information, if we look -- I think Tom presented some of that. Certainly, some of it is in the FDA review, some of it's in the sponsor briefing package. You know, I've been looking at sort of this zero to two and a half hours, and then zero to twenty-four hours, and assuming that at the end of the twenty-four hours, what you're seeing in the placebo group is a function of largely spontaneous events, plus the percentage of patients who got cardioverted. And then looking in the drug group, zero to two and a half hours, a lot of the drug effects, and then after to twenty-four hours, some of that now includes the cardioversion.

So you're right, we don't have the direct evidence that randomization would provide, but I do think you get a sense that yes, there are some things that are occurring in the placebo patients, and I think these guys have nicely shown us how it breaks up in the different time points.

DR. LINCOFF: I agree, and I don't want to be -- I'm not perseverating, and I don't want to belabor the point. The reason I bring this up, or belabor it, if that's what I'm doing, is because I think because we're talking about at the end of the day, sort of the same outcome, that the efficacy is important, but I think the overwhelming issue here is the safety, because if we're looking at this as an alternative way of getting to the same place, that avoids unpleasant, but we can't really prove a morbid procedure, then it better be safe in doing so.

DR. HARRINGTON: And that's what our FDA reviewer asked us. Right? He says he agrees that it works, he puts in big letters, but is the tradeoff worth it?

CHAIR HIATT: I think that's a good point to maybe pause for a second, and take a ten minute break.

(Whereupon, the proceedings went off the record at 2:31:09 p.m., and went back

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on the record at 2:45:08 p.m.)

CHAIR HIATT: I think we're going to begin with -- the sponsor would like to just make a comment on dose, and then I think, once that's done we'll turn to the questions.

So please go ahead. Dr. Straub, did you want to -- we'll wait just a second here.

(Pause.)

Would you like to say anything?

DR. STRAUB: No.

CHAIR HIATT: All right. I think we'll then transition into the questions. Maybe I can assume that the Committee has read the first two paragraphs of the --

(Laughter.)

DR. STOCKBRIDGE: They look fairly familiar, I think.

(Laughter.)

CHAIR HIATT: So if you forgive me, I won't read that. Let's go to question

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number 1. If you feel that you can answer these -- some of these questions rather quickly, please do so. If you feel that you need to discuss them at length, please do that.

First question, what clinical benefits were demonstrated in the development program for tedisamil? For which of them are there beneficial and meaningful trends? Reduction in thromboembolic events, reduction in hemorrhagic events, reduction in hospitalizations, reduced symptoms, avoidance of cardioversion. Let's go through those one at a time.

Thromboembolic events -- I think the data show a slight numeric excess on treatment. Anyone like to disagree with that assessment? Please.

DR. LINCOFF: The numbers are small, but a lot of these "thromboembolic events" are thrombotic events, such as pulmonary embolus. I mean, it's initially

thrombotic. In other words, they're not -- it's not a reasonable mechanism that that would come from an atrial thrombus.

CHAIR HIATT: Right.

DR. LINCOFF: A myocardial infarction -- I mean, how many -- very rare myocardial infarction is truly embolic. It happens, but realistically it's relatively rare. So although they are thromboembolic, I think to try to put a mechanism behind especially these events occurring seven days out, it's an interesting observation that there's a slight numeric excess. But that I would be very cautious about.

CHAIR HIATT: I really wouldn't want to overinterpret it. But there are certain things that you would expect from a mechanism of action, and certain things might be unexpected with drugs. And so I'm just making note of that.

Anyone else like to interpret this first part of the question? No?

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DR. HARRINGTON: No. I mean, I -- you know, when you said go one at a time, I think we can jump all the way down to avoidance of electrical cardioversion. But I'm happy to go one at a time.

CHAIR HIATT: Well, so was there a reduction in hemorrhagic events? I don't think so.

DR. HARRINGTON: We didn't see any data on that.

CHAIR HIATT: There isn't any data. Hospitalization?

DR. HARRINGTON: No data.

CHAIR HIATT: Did you all capture length of stay? Do we know that this therapy might have shortened a hospitalization duration? Don't have any idea?

DR. RACZKOWSKI: We did not capture that information.

CHAIR HIATT: Okay. Reduction in symptoms attributable to atrial fibrillation. This is actually a little harder, because they

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didn't capture symptoms. What do you all think?

DR. HARRINGTON: You said not to bring it up from yesterday, but I will anyway, that I thought Dr. Pritchett made a pretty compelling case that symptoms track the resolution of AFib. He cited not just yesterday's data, but long experience in research in this area. So I'll be willing to say that it's likely that symptoms were reduced.

DR. STOCKBRIDGE: Yes, that's question 2.

DR. HARRINGTON: Okay. That's my fantasy question.

DR. STOCKBRIDGE: That's right.

(Laugher.)

CHAIR HIATT: The word in italics is "demonstrated."

DR. HARRINGTON: There was no demonstration. Fair enough.

DR. STOCKBRIDGE: Avoidance of the

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surrogate for --

CHAIR HIATT: Yes. Surrogate for a surrogate. Avoidance of cardioversion.

DR. HARRINGTON: Yes. I mean, I thought Tom's chart there at the end was very helpful to try to quantify that -- what you were -- you know, what you were getting.

CHAIR HIATT: Did you think the number of cardioversion events avoided was a significant number?

DR. HARRINGTON: I guess if you're the one patient that didn't have it, but --

DR. LINCOFF: In part, though, the protocol discourages it until after -- well, actually not for cardioversion. It seemed the low rates of cardioversion were lower than we had seen in some other data, but they may have been part of the protocol. So I think that's hard to say.

CHAIR HIATT: Okay. Well --

DR. MASSIE: I interpreted it as having a substantial proportion of people who

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-- with years of AFib. You know, there were people -- what did they say, the median was three to -- three years or so of chronic AFib for those that were -- three to five.

CHAIR HIATT: They had the population divided in one of those slides into those with very recent onset and those who are more chronic. As I recall, it was about 50/50.

DR. MASSIE: Yes. But the number of chronic was really chronic. I'm not sure I know that from other programs, but it's --

DR. CANNON: Well, I didn't necessarily interpret that to mean that they had been at atrial fibrillation for four or five years, but that they had a history of atrial fibrillation. So maybe we could get clarity on that.

DR. KOWEY: That's correct.

DR. CANNON: I'm sorry. Which is correct?

DR. KOWEY: It was a total history

of atrial fibrillation. It's the --

DR. CANNON: Oh, okay.

DR. KOWEY: -- not that they had been in it for five years.

DR. CANNON: Okay.

DR. MASSIE: But even that, but certainly not as much as I imagined. If you're in atrial fibrillation for five years, your chances, I think, of getting cardioverted out of it, if you're an older sort of person are pretty tough.

So I interpreted the relatively low rate of excess -- extra cardioversion on the drug, but maybe that's wrong because in fact the control group had a pretty good rate of spontaneous cardioversion, if we could interpret the data as well. And it came out of the same pool of patients, so I -- I was surprised about the narrowness of that difference, but I think it's real. And it's probably meaningful to those people that experienced it.

CHAIR HIATT: So we all agree that the treatment avoided cardioversion.

DR. MASSIE: Yes.

CHAIR HIATT: All right.

DR. CANNON: But I'd also say I think that the data are more compelling for men than for women. I think it was less impressive --

CHAIR HIATT: Yes.

DR. CANNON: -- a delta for women.

CHAIR HIATT: Okay.

DR. MASSIE: And I guess -- I don't know. Is it going to come -- atrial flutter going to come -- is there a separate question on that? Because it certainly was less impressive for atrial flutter than fib, as well.

CHAIR HIATT: Yes, this question doesn't specifically ask what you think of the efficacy. So we'll definitely get to that.

Anything else demonstrated?

(No audible response.)

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Okay. So let's do number 2. What clinical benefits would you -- should have been expected through the use of tedisamil? Compared with what treatment -- electrical cardioversion, rate control, another drug -- are these clinical benefits expected?

So, kind of thinking about this again, as we did yesterday, would you expect that quicker conversion with a drug would result in a reduction in thromboembolic events? We had that sort of thing, about how long you're in atrial fibrillation and that the risk of cumulative, and, if you shorten it by an hour or two, is that going to mean less thromboembolic strokes? So does anyone have anything --

DR. HARRINGTON: I guess it depends what the comparator is, and Norm gives us that out. He says compared with other treatments, electrical rate control -- you know, I think you could make a lot of speculation on the other side of the equation here that -- I

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think I brought this up yesterday in AFFIRM. One of the reasons that rate control may have been better than electrical -- than arrhythmic control was that people used more anticoagulation in the rate control group as opposed to the other group.

CHAIR HIATT: Right.

DR. HARRINGTON: They just assumed you didn't need it. And, again, somebody said it today, that -- don't assume that you don't need it in any of these conditions. So for me it's a stretch to say that quicker conversion with a drug would result in less thromboembolic events. I think if a person is going to need anticoagulant therapy, they're going to need anticoagulant therapy, it's unlikely that you would reduce these events.

CHAIR HIATT: And another way to interpret this a little bit literally is that, if the watchful waiting strategy was wait 24 hours and then cardiovert, or maybe even out to 48, and then you've saved yourself those

many hours in atrial fibrillation.

Therefore, you've reduced that exposure a little bit. Is that delta meaningful in terms of subsequent risk? Because it's going to be driven more by practice patterns --

DR. HARRINGTON: That's --

CHAIR HIATT: -- to chronically anticoagulate may influence that outcome far more than saving a couple of hours in atrial fibrillation.

DR. HARRINGTON: Yes. It's awfully complicated, because you could make the other case that, well, if I'm going to do watchful waiting, let's put them on some heparin and wait. So I think, Bill, this is -- it's hard for me to -- even the fantasy world of expected, it seems unlikely that that would be expected, but --

CHAIR HIATT: So, yes, I can imagine that you'd expect there to be that benefit. How about reducing hemorrhagic

events, need for anticoagulation? You're sort of saying we'd rather them -- people -- even if they're in sinus, they may still be at risk unless they really totally convert.

DR. HARRINGTON: Yes. I mean, what the guidelines tell us is that it's -- it's not -- if you -- that you make your decision based on -- for anticoagulation, based on what the baseline risk of the patients is. And if, for example, you have a high CHADS Score you end up on anticoagulation regardless of whether or not you're back and forth. That doesn't matter. That's not part of the equation.

DR. MASSIE: And we have pretty good data internally from the trial, which -- that most people remained on anticoagulation, too. Were discharged on it.

CHAIR HIATT: So we wouldn't expect that this treatment would reduce hemorrhagic events then, right? Would reduce need for hospitalization? Might shorten it, but maybe

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not if we had to monitor people for nine hours.

DR. HARRINGTON: But if you did a study -- well, let's say, you know, Peter's example when Mr. Simon asked him, "What would happen to me?" and Peter gave the example of, you know, maybe he would do this in his emergency room and monitor him for two to three hours and send Mr. Simon home, as opposed to admitting you to the hospital doing something else, it might. I think you could create a case.

I don't think the data here demonstrate that, but you might imagine a treatment strategy that was, you know, observation unit-based that reduced the risk of hospitalization.

CHAIR HIATT: So it might be less resource-intensive.

DR. HARRINGTON: It might.

CHAIR HIATT: Okay. Does everybody agree with that? I think -- well, except if

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we really think that nine hours is necessary, you know, you might have -- you might have consumed all of your savings just by that recommendation alone.

DR. CANNON: But not everybody would have to be monitored nine hours, perhaps. If the QTc intervals, as Peter said, return to normal by two hours, well, why keep them seven more hours?

CHAIR HIATT: You can bet that knowledgeable physicians would make that choice. So maybe in the end it would play that -- play out, and maybe the observational study would help clarify that a bit, too.

DR. MASSIE: I would say the answer to that question is really going to be determined by organizational factors rather than probably different --

DR. KOWEY: Can I answer -- continue to talk to you, Bill, or --

CHAIR HIATT: Sure.

DR. KOWEY: -- am I supposed to sit

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down? I'll be careful, and I'll be very discrete and short. But one of the things that has been bothering me the last couple of days that -- and I think Dr. Cannon may have said this previously, and that is that we keep thinking that we know when people go in and out of AF.

And this whole idea of waiting 24 hours is making me very nervous, because, for example, in the TEE literature you -- if you look at atria and patients that have been in atrial fibrillation for 24 hours, you begin to see smoke and spontaneous echo contrast. And there is an incidence of stroke that occurs earlier than 48 hours.

The 48-hour recommendation is based on an Annals article from 1999, and out of 200 patients that were observed there were three events. It was just -- they thought that was pretty small and they said, "Well, we can wait 48 hours." Well, 48 hours is pretty long, number one. And, number two, I don't know if

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my patients really know when they -- exactly they go in and out of AF.

So this -- Mr. Simon is --

(Laughter.)

So I'm not disagreeing with the idea that waiting sometimes isn't such a bad deal, but you've got to remember that when I see a patient with atrial fibrillation, I'm pretty nervous about -- if I make a decision -- and Bob said this earlier -- if I say I'm going to cardiovert this guy, if that's the decision that I've made, I'm going to cardiovert this guy -- whether you -- whether I do it with a drug or I do it with electricity -- that's the path I've chosen. I don't sit around and wait. And one of the reasons I don't wait is because I don't know if I have the timing right, and I'm very concerned about a thromboembolic event.

And I don't want to start heparin, Bob, because in our hospital the first PTT we get on heparin is infinity, it seems like, to

be on the protocol. So I really think that you need to be careful just a little bit with this waiting thing.

CHAIR HIATT: Well, then that would mean that you really would never expect a cost savings here, because you're going to do something based on what that patient is presenting symptoms and if it's -- the drug weren't available, you'd shock them.

So that what I was going to say to the sponsor is, you know, in the observational context of the study you are proposing to do, maybe some healthy economic data would be very helpful, because that would give us another lever, you know, another compelling reason to do a drug, because it might save dollars. I mean, minutes in the emergency department or avoidance of a hospitalization might be another thing that we hadn't really talked about in the last 48 hours in any kind of formal way.

But we've all been patient-centric.

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But maybe we should think about the system a little bit, too. And you have the ability to do that.

DR. STOCKBRIDGE: I just want to point out that getting people out of the hospital is an acknowledged clinical benefit and a basis for approving a drug. Saving the health care system some money is not.

DR. HARRINGTON: But the two of them are intrinsically linked.

(Laughter.)

CHAIR HIATT: Yes. But, remember, that's FDA versus -- I mean, that's -- but still, our job is to --

DR. STOCKBRIDGE: Depends on how much the drug costs.

(Laughter.)

CHAIR HIATT: Yes. You can interpret that any way you need to.

(Laughter.)

Do you think that you would expect to reduce the symptoms attributable? So, Dr.

Harrington would say yes; right?

DR. HARRINGTON: So now Norm will let me say yes. I think Dr. Pritchett made a compelling case that resolution of fib ties to symptom resolution. I believe it.

CHAIR HIATT: Me, too.

DR. LINCOFF: But only for the couple of hours, so you can get the electrical cardioversion working in the other patients as an alternative, or if you want to expand the definition of symptoms, the symptoms associated with going through an electrical cardioversion.

CHAIR HIATT: I think you have to count both. I really do. I think it's avoiding a bad thing, and it's feeling better quicker. And those two have to be included.

Once again, I think in an observational study, gathering that kind of information would be very helpful.

Avoidance of cardioversion -- yes, we already said that.

Okay. Anything else on question number 2?

(No audible response.)

Cited conversion rates, excluded patients who underwent early electrical conversion, those who converted prior to receiving study drug, those who otherwise did not receive study drug -- are these exclusions reasonable? If not, how should the cases be handled?

And we actually saw some additional data that addressed that issue. Does anybody have a concern with how the sponsor dealt with that data?

DR. MASSIE: Well, just the one point that the people who got shocked for non-cardioversion reasons, but for the torsade, I think it should be handled as failures. But the others we saw it didn't make much difference in how it all came out anyway and --

CHAIR HIATT: Yes.

DR. MASSIE: -- so I thought it was reasonable.

DR. HARRINGTON: Again, the FDA handled it the opposite way, along the lines of what Barry said. And we could argue that the magnitude of the effect was somewhat diminished, but there is still an overall effect.

And so, I mean, I think they were very transparent in their -- in their showing of the data, which is important, and I have no quarrel with using the modified intention to treat in a blinded study, and they walked us through the patients. I'm okay with that.

CHAIR HIATT: The one thing we didn't hear was that initial step from consenting to randomization, how many people were lost, how many people did you have to screen to get one in? I don't want to digress. I don't want to have you start pulling up slides. Can anyone give us just a sense of -- a lot probably. Pardon?

THE COURT REPORTER: Please come to a microphone.

DR. RACZKOWSKI: Dr. Driessen was estimating approximately 10 percent.

CHAIR HIATT: Ten percent got in.

DR. RACZKOWSKI: From consent to --

CHAIR HIATT: So 90 percent did not. Other way around.

DR. HARRINGTON: He said consent to randomization, 10 percent dropped out. You're asking the question screened to consent --

CHAIR HIATT: Correct.

DR. HARRINGTON: -- how big that number was.

CHAIR HIATT: Yes. Unless they kept screening logs, et cetera, you wouldn't know.

DR. HARRINGTON: Wouldn't know.

CHAIR HIATT: Okay. Anything else on 3?

(No audible response.)

Number 4. In a restricted sense,

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tedisamil is clearly more effective than its placebo. Among patients who had been in atrial fibrillation for three hours to 45 days, the rates of spontaneous conversion on placebo within a two and a half hour window were three to 10 percent, while conversion rates on drug were 18 to 55 percent at proposed doses.

How well characterized is the relationship between time in atrial fibrillation and spontaneous conversion? Three percent of patients converted spontaneously after randomization but before the steady drug administration, and maybe that randomization -- that conversion rate on placebo might have continued.

So very much like we've just deliberated previously.

DR. MASSIE: I thought this was, you know, enlighteningly different in the sense that there was not the universal cardioversion at the end of the treatment

window, and we did get to see that there was more spontaneous cardioversion, at least in the group that hadn't been in AFib for very long, than I might have guessed from yesterday. But I think it's pretty well characterized in the study. I mean, that's the question.

DR. LINCOFF: The caveat of that, of course, is that we don't know they chose not to cardiovert. They may have chosen not to cardiovert because it was the physician's clinical estimation that that patient was likely to convert on his own anyhow. So it doesn't necessarily apply to all comers.

But that having been said, we actually saw a lot more data today than we did yesterday, including a nice review I think in the literature by the FDA reviewer that I found very helpful.

DR. MASSIE: And we also saw a fair number of people who were chosen -- where they didn't cardiovert also spontaneously. so I

think we got a picture that this happens in at least the early subgroup.

CHAIR HIATT: You know, what did we say, half the men at the end of 24 hours were still in AF, and about 60 percent of the women were still in AF?

DR. HARRINGTON: And then, if we look -- I'm just looking at the slides we saw this afternoon -- with no DC cardioversion, the placebo group men were 30 percent at 24 hours, and for the females it was 18 percent. So there is a continued accumulation.

What I think Barry asked that we -- or you asked that we don't have the data on the relationship between time in AFib and subsequent spontaneous cardioversion. Or did we see that? Oh, did you show us that, Tom?

CHAIR HIATT: Well, we saw that, if you had been out more than seven days, the probability was about zero, right?

DR. HARRINGTON: That's right. I'm sorry, you're right. That's right. You lined

it up nicely for success rates.

CHAIR HIATT: How does that look now? How well characterized is the relationship between time in AF and conversion on tedisamil? So we didn't see quite that curve that we were looking for, but I think that we got at it in terms of this 48-hour window. We didn't see 24 so much. But I also found it interesting that there were still conversion rates occurring late.

DR. LINCOFF: I don't want to compare, but what -- how much of a conversion rate do we consider is relevant late? Because if you recall, yesterday we saw conversion rates late, too, but said, you know, that has really fallen off already. So, you know, in the teens is about where we saw today, and I think my recollection is that's what we thought was diminishing already by yesterday. So I'm not sure it's all that different.

DR. HARRINGTON: I mean, the data were, three to 48, 48 to seven, and eight to

45. For me, it was 52, 28, and then 13. For women, 32, 16, eight. So it is -- I would say that we've got it characterized reasonably well. We didn't see that nice histogram broken up by 24-hour blocks, but I think we've got the essence of the answer here that it's more effective early and it diminishes with time.

CHAIR HIATT: I agree. Any other comments?

(No audible response.)

What length of time in atrial fibrillation is clinically meaningful? Any new thoughts on that? Anyone want to voice any opinion? We've heard Tom's opinion.

(Laughter.)

DR. HARRINGTON: Well, I thought Peter just helped us out with this, too. He said that, you know, the guidelines -- I had made reference to the guidelines saying 48 hours is your -- sort of your anticoagulation go/no-go.

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And Peter just told us that it might be in fact earlier than that, that the -- that atrial smoke begins to be seen on echo, which is a sign of potentially thrombotic risk. So perhaps it's fairly short, maybe a day or two. I don't think we can be -- I don't think we have data that would say more than that.

CHAIR HIATT: So even short time today that may be symptomatically relevant and puts you at a pro-thrombotic risk. Any other comments on that?

For patients who have been in atrial fibrillation for what duration is the time-saving attributable to tedisamil clinically meaningful? So what have we got in terms of clinical benefit here? It actually might be nice to go around the table a little bit on that one. Fred?

DR. KASKEL: Well, I thought we were looking at a 48-hour window as our --

CHAIR HIATT: No, we're talking

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about what time savings. So you're going to save that patient a couple of hours, maybe more, of being in the state of atrial fibrillation. Is that clinically relevant? Would the kidneys like that?

DR. KASKEL: No, I don't think the kidneys want to be like that either.

CHAIR HIATT: Okay.

DR. KASKEL: I think it is meaningful to get them out early. It has an advantage, and we talked about it yesterday, how this may set up mechanisms we don't know about that would preclude being -- having long durability. You might go back in quicker than if you got them out of it earlier, so I would think that's --

CHAIR HIATT: So you think it is clinically relevant, then.

DR. KASKEL: Yes.

CHAIR HIATT: Okay. Rich?

DR. CANNON: So maybe this belongs better under question 2 about what we -- what

might be expected. I would think that there could be a considerable time savings if this drug is safe and effective and gets them out of atrial fibrillation, gets them home very quickly, as opposed to watching them in the hospital, watching them overnight.

So I think there could be a time -- now, if the comparator is electrical cardioversion, you know, maybe that's shorter than putting them in the hospital, putting them on heparin, and just watching with a beta blocker to see if they convert on their own. But we have no data, so I'm just speculating that there might be a time savings.

DR. STOCKBRIDGE: Again, if I may --

DR. CANNON: If that's what the question is driving at.

DR. STOCKBRIDGE: Well, the purpose of the question was to get you to say, "I think people who have been in AF for three hours to 45 days are likely to benefit from

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receiving the drug." It's to name that interval again.

DR. HARRINGTON: So this is -- you want us to answer the -- what duration of AFib --

DR. STOCKBRIDGE: That's what it asks.

DR. HARRINGTON: Ah.

DR. CANNON: Well, so we've -- I think we're in agreement that the longer someone has been in atrial fibrillation, the lower the efficacy. And I think that it goes down day by day. It's highest within the first 24 to 48 hours, and then it goes down gradually. And I would think by the end of two or three weeks it's probably not worth doing it.

CHAIR HIATT: In fact, we have probably flushed that one out a fair amount.

DR. CANNON: Yes, I mean -- I mean, personally, I would go with electrical cardioversion and anticoagulate them -- for

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someone who has been in -- I think they've been in it over 48 hours, I would anticoagulate them or use a TEE-guided approach and use electrical cardioversion.

DR. MASSIE: I would say that to answer this question we really have to talk about safety, because I think the effect is not very impressive after 48 hours. Whether it's impressive enough to be worth doing it for less gain is a safety question.

MR. SIMON: I guess from a patient standpoint, if I'm in atrial fib, and it's 100 beats a minute, it's a lot easier to withstand that than if you're at 150 or 180 or 200. The difference, the restrictions, et cetera, et cetera, go up obviously with the higher the rate. So the faster you can get the rate down, even if you're in AFib, the higher -- the faster you can get the rate down, the better off it is for the patient.

CHAIR HIATT: Well, we'll come back to risk-benefit, too.

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All right. Anything more on question 4?

DR. HARRINGTON: So are we agreeing that, after 48 hours the benefit really drops off?

CHAIR HIATT: Yes.

DR. HARRINGTON: I mean, I think so, but I would say it's not no benefit, but it drops off substantially.

DR. CANNON: And then, this gets at the risk issue. There is no evidence that the risks drop off with time, so that that risk-benefit ratio stays proportionately the same. So you have the same risk but diminished efficacy. It seems to me that the argument for using it drops off considerably after 48, 72 hours, somewhere in that range.

DR. LINCOFF: Unless your expectation of efficacy is principally the avoidance of DC cardioversion.

CHAIR HIATT: So, then, if it had no risk, you could always start with this

strategy, even if you only got a one percent net benefit.

DR. LINCOFF: Because otherwise we're just -- we are talking about time, which is more dependent upon your hospital system and your ability to just get mobilized with electrical cardioversion. If there wasn't the desire not to have electrical cardioversion, it would strictly be -- make your hospital more efficient, and you don't need any of these drugs.

DR. HARRINGTON: So let's talk about that for a second, Bill. So if we look at the data that they showed us, in the first 48 hours, 52 percent of men and 32 percent of women convert. Sounds like we all accept that those numbers are reasonable, because we're assuming, then, you avoided electrical cardioversion in 50 percent of men and a third of the women.

In the next bucket, 48 to seven days, it's now 29 percent and 16 percent. Is

the 29 percent for men -- that's awfully close to the 32 for women. Do we accept that, or do we say that -- and then, the 16, are we now starting to get into Mike's place of the teens seems a little low?

DR. LINCOFF: Well, I actually wasn't in favor, if you recall yesterday, of truncating a time, because I thought whatever it is -- again, to me, the only issue is; does the risk offset this benefit in preventing DC cardioversion? Except, you know, the other issues like cost, which we -- you know, we can't -- the physician and the health system is going to have to evaluate that.

But if we set those aside, as we must, to me the only issue is, how valuable is it to avoid a DC cardioversion, even if it's in 16 percent of patients? And how many -- if we expose 100 percent of patients to the drug and get some risk with that, is it worth preventing 16 percent cardioversions?

DR. CANNON: But the other issue --

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and I tried to raise this yesterday, and perhaps not well, is that when we talk about late treatment -- so someone who has been in atrial fibrillation four days, five days, six days, two weeks, three weeks -- unless they have been on anticoagulation, unless they were already on coumadin, then I don't understand the strategy, because you will either have to use a TEE-guided approach, in which case go ahead and electrically cardiovert them because they are going to be sedated for that, or you're going to have to send them home on coumadin for three or four weeks and bring them back.

So the --

DR. LINCOFF: But a lot of these may well be. They may be chronic valve patients, they may be chronic AFib patients who are on it, and, you know, were traveling and didn't have time to come into a hospital when they went into AFib, because they're not at 250, so it wasn't a mandate.

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DR. CANNON: Okay. But --

DR. LINCOFF: And there's a lot of --

DR. CANNON: -- there is going to have to be that proviso, but I think for many patients they may not have been on anticoagulation during that period of time.

DR. LINCOFF: Right. But that's still -- that gets back to my original idea that it's not the time as -- that's as important as preventing the cardioversion, because you're right, if you've got the leisurely pace of instituting cardioversion, of anticoagulation, et cetera, then time doesn't matter anyhow. To me, it's strictly avoiding electrical cardioversion.

CHAIR HIATT: Anymore on 4?

(No audible response.)

So 5, what effect does unsuccessful conversion with tedisamil have upon subsequent attempts at electrical conversion? I think we asked that question. I don't remember if we

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saw something about it that --

DR. MASSIE: I asked whether they -- I asked that general question whether it worked as well and was there any additional problems, and I think there wasn't data. Is that correct?

CHAIR HIATT: Any comments?

DR. STRAUB: We've been showing some data on defibrillation threshold at one of our core slides showing that there is no detrimental effect. There was even a benefit in one of those finding -- studies in the very beginning.

CHAIR HIATT: Yes, thank you. I thought we had seen that. So the answer to that would be -- well, it doesn't seem to have an effect on your ability to respond to an electrical cardioversion. So how would --

DR. MASSIE: I would guess if there were a difference, it would probably be favorable based on favorable --

CHAIR HIATT: Okay.

DR. MASSIE: -- even with some of the other drugs. But the real question was really the safety question, whether it alters that issue.

MR. SIMON: If you have unsuccessful from the pharmacological effect, that obviously lengthens the time that you are still in atrial fib. Does that have an effect on the electrocardiogram, then, if it's two, four, six, eight?

CHAIR HIATT: The question I think is whether the drug does something to the atrium that makes it refractory to cardioversion, and then I think the answer is no.

DR. HARRINGTON: If you look at slide 32, if anything, as the sponsor indicates -- it's a small number of patients in this proof of principle, but it suggests that it's better, if anything, the defibrillation threshold. And that would make sense with the effects of the drug, right? It

was also being looked at as an oral agent for treatment of these patients.

DR. KOWEY: The answer -- I'm sorry, the answer to Mr. Simon's question -- does the delay, by giving a drug, have an influence on the effectiveness of eventual electrical conversion? The answer is no. Actually, it has been fairly well studied.

Barry said earlier -- or someone said earlier, if you get out to two, three, or four years of atrial fibrillation, then obviously electrical conversion is much less effective. Within the time frame we're talking about, there's no impact.

CHAIR HIATT: Okay. Number 6, how is atrial hemodynamic function affected by tedisamil? Does this matter? So we kind of wrestled with that a bit yesterday, too. I don't think we have any data here to comment on this, do we? Do you guys have any data?

DR. HARRINGTON: None that we saw.

CHAIR HIATT: None that we saw.

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Probably none that -- you didn't do echos on people looking at atrial function. So probably not known.

DR. STOCKBRIDGE: So I enter that as no data, don't care, is that what I hear?

CHAIR HIATT: No data. We tried to speculate, why would we care? And it would seem that it would -- you would care because it has some clinically relevant sequelae.

So that you could -- you know, if it changed your response to something, either other alternate therapies or if it set up somehow -- it changed atrial function, but it seems to me whatever it would do would have to be relatively transient to a hemodynamic state of the atrium, or maybe it could become pro-thrombotic, maybe it would set up the atria in a way that would be more likely to have clot. And that's all highly speculate.

DR. CANNON: Well, we heard from Dr. Waldo. I believe he mentioned that there are studies to show that with any

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cardioversion, whether spontaneous, electrical, pharmacologic, that there is atrial dysfunction for a period of time.

DR. STOCKBRIDGE: But that was not this drug.

DR. CANNON: No. No, no.

DR. STRAUB: We have conducted a hemodynamic study to address hemodynamics with oral tedisamil. I've made the statement in the beginning that we consider tedisamil to be hemodynamically neutral, so we have done a series of studies for the oral program. We have also an IV study.

I'd like to show you what it does in an oral setting, 40 milligram BID was given over two weeks followed by 80 milligram BID over 10 weeks versus a placebo. The 80 milligram starts off in the uses of peak plasma concentration, which is comparable with an 0.32. The AUC would be higher, much higher.

So what you see here is right

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atrial pressure at baseline, and you see at week 9 data, you see change from baseline versus placebo. It's not significantly different, so we saw a slight decrease, but it did, for sure, not show an increase. And systolic right ventricle pressure, also a slight decrease but not significant. And diastolic right ventricular pressure, the same trend.

We also have data -- so this is the data on the wedge pressure in these patients. You see in millimeters of mercury at baseline was 18 and 19 millimeters of mercury. At week 9 it was down to 16. That was slightly less decrease than in the placebo; however, not significantly different. But at least it didn't show an increase.

3.5.6 -- I'd like to show you a study with intravenous-applied tedisamil. That was a single intravenous rising dose, open study, of tedisamil dihydrochloride investigating human dynamics in patients with

documented ischemic heart disease.

3.5.9 -- you see here the preliminary -- the pressure in the right atrium, which shows a decrease at the lower dose. At .3, it showed a slight increase following intravenous, but not relevantly so. The results were not significantly different from baseline.

Pulmonary artery and diastolic pressure was showing a tendency to increase. There was also a significant value at rest here, but not at maximum workload. If you look at the wedge pressure, there was a slight increase at rest in this function, but it was not even with the higher dose at maximum workload.

So this is the data we have for hemodynamics.

CHAIR HIATT: That's helpful.

DR. STOCKBRIDGE: Was it?

CHAIR HIATT: Well, I mean, we --

DR. STOCKBRIDGE: What did that

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have to do with how well your atria work after you've been converted?

CHAIR HIATT: We don't know that.

DR. STOCKBRIDGE: Oh, okay. So why was it helpful?

CHAIR HIATT: It looked rather neutral in terms of --

(Laughter.)

DR. MASSIE: I would say that it's not helpful for that question, but as a heart failure doctor it -- it's nice to know the hemodynamic effect of the drug on ventricular function, because some of the drugs we use make it worse.

CHAIR HIATT: Yes. I mean, that sort of makes you think that -- it doesn't look like it's a drug that's going to have a pronounced effect. But in this --

DR. MASSIE: But ventricular function is a reflection of the ventricular function in most cases. And if you want to see if it moves, you probably have to look at

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it and see whether it moves.

DR. STOCKBRIDGE: So is this something that anybody needed to study further? So no data doesn't matter? That's --

DR. HARRINGTON: No data, we don't know if it matters. I don't think we know that.

DR. LINCOFF: Nor do we know it for any other intervention to convert atrial fibrillation. So why start here?

CHAIR HIATT: How much of a safety concern is torsade? Have the rates of torsade been adequately characterized in the patient population at the dose for which tedisamil should be used?

DR. LINCOFF: This is my biggest concern regarding safety, and I think that at the doses it should be used, they've tested that. But I think there has been a lot of concern here about the population that should be -- in which it will be used, even on label,

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and that is with concomitant medications, a broader spectrum of real illnesses, less exclusion criteria, and the fact that it's a relatively small number.

The upper limit of the confidence interval is close to 3.0 percent, so I think that that's my concern, that we have too much uncertainty regarding true torsade risk.

CHAIR HIATT: So wait a minute. So the uncertainty is based on the fact that it hasn't been studied in all possible populations, and it hasn't been studied on potential drugs that may be used in the real world.

DR. LINCOFF: And it's a relatively small sample size. That doesn't even begin to approach other issues such as what will be the real rates of errors in practice, because we can assume there will be a very strong good faith effort to minimize those, but that's also a factor that's -- that is very difficult to quantify. But all of these issues could

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well serve to increase the torsade rate beyond what is already a wide margin.

CHAIR HIATT: Okay. So tell me, in the setting it's going to be given, how much of that is going to matter? I mean, how is that going to change the fact that they are going to be highly monitored and you can shock them out of it?

DR. LINCOFF: Well, that wasn't the -- I mean, the question is the incidence of torsade, because a proportion of torsade isn't as easily -- I mean, some people will -- will die of torsade, especially out in practice, where, as time goes on and people become more -- as it becomes diffused into practice and people become more comfortable with using it, I mean, you can easily -- people die of torsade. They die of ventricular arrhythmias. People die of things that, you know, 99 percent won't, but one percent will.

So I think if you have torsade, you've got to expect a proportion of patients

to have a bad outcome, if not death, anoxic encephalopathy, et cetera. It's an undesirable event.

Now, I'll grant you it's much less undesirable if it happens in the first period, the short period of intense observation, than it is if it happens on the street. So certainly we're not -- it's not like an oral agent where you send somebody out on it. But nevertheless, it's an undesirable outcome, and I'm concerned that we -- we don't have enough certainty what the real risk would be in this population.

DR. CANNON: And I would extend that, based on our conversation this morning, about not knowing how Type 1C drugs -- this gets to the second sub-bullet -- that are metabolized by SIP 2DC, might interact with the disposition of this drug, or this drug could interfere with the disposition of the Type 1C agents, and that they might have additive effects on QT interval or additive

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risk or synergistic risk on torsade.

So that what we've seen here might just be the minimum frequency, that in real world it could be considerably greater. And then, it gets at the monitoring. Well, then, how long -- if somebody gets -- takes a pill in their pocket home, it doesn't work, they come to the hospital and get this drug, or the other way around, what does that do to the monitoring interval? Does it have to be doubled, tripled?

CHAIR HIATT: So that just -- hold on just a minute. So, yes, I totally agree, because I think you have a dose administration relationship to this event. It appears to be dose-related, higher at the doses above recommended.

But how well do we have it characterized is based on a very low frequency of events, and there you never know how well characterized it is. And I would say that it could -- it probably would get worse out in

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the real world. But when you don't know -- the confidence interval around these small frequency events are still relatively large, so you have to acquire more events to get any certainty about the real risk of that.

DR. LINCOFF: And it's okay to say you're going to do that in post-marketing if it appears in the relatively small numbers that you have pre-market, that it's a very small number. But I don't think this is a very small number, and it is a number that is in a very low -- relatively low-risk population -- again, because of the exclusion criteria, the absence of the concomitant medications.

DR. HARRINGTON: So if you -- you know, what the FDA reviewer did is that he tried to -- recognizing that it was an infrequent event, tried to increase the sensitivity by calling it VTac, VFib, or arrest on day one. In women, the placebo event rate is 2.9. At the recommended dose,

it's 3.1. But the dose above that, with an exceedingly small group, is 29 percent. In the men, it's 5.6 with placebo. At the recommended dose, it's 11.1.

So ,for torsade specifically, I agree with Mike that, you know, it's infrequent, but it's a small number of patients. Therefore, the confidence intervals are broad.

In broadening our sort of net, it seems a bit higher. And the women -- we've talked about this earlier, the steep portion of the curve is perhaps bothersome.

CHAIR HIATT: So we would say it's not well characterized, and it represents a significant concern.

DR. KOWEY: I can't disagree with that answer, but there is a couple of points of clarification, just so that you're aware. First of all, 1C drugs don't cause torsade. They prolong conduction, and they can be pro-arrhythmic if they're given in appropriate

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patients. But they don't prolong the QT interval, and they don't cause torsade. So that's why I thought that putting a 1C drug on top of this drug would not add to the risk of torsade, because 1C drugs don't cause torsade. It's a different risk.

I don't disagree with the -- I was just going to say I don't disagree with your premise that if a -- for example, propafenone, which is a 2D6 metabolized 1C drug, were given with this drug, I have no idea -- and that's why I certainly wouldn't load with the drug, I wouldn't give a big dose of the drug. But if you were to dose -- and the usual dose recommendations of propafenone is to start at a very low dose and work up -- I doubt if it would be an issue, but it needs to be studied, and I don't disagree with you.

To Bob's point about the VTs, we adjudicated the VTs, as you saw, very intensively, very intensively. And there are a lot of VTs in this clinical program. I

don't have any explanation for why there were more VTs in this program than you saw in other programs, but they were also in the placebo group.

I can promise you that, what you saw for what was not classified as torsade by our Committee was not torsade, and that is -- since it was not torsade, I have no way to attach it to the drug. This drug, if it's going to cause pro-arrhythmia, it almost certainly has to be through its QT-prolonging effects in torsade.

And so I would not do what Dr. Marciniak did. I would not try to increase your sensitivity by increasing VT cases that were not torsade, because in my estimation that's background noise, don't know why it was there, it was in the placebo, but don't count that. Don't put as much reliance on that stuff. It's not really reliable.

DR. HARRINGTON: But how do we know that? I mean, you know, I'm looking at 231

male placebo patients, six percent, 5.6, 207 male treated patients, 11.1 percent. And I'll agree with you that, I mean, if I test that, they're not likely different from one another. But numerically --

DR. KOWEY: Yes. No, all I'm explaining to you is that the biological plausibility of the connection between this drug and VT is torsade. And I have no other way to connect this drug based on its basic electrophysiology or anything I know about it with any other kind of VT.

CHAIR HIATT: Let's not go there, because it makes me really nervous. Just because the mechanism of action wouldn't suggest that that could happen doesn't at all rule it out.

DR. LINCOFF: Anti-arrhythimics have been notorious for biological plausibility not matching with clinical outcome.

CHAIR HIATT: And I think, to

summarize what we're -- I think what we're all saying is -- even if there weren't other concomitant medicines in the picture, we still feel that it has not been well characterized, and it poses a significant concern, even if nothing else changed.

Now, we also speculated that in the -- with broad use, there may be other environmental or concomitant medicine risk factors that, if anything, could accentuate that risk; at best case, might be neutral.

How long -- either hours or QT prolongation -- should the rhythm be monitored after exposure to tedisamil? Does this time need to be adjusted for 2D6 inhibitors or for poor metabolizers or phenotypes?

So we've got very widely dispergent recommendations between the sponsor and FDA. What does the Committee think?

DR. MASSIE: I don't really know how to answer the question, so I will err on the side of caution. Why wouldn't you want to

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monitor them longer, until we know?

DR. LINCOFF: It has real implications, because it changes the whole possibility of a quick outpatient hospitalization. That isn't the rationale for doing something unsafe, but I think it's a very important question. But I don't know how to choose between the different QT measurements as a guideline for hours.

All I can say is what I've said before, is I don't think asking clinicians, particularly non-electrophysiologists who will be administering these drugs, to use the QTc as the criteria for discharge as realistic. I think it's prone to error, it's prone to just being skipped, and I think you either pick a time -- I think you should pick a time.

CHAIR HIATT: Okay. But we've just heard that the QT isn't correlated with some of the other serious arrhythmias that happen -- the VT -- because they may have -- by a mechanistic plausibility, I don't know that

the QT is the marker for all of the potential arrhythmias that might happen in this period. And then, we do have the factors of the other medications that these people might be exposed to.

I mean, the thing that gives me a little bit of a nightmare, although I'm a little bit helped by the experience with ibutilide is we're going to have people on amiodarone that are going to come in right and left. I mean, most of these people -- most of these people are on amiodarone, and we have no idea what this drug does.

Now, it seems like giving ibutilide in the presence of amiodarone didn't turn out to be as bad as one imagined it might be. But I don't know that one can extrapolate, and I don't know that that was experienced. And I think there was one article that said the opposite, but certainly in my institution they wrote a series that -- where there was not a bad outcome.

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But, you know, you're not going to have a large group of patients who aren't exposed to amiodarone in this orbit I think here. And any exclusion criteria was within three months.

DR. HARRINGTON: Yes, that's the part that gets -- that I totally understand from a trial design perspective. In fact, I applaud the investigators for asking the question in a relatively anti-arrhythmic-clean group, and keeping them clean for the whole 24 hours, let's study our drug.

Rational scientific design, but now with the clinical implication piece of it we now don't have any data for, well, what if you're part of the 50 percent who doesn't convert? And in order to increase my chances of converting, I want to add something.

Now, we may say, as I think was said earlier today, well, you might do that over the next day or two and then bring them back, but you might also say, well, they're

already here, let's load them up with something, try to cardiovert them.

We don't have any data for that, and so I think that you would have to err on the side of a longer observation -- perhaps you have a twofold observation period, that if they have successful conversion, it's one length; if they don't have a successful conversion, and you are going to think about adding other things, that you put some very specific language about lengthening that.

CHAIR HIATT: Well, there are concerns, too, about how complicated you want to make that. So I think -- so what about the "or" statement? Normalization of QT, which is best assessed in sinus, or some hourly rate.

DR. HARRINGTON: I'm with Mike. You know, as an interventional, you know, knuckle-dragging cardiologist, you've got to give me the time and not ask me to look at the QT.

CHAIR HIATT: Yes, I agree.

DR. HARRINGTON: And Barry is probably even worse as a heart failure guy.

(Laughter.)

CHAIR HIATT: So it sounds like the consensus is sort of away from normalization of QT and really towards defining kind of an upper window of a follow-up period. How long would that be?

DR. HARRINGTON: Now, you probably should put in there, you know -- you know, whatever you want to pick: four, six, eight hours, but there should be some qualifier, you know, if the QT is obviously prolonged, don't let them go.

DR. LINCOFF: I agree with that. I mean, it may not get done, but at least you may -- you're not going to be discharging people who someone has done an ECG, observed a long QTc, and not --

DR. HARRINGTON: They said four hours.

DR. LINCOFF: Yes, they said four

hours, I'm fine.

CHAIR HIATT: So we want to go for the, what, eight or nine hours that the FDA is recommending?

DR. HARRINGTON: I don't think the FDA said eight or nine, did they?

CHAIR HIATT: What did they say?

DR. HARRINGTON: They said like 14 or something.

CHAIR HIATT: Tom, what do you think? What did you want to do?

DR. MARCINIAK: I believe with some of the various reviews it was either eight hours or eight or nine, or longer.

DR. HARRINGTON: He said six to eight.

DR. MARCINIAK: Six to eight, okay, correct. I believe that was based on normalization of QT. One could consider whether in fact one has to wait until it's completely normalized. That's another possibility.

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CHAIR HIATT: But we're sort of saying that's hard to assess.

DR. MARCINIAK: No. But, I mean, give it time based -- the eight hours is based on normalization. Okay. It's not based on returning to within 10 milliseconds of baseline. One could consider doing that as another way of trying to give -- you know, define the interval.

When do you think the risk is -- the other thing is, of course, again, looking at the event rates, it's probably just as useful, and we'll probably try to pin that down a little bit more thoroughly. Is there an obvious time when the event rate has gone back down to, you know, what we consider as comparable placebo or some other such criteria?

CHAIR HIATT: That might be tough, given the numbers. So maybe we can't give you a number, but it sounds like longer is better.

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How about the metabolizer status? It didn't seem to affect things. Fred, you might say, though, the -- perhaps severe renal insufficiency might be still a note of caution, not as well explored?

DR. KASKEL: I think that's a subgroup that I'd like to see more done on.

CHAIR HIATT: Okay.

DR. KASKEL: I think there are some answers there we need to find out.

DR. HARRINGTON: We do know in the oral data that it was noted that it was -- that the safety was worse in the renal-impaired patient. Now, I thought the sponsor fairly said with the diarrhea, the electrolyte changes, it's hard to tease it out. But I do think Fred's caution is probably warranted.

DR. KASKEL: I would just add that the major cause of death in the CKD population is cardiovascular events. They have bad vessels, right?

DR. HARRINGTON: Sure.

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DR. MASSIE: And I believe that in the trial, people with severe renal dysfunction were excluded, too. So we don't really know anything.

CHAIR HIATT: No. We did see some data dichotomized by GFR.

DR. MASSIE: But as Fred said, it was dichotomized not --

CHAIR HIATT: GFR with potassium over four, and things like that, right? Is there anything that you think would enlighten us on that?

DR. DeVRIES: I can show some data in really impaired subjects on the kinetics, which might help to define it among monitoring --

CHAIR HIATT: Okay.

DR. DeVRIES: -- you asked for it. Yes. So what we know, because it's renally excreted tedisamil, it's -- of course, the kinetics is affected by renal impairment. But since it's a single-dose infusion, the Cmax is

not affected, and that's what you see in the graph. So in both groups -- moderate renal impairment and in the group normals -- you see that the Cmax is around just below 1,000 nanograms per mil.

But because of the distribution kinetics of tedisamil, you see that, immediately after stopping the infusion the plasma levels go down very quickly. Within two hours after stopping the infusions, the plasma concentrations are back to around 20 percent of the peak level. And you'll see that's not so different in subjects with moderate renal impairment and in subjects with -- in normal subjects.

And, indeed, of course, in renally impaired subjects, the half-lifetime is longer, but that's -- predominantly you see that only in the terminal part, because the first part is distribution kinetics.

So based on these data, we think that the monitoring window needs not to --

there is no need to adapt that for renal impairment. And I think we have also seen that in the QTc data. I showed that earlier this morning. I think that was slide 994.

DR. KASKEL: That's good. That's helpful.

DR. DeVRIES: Yes. You see that in both groups, the QTc go -- go in the same order. So there is no difference between the QTc in both groups.

DR. HARRINGTON: What was the median creatinine clearance in the less than and greater than group? In other words, are these all -- in the less than group, is the median creatinine clearance 50, or is it 35? I'm trying to get a sense from Fred's earlier concern; are these mostly people who are hovering around 60, or are these mostly people who are much more reflective of -- you know, take for example the average acute ischemic heart disease patient in this country has a median creatinine clearance of 50.

So a lot of the patients that we see as cardiologists have diminished renal function. Is that fair, Fred?

DR. KASKEL: Right. I mean, I think that would be a CKD Class 3.

DR. DeVRIES: Yes. In this group, the mean creatinine clearance in the Model 3 non-impairment was around 40 mils per minute.

DR. KASKEL: So that is helpful, then.

DR. DeVRIES: Yes.

DR. KASKEL: Okay. That's just one stage before needing renal replacement therapy, so it's significant. This is a Stage 3 CKD. Stage 4, they're on dialysis.

DR. HARRINGTON: So that data is useful with --

DR. KASKEL: It's useful, yes.

CHAIR HIATT: Okay. So the sponsor recommends a lower dose to try to avoid some risk of torsade, and the lower dose should trend towards lower risk for torsade.

However, women also tended to have lower rates of conversion on drug at any given dose than men. Does this tradeoff lower effectiveness, lower risk, make sense?

I think we kind of danced around this issue about this really fairly narrow toxic therapeutic ratio, which, you know, might be more accentuated in women a little bit. There are certainly more deaths in women, but it might be there in men, too.

DR. LINCOFF: Perhaps I can make a stab at balancing this. From my standpoint, again, the most we can expect from effectiveness is to prevent a cardioversion. However, from a safety standpoint, we can -- those can be real bad things. So from my standpoint, anything that diminishes the risk, even if it carries with it a somewhat -- something of a diminution of effectiveness is an appropriate thing to do.

And so it makes sense in this question from my standpoint. I'm willing to

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accept quite a lot of decrease in efficacy if that also decreases the risk.

DR. STOCKBRIDGE: I guess I'm -- the reason I have trouble with this part is, I've got two points on a sort of risk-benefit relationship here, if these are the only things I'm concerned about are avoiding shocks and -- avoiding shocks for torsade or avoiding shocks for AF. And I don't think I have a good sense for why you prefer one place on that curve versus another.

DR. MASSIE: What was wrong with what Fred said?

(Laughter.)

CHAIR HIATT: Well, let me chime in, then. Are you saying that the precision with which the safety has been -- shown us to date, which is very, very low numbers, is so imprecise that we really don't know that a lower dose is safer?

DR. STOCKBRIDGE: Well, I mean, if your goal was to avoid torsade, then lower is

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obviously better. But then, you know, you're down in an area where you're not getting what you were trying to get achieved with the drug.

And I don't -- I still don't understand why -- why having -- if the ratio of torsade to conversion was acceptable at the lower dose, why isn't it acceptable at the higher dose, which is on the order of about the same?

DR. MASSIE: Well, I think that's the question. But I don't think that one stretches to increase the efficacy by increasing the risk. One may decide not to use the drug, based on feeling that the dose that you feel comfortable using isn't very effective.

So, I mean, I think the worst thing to do is to, you know, find a dose that's moderately effective, but really increases the potential risk of death. We don't need this drug, really. I mean, it might add something

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all together, but until we know more about it, do you really want to do that? Or do you want to give the data and let the doctor decide? But not -- I don't think we want to offer the higher risk of torsade, or a lower one.

DR. LINCOFF: No, you're right, we don't want to offer the -- so you just don't approve it in women. But that would be tricky, too.

DR. MASSIE: Well, that's an option, but I don't think that's the point, because I think we -- whatever the efficacy is, it's an incremental efficacy over what else is available. It is preventing a certain number of cardioversions. Maybe it's 17, maybe it's 32, maybe it's 40, whatever the groups are.

But, so -- and whatever that is, setting aside the cost issues, it's an advantage for those patients in whom cardioversion doesn't have to be performed. We're still left with the issue of: are we

willing to take any of those benefits at the cost of some risk?

And I think that speaks more to the issue of whether or not you approve the drug or not. But if you approve the drug, then I think you say that the sponsor has made a good faith and as careful as anything -- as any developmental effort to find the right dose in women and in men, and that we go with that if we go with the drug.

DR. STOCKBRIDGE: Let me take one more stab at this. If the goal here is to minimize cardioversion, and it turns out, maybe I can exchange, you know, a cardioversion for AF, for a cardioversion for torsade, if that were true, you know, depending on which place I -- which point I chose on the curve, those things would seem to be the same to me. It's not the absolute rate; it's whether or not I have, on the whole, less cardioversion on one of these doses than on the other.

And if you -- if that's what you thought, you'd go with the higher dose, because the increment in torsade-related conversion is smaller than the absolute reduction that you get in terms of cardioversions for AF. So once more, why --

DR. MASSIE: You're assuming that you could get the type of instantaneous response effective -- and effectiveness without the rare person of torsade who actually doesn't get out of it, in the setting in which this is occurring. I don't know that we know that. You know, I mean, one is a risk that if they stay in AFib and they don't -- you know, it's one thing. But they might die of torsade, and somebody will die of torsade. It's not just the shock that bothers me, it's the other outcomes that could be downstream.

DR. LINCOFF: Yes, it's not an apples to apples comparison.

DR. HARRINGTON: Yes. You're saying a cardioversion is a cardioversion is a

cardioversion. And I think if you present this to the clinicians who are going to be doing this and say, "You know, you're going to end up with 10 cardioversions. Ten of them are going to be for AFib, or seven of them are going to be for AFib and three are going to be for torsade," they're going to view those two very differently, because, as Barry said, that's not the same thing, and there may be patients that -- yes, Peter said in the ideal world you'll get everyone out of it. But what if you don't? I don't think that's a sellable point.

DR. STOCKBRIDGE: So why is .32 the right number? Why isn't it .16? .08? .02?

DR. HARRINGTON: Well, because then you do start dropping off. I mean, already with women we are going from, what is it, three to four -- so the short durations where we all have a sense that the drug works better, in men it's 52, in women it drops down to 32. So you've already given up 20 absolute

cardioversions, 20 absolute percent for --

DR. STOCKBRIDGE: Okay. And the benefit is now half of what it is in men?

DR. HARRINGTON: Or three-fifths, right. A little more than half. Your question is a tough one. I mean, how much are you willing -- how much risk are you willing to accept for, I think admittedly, a rather modest benefit?

DR. STOCKBRIDGE: I can obviously cut the torsade rate in men, too.

DR. HARRINGTON: You can cut it to zero if you don't give it.

DR. STOCKBRIDGE: Well, that's an option you have, too. But, you know, again, if your goal is to avoid torsade that might be fatal, you should be giving the lowest possible dose to both men and women.

DR. MASSIE: But the lowest possible dose that has a demonstrable effect. Otherwise, why would you give a dose that has no effect?

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DR. STOCKBRIDGE: I agree with that, too. And that may be what we should be doing. I think that -- I actually think 32 comes pretty close to that. If you go below that, I don't think you have a demonstrable effect, and the risk of torsade is less than it is if you gave 48. And I'm sure there's the same data in men -- 48 and 64.

DR. CANNON: I think it's reasonable to accept a small risk, because anything we do has a risk. I mean, there's no -- there's no option that has no risk. I don't care what you do. There's no option, whether you -- watchful waiting, electrically cardiovert them, give them ibutilide, tell them -- no matter what you do, there is a small risk.

CHAIR HIATT: Small risk of?

DR. CANNON: There's no zero risk.

CHAIR HIATT: Of? Of torsade?

DR. CANNON: Of a severe ventricular arrhythmia. Depends on what the

agent is that you use.

CHAIR HIATT: But you'd have to say that there is --

DR. CANNON: Electrical cardioversion wouldn't be --

CHAIR HIATT: -- but there are drug-related torsades that would not be seen with cardioversion or waiting --

DR. CANNON: No. But cardioversion has its own risks.

CHAIR HIATT: Right.

DR. CANNON: So I've seen asystole, I've seen a patient have to be paced after electrical cardioversion, I've seen VF after electrical cardioversion, somebody had to be defibrillated. There is no free lunch.

DR. LINCOFF: And this comes back to the -- at least what I think is a practical difficulty, or impossibility, because of the lack of data, of actually doing this numerically. You know, we can't say, okay, if I can save 20 cardioversions, I'll trade one

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torsade, because that will neutralize out the risk of the -- that's associated with those 20 cardioversions, because I don't know if --

DR. STOCKBRIDGE: You really need to be able to do that.

DR. LINCOFF: Well, but if we do, then we wouldn't approve any of these drugs, because to my knowledge, no one has well characterized the risks associated with the cardioversions in the current era, especially with a background med.

So if that were the requirement, then how do you approve any of these agents? We have to factor in sort of the utility or the -- yes, you know, the -- if we're just using the exact apples to apples comparison, how many ventricular arrhythmias am I going to prevent from cardioversion in exchange for the ones I'm causing by the drug, then I don't know how we can do that.

It has to be sort of the integration of all of the adverse experiences

and events associated with cardioversion and a judgment of how much risk we think we're willing to take to do that.

DR. HARRINGTON: You could actually -- you said the key word, Mike. You said "utility." You could actually do this quantitatively. You could do -- use the techniques of decision analysis and walk -- and quantify all of the nodes along the way for what the decision is. I mean, it could be done and give you just what you asked for.

DR. LINCOFF: But part of that would require sort of a judgment of quality adjustment for --

DR. HARRINGTON: That's what decision analysis takes into consideration.

DR. LINCOFF: Right. So you'd have to, you know, ask patients who had had a cardioversion, "How many years of life would you give up to avoid being shocked?" And, I mean, those introduce so much subjectivity that I don't know how -- how you would

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practically do that.

CHAIR HIATT: But I guess the thing that's hard about this is that we probably have a good, reasonable idea on the efficacy side, given the sample size. But how much certainty do you all have about the real risk?

If you all think that any torsade is bad, even in this monitored situation, I mean, I think we have a reasonable sense of how this drug meets placebo, right? And we have pretty tight confidence intervals, I would think, around the point estimate of that benefit, but all of these arguments assume that we actually know what this risk is.

DR. LINCOFF: No, I think that's the key. I mean, when you do a small study --

CHAIR HIATT: Right. Right, that is the key.

DR. LINCOFF: -- you do that study, and you power it to efficacy, and you're okay if you win on the efficacy, and you don't have

a signal for risk or much of a signal. But if you get a signal for risk, and you're clearly empowered to do that, then it becomes a much more difficult story, and I think that's exactly where we are here.

CHAIR HIATT: I mean, so that we're assuming that torsade is bad, and that that conversion is not the same as a conversion for AF. But if we did 10,000 patients and knew that every torsade was shocked into sinus and nothing bad happened from that, you might think differently.

And if a few of those snuck by as arrhythmogenic deaths, you might think differently, too, right? So the problem with the whole argument -- the strawman here is, a little bit, we don't know what the real risk is.

DR. HARRINGTON: But we've got -- you know, if you go to slide 94, you've -- where they actually have done all of the adjudication of the torsade-like events by

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dose, by gender, they give us the point estimate, they give us the associated confidence intervals, but the numbers are -- I mean, you know, it's one case.

CHAIR HIATT: But that's the whole point.

DR. HARRINGTON: That's the problem.

CHAIR HIATT: That's the point is that we're assuming a couple of things in this setting. And, of course, if you throw in the con meds, that might muddy the waters even further.

So it's back to where you always are with symptomatic therapy, isn't it? You know that it works to treat the symptom. It works to avoid the cardioversion and make you feel better for a period of time. But do we know the real risk here?

MR. SIMON: Can I -- I'm sorry. Can I ask a question? If I have atrial fib and I'm a woman, and I take the drug, was it

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30 percent, 35 percent effective? On a dose of say 32 -- at 32, and it doesn't work, then I normally would go to the electrical cardio? So I have put myself at risk, number one, of the drug as well as at the electrocardiogram. So haven't you doubled or incrementally added to the risk?

DR. HARRINGTON: Well, they have shown us -- your point is well taken -- that it is -- and that was the point of looking at the 24 hours, because in 24 hours you're taking the drug risk that you got for two and a half hours, and then you're taking the rest of the risk that whatever they did to you for the rest of that time.

But I think part of the uncertainty that is being raised is in the trial, understandably it was very clean, they didn't give people additional drugs, et cetera. In real life, that may not be the situation. But you're absolutely right -- for you as an individual, it's a cumulative risk.

CHAIR HIATT: It's a treatment strategy. We said a fair amount here that this doesn't exclude -- using a drug doesn't exclude another strategy following the use of the drug.

So let's see if we can summarize this question here. So women have higher risk at higher doses, less conversion rates. Does the tradeoff make sense? I'd have to say that we don't know. I don't know. Because I don't have a really -- a great sense of confidence around what that risk is.

I think I know what the loss of benefit looks like. And if I'm just trying to convert patients, I would push women to higher doses. But I don't know what the tradeoff is in terms of real clinical, meaningful, adverse events.

DR. HARRINGTON: And we don't know --

CHAIR HIATT: Anyone disagree with that?

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DR. HARRINGTON: And we don't know, given the small numbers -- you know, it looks like you go -- you're on a really steep portion of the dose curve, that you -- or the risk curve. You go from .4 to 9.1, but, as was pointed out this morning, the confidence intervals are so broad, it may be the same as the -- we just don't know. And I don't think you're going to be able to get that data.

CHAIR HIATT: So fundamentally we need more events on drug and how they were managed to have a better sense of what that risk is.

DR. MASSIE: But just to point out something that has come up earlier -- you do know that if you're a woman and you get this 32 milligram dose, or .32, it's not worth it probably if you're more than 48 hours out, because then you go from the 30 down to the low --

CHAIR HIATT: Well, but remember, if -- even at those low response rates, if in

fact nothing bad ever happened --

DR. MASSIE: Right.

CHAIR HIATT: -- you'd do it.

DR. MASSIE: But we don't -- or at least I don't believe that nothing bad will ever happen. Something bad has happened --

CHAIR HIATT: Yes.

DR. MASSIE: -- even if it didn't end up awful. I believe torsade is bad, because I know that -- as Peter said -- if 500 people get torsade, there are going to be people dying in the real world.

CHAIR HIATT: But in the context of delivering this drug in the way that we'll go forward, we don't know.

DR. LINCOFF: All I can say is that I think that it is reasonable to try to equalize the risk between men and women. We can decide in the end -- we will with the vote -- if we accept that risk at all. But I think that this is an effective strategy that they have proposed to equalize the risk, and it is

reasonable to do so even, if that means diminishing the efficacy in the women.

DR. HARRINGTON: That's actually a fair way to think of it, Mike, or -- nicely said, because you do go from the point estimates are now the same, the confidence intervals are now the same. I like that way of expressing it.

CHAIR HIATT: So we would not be recommending that somehow, like maybe men should all -- to avoid dosing errors, maybe men and women should all get the same dose. We don't think that's a good idea. No.

Any more thoughts on that?

(No audible response.)

Okay. How much of a safety concern is bradycardia? Anybody really worried about that? If you are --

DR. CANNON: For the group, I don't think it was a problem for men or women. But we reviewed fairly extensively one very dramatic case of a women who become

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bradycardic, AV block, virtually asystole.

Now, Dr. Waldo says, "Well, any drug that affects the AV node could have done that." Maybe yes, maybe no. But I think for the group it doesn't appear to be a problem.

CHAIR HIATT: Any other bradycardia concerns? No?

(No audible response.)

How about the thromboembolic events, including strokes? We did see a couple of those events, I think numerically in excess, on the drug. But you're not convinced.

DR. LINCOFF: Yes. As I mentioned earlier, that numeric excess was summing a lot of events, unless I'm wrong -- myocardial infarction, pulmonary emboli, the whole deal. And if that's the case, I think that's too heterogeneous of a group. So I don't buy it.

CHAIR HIATT: So just so I understand this, so you all are pretty convinced that this torsade that is picked up

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is in fact a far more greater safety signal than these thromboembolic events? And, if so, how do you -- are you convinced of that?

DR. LINCOFF: Am I incorrect? I see some heads shaking? Am I incorrect about what these pooled thromboembolic events were?

DR. MARCINIAK: Right. But if you consider them separately, MIs and strokes, it's greater for each individually. Again, smaller number events. I mean, sum is going to be greater than --

CHAIR HIATT: See, I think -- yes, I think it may be slightly myopic to just highlight this one arrhythmia as the thing, and assume that these small frequency events don't mean much, because they scatter around neutrality. I mean, I don't know.

I think I have the same uncertainty about deploying this out in the world, about those events, as I do about the torsade. You know, they may go away as issues, and they may stay as concerns. I don't know that this drug

isn't pro-thrombotic at some level. I just don't know that. I mean, how could you argue differently?

DR. LINCOFF: Well, I mean, if it's -- an increased risk of torsade would be unlikely to have any connection with the increased risk of thrombotic events. So now you're postulating this is an independent thing, a different mechanism, which may well be. And I just criticized talking about mechanistic reasons in favor of empiric data, so I'm less focused on that.

But the mechanism of these different thrombotic events are very different. I mean, a myocardial infarction overwhelmingly is in situ thrombosis. Yes, occasional emboli, but you can usually tell, and it's usually something that's pretty clear.

The pulmonary embolus -- I mean, as I recall, there were two of them. One was quite late, one was very early, but that

patient may have had an early pulmonary embolus as the cause of their AFib in the first place. So, you know, that's probably different, and how many pulmonary emboli come from right atrial thrombus? I don't know how often that happens.

So, you know, we're talking -- we've taken a bunch of events which can be defined thromboembolic because they involve thrombus, that goes somewhere maybe -- thrombus that stays or goes -- but I don't really think they are the same thing. And so I think we're talking really tiny numbers as compared to what you have with the torsades, which is more numbers and is mechanistically linked.

CHAIR HIATT: But if you then acquire more safety data in some way, then you would certainly start to sort that out, right?

DR. HARRINGTON: Yes, that's what I would say -- is it fair to say, Mike, that this -- the thromboembolic event rates need to

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be better characterized? I mean, because I have your perspective is, that if you look at the dose of interest, the .48 for men, it's 1.0 percent, and the pooled placebo is .4 percent. I mean, they're small numbers. There's excess numerically.

But I would -- and I'm one that rarely believes in mechanism, so I would say it's -- it's there and see what happens. Needs to be better studied.

DR. MASSIE: Well, I think it's like all of the other uncertainties that we're facing here, which is you've got to play it off against the efficacy in your final thinking. I agree with the statement that we need to characterize this better.

We need more safety data in the population that is going to receive this, and I don't think we can do -- well, never mind. I think we just need more data, because I don't think this is -- I agree that, you know, the intellectual pathway doesn't make me as

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concerned, but it's there and we just have to know whether it's going to be there in larger populations.

DR. HARRINGTON: Yes, here is -- I would even take it a step further and say, look, we didn't look real carefully, for example, at the baseline demographics. We talked about patients with ischemic heart disease, but we didn't well characterize, you know, what was the actual balance of ischemic heart disease, previous CABG, previous angioplasty, the LV function by group? Because with an overall small sample size, even relatively small imbalances in characteristics that then do lead to things like MI and stroke could tip the arm one way or another. So to me it's a problem of the overall small sample that is problematic.

CHAIR HIATT: And what you're sort of saying is these are unadjusted raw rates, and that's also a fair --

DR. HARRINGTON: In a small sample

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size.

CHAIR HIATT: Yes, sure. Okay. So the concern didn't go away. Need more data.

Any other safety concerns?

(No audible response.)

Hypertension? No? Okay. Anything else?

DR. HARRINGTON: You know, I was thinking about this earlier today and I didn't ask it. It was noted that the blood pressure can go up. We've had some recent drugs where the blood pressure mean for a population goes up a little bit, but there are some real outliers. Did you see any data on the hypertension front? Are there any outliers where there is a few patients where the blood pressure goes way up? Because then you do start to bring in the stroke question and --

CHAIR HIATT: You know, but, again, you have to ask about the exposure.

DR. HARRINGTON: It's very short.

CHAIR HIATT: Well, so, as I

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recall, looking at the first VA cooperative randomized trials for blood pressure, for very severe hypertension, the events started accruing over the next year. So -- and they could occur at two months.

You have to ask yourself: is a little bit of hypertension for an hour --

DR. HARRINGTON: Probably not. We had our placebo control hypertension trial meeting, and we determined that it was okay --

CHAIR HIATT: And it was determined that --

DR. HARRINGTON: -- to do it.

CHAIR HIATT: Yes, exactly, you could go for four weeks and not cause harm.

DR. HARRINGTON: But we can assume that there wasn't some extreme outliers.

CHAIR HIATT: Yes, that's a good point. We could anchor that to another meeting.

DR. LINCOFF: Yes, assuming SAE would have been filed for a blood pressure of