. PACKER: It just strikes me it leads

one to the most interesting and complex. I can just imagine that if this became widespread because a number of drugs that prolong QT became so common place and the issue became so important that one could imagine high school counselors talking to people, "Well, what do you want to be when you grow up?" They say, "Well, I don't know." They said, "Have you considered having an ICD implanted and charging as a volunteer?" Never mind.

DR. RODEN: Well, you've got to make a living.

DR. PACKER: Okay. I think we've covered No. 4 and we've covered No. 6. We have 5. Are there other observations, drug induced changes and fibrillation thresholds that can be made during trials in ICD patients and then extrapolated to non-ICD patient populations? My question is for what purpose? Dan?

DR. RODEN: Yes. Well, there are observations and we've talked about them. Fibrillation and defibrillation, energy requirements are of interest. But you're right. I'm not sure they

would be of interest to other populations. Slowing of tachycardias might be of interest. Again, that assumes that there will be some population that eventually doesn't get implanted with an ICD -- fitted with an ICD. I like that word better. Fitted with an ICD and you would have some sense that the tachycardias would be slower or something like that. I can't think of anything else off hand.

DR. PACKER: John.

DR. CAMM: I think that one of the parameters that was going to be explored in many of these trials was the ability of program stimulation using perhaps an ICD in this kind of trial to predict long-term events with the ICD with the implication that such information might be qualitatively useful in applications in non-ICD patients.

DR. PACKER: Okay. Before we go onto 7, I just want to ask Bob Fenichel have we adequately at least discussed and addressed all the issues you wanted us to address in questions 1 through 6?

DR. FENICHEL: Well, as i said before, the questions were essentially a menu, a smorgasbord menu

to be chosen among as you desire. I think you have done that.

DR. PACKER: And I think we have gone through actually in reading this all the issues including the concept of surrogacy, the concept of what kinds of observations might lead to what kinds of claims, the kinds of patient population, the extrapolation of ICD studies to non-ICD studies.

Although we would all hasten to add that all of the thoughts are going to be modifiable based on future data, and especially modifiable based on when they are applied to a specific data set, many of the situations we talked about had been described a priority as being "ideal" and data sets are rarely ideal. These are simply thoughts that provide some sense of guidance.

DR. FENICHEL: I think there is something more about 6 before you get to 7.

DR. PACKER: Sure.

DR. FENICHEL: People have made various illusions in the course of the day to the -- Jeremy certainly referred to a number of coming developments

and so forth. What was behind 6 was the idea that there might be possible advances in ICD's which really were not especially valuable to ICD therapy per se that really didn't help the physician taking care of the patient with the ICD an awful lot, or not in any obvious way, but might be of considerable value when patients walked around with that ICD and then were used as subjects for other drug development.

So the idea was is it something that the antiarrhythmic community might somehow unite around and come and say, "Look. This is the thing that we really want." Every one of these things has a certain cost, although the cost now of some things like additional memory is very small. Every one of these things has an evolutionary cost so that anything you have to carry around has a cost.

Is there something that the antiarrhythmic community might unite around saying, "Look. This is something that ought to be in ICD's. Some particular feature. Not all these other potential features necessarily. You were thinking about features with exact purposes obscure. Here's where to put your

money and we perhaps will even subsidize putting this into devices on the grounds that they allow data to be collected which is, indeed, in the patient's interest although it's not especially in the interest of the people who make devices. It's not against their interest but it doesn't really serve their immediate purpose."

That was really the idea around 6. Are there specific device enhancements that might serve the drug community which the device community might not be aware of.

DR. CAMM: I think that there are a few enhancements of this kind. For example, the generation of atrial fibrillation can be logged by a device. It is of very little relevance to the device manufacturers in their building of pacemakers, for example, or defibrillators but it could well be a parameter put to the agency as an indicator of the usefulness of a particular therapy.

I think we ought to be well aware that the implantation of devices for monitoring purposes will become greater and greater. Some of these devices

will have therapeutic arms to them, therapeutic potential to them, which may perturb the signal in the same way that we've been discussing this morning with defibrillators.

Some will not have such therapeutic potential. All of them will have some degree of difficulty associated with the interpretation of the data which they collect in exactly the same way that we have discussed today. I can foresee in the next five years that the agency will be presented with many data sets of information derived from implantable diagnostics and it will be critical that the limitations of those data sets are well understood by the agency.

DR. RUSKIN: Just to add a few specifics. There are a number of things that are being looked at. I think that John's comment about the duration of monitoring is very important. Since memory is getting a lot easier and cheaper to install, we will have the ability to do much more closely -- excuse me, get data that is closer to Holter monitoring than it is to the kinds of isolated events that we get now.

QT sensing, heart rate variability assessment, hemodynamic monitoring. The technology for all those things in implantable devices is here. The key is, I think, as John suggested, is to learn how to use them productively in a way that alters our care of patients. I think you will see them in devices and their use is primarily diagnostic right now.

DR. DiMARCO: Yes. I think that the other thing is there is not enough market just in drug development to cause people to introduce something that has no clinical value. Many of the things that we use in drug development have some clinical value and the device companies are in competition to provide things that are of clinical value so that if something gets established as being clinically relevant, it will be both useful in a device for a physician who is using it in a clinical setting as well as for some company that wants to use that parameter in their drug development program.

DR. PACKER: Especially if the primer was something that was a very common comorbid condition in

patients who get a device like heart failure or coronary artery disease that you would monitor. Something that is relevant to those, then it would provide, I guess, a marketing advantage and people would go out and do it.

Lastly, is it plausible ICD's will become so effective, inexpensive, easily implanted that antiarrhythmic drug therapy for life-threatening ventricular arrhythmias will no longer be of interest to developers. If not, what is to be done. I have no idea what the last sentence means because it is sort of like saying if people declared peace on earth, what would happen to people who made military equipment?

We've already heard some specific descriptions of what antiarrhythmic drug therapy would still be used for including -- well, Jeremy?

DR. RUSKIN: I think the answer is that drugs won't go away. The reason is that the devices as wonderful as they are in aborting these events; that is, converting a sustained event to an aborted sudden death, they do not prevent arrhythmias and there is nothing on the horizon that suggest that they

will. This will continue to be a hybrid therapy that involves both devices and drugs certainly for the foreseeable future. Drugs that decrease the events will continue to be needed.

DR. PACKER: Bob, any other issues to the committee? Does anyone on the committee have any other comments or questions or points to raise? Bob.

DR. TEMPLE: I guess the only thing I would say is that there seems to be a fairly urgent need for updated -- actually, I'm not sure what the state of our guidelines is on all this. I think nothing too recent. It seems an urgent matter to start to put some of these thoughts into writing even where we are not quite sure what to do.

DR. PACKER: Let me just echo that by just indicating I think the sense that the committee has that the data which has been described today has been of enormous interest and I think represents a major educational experience at least to the nonelectrophysiologists and maybe to the electrophysiologists on the committee. I know of no general knowledge of all of these issues in the

cardiology community and it would be really valuable to write this up in documents other than guideline documents so that the issues are clearly understood by cardiologists who would prescribe devices as well as antiarrhythmic drug therapy. That seems to be a general purpose for practitioners as well as from a regulatory purpose.

With that, we are adjourned.

(Whereupon, the meeting was adjourned at 12:58 p.m.)

**CERTIFICATE**

This is to certify that the foregoing transcript in the matter of: Cardiovascular and Renal Drugs Advisory Committee Meeting #88

Before: DHHS/PHS/FDA/CDER

Date: April 30, 1999

Place: Bethesda, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.