that it has to be an active control. So that's number one. There is uncertainty there.

I don't believe, by the way, I ever claimed that the U.S. regulations said you had to use a placebo. We can check the transcript when it's out but I said it was oriented towards placebos. I do believe that is true and is correct.

DR. CALIFF: I work with a statistician who does what you just did and says it's just fine. I'm interested in Tom's opinion as to whether adding the variances takes care of the uncertainty about the populations that were actually in the two trials.

DR. FISHER: No, it doesn't, because they are not randomized within the same trial. You will never get exactly the same baseline characteristics. Usually they are not totally contemporaneous in time, those two comparative trials. There is additional uncertainty there that we statisticians do not have a good method to quantify. It's up to your scientific judgment to decide how much that bothers you in this situation.

I am not going to stand up here and say we

can just start using historical controls. There is an infamous paper among statisticians in the New England Journal by Gehan Freidrich that got totally torpedoed from every possible side and appropriately so. What I'm saying is this is the best that I know how to do to evaluate this information. It has weaknesses above and beyond the confidence intervals.

DR. CALIFF: My second question is did you do a sensitivity analysis on the overview to see what the least beneficial assumption for heparin could have been to still end up with a convincing p-value? In other words, you're asking us to believe that heparin reduces the risk of events by 70 percent which is probably an over estimate most of us would think. What if heparin only was half as good?

DR. FISHER: If you look at the confidence interval, of course, it goes up to 85 percent. I'm looking at OASIS-1 plus OASIS -- no, that part remains the same. I'm not asking you -- what I'm asking you to accept is basically a distribution of values centered around the point estimate but with the spread that I can account for statistically. As I mentioned,

for most of us the real concerns are not that part of it. It's the assumptions that you have.

DR. CALIFF: But I'm driving at an issue here and I'm partly biding time but I think this is an important issue. We can assume that what was reported in the early days on heparin versus control was highly selected for positive study.

It is much more likely of publishing a study now even if it's negative than there was 15 years ago. What I'm really trying to get at is how much less impressive could heparin have been having still come to the same conclusion?

DR. HIRSH: As far as I know, no statistician has ever ventured a quantitative statement to that effect. We have played around a little. You saw some of the things that the agency reviewer did. They said, "Gee, in FRIC and FRISC if we change data events this would happen." You can play the same game the other way. If we change it in the other direction, it really would have looked great. I tend to like --

DR. PACKER: Sue-Jane, you're on.

DR. HIRSH: -- to stand with the data that's there. By the way, I did a few conservative things. Oler looked at the end of treatment. The end of treatment here is 72 hours where the data looks even better but I didn't want to do that because I thought it was fudging things.

Not fudging but it went in a favorable direction and the primary endpoint was at seven days so there are certain things I could have done but probably -- I mean, it would have made things look even better and I'm sure if I set my mind to it I could find things to do --

DR. PACKER: I think we're ready. I think this thing finally came on. Dr. Wang.

DR. WANG: Hi, everybody.

DR. PACKER: Speak up, Sue-Jane.

DR. WANG: Can you hear me? Good. All right. I just like to make a point before I start. I've been working in this area of research with an expert statistician from the FDA, Dr. James Hung, in the Cardio-Renal Division. We actually had done a lot of work regarding this particular issue of putative

placebo. It just so happened here we have the application comes up and we can try to put these two things together to shed the light on what is going on in this particular NDA.

I was called on to discuss this virtual method used in this particular reflected in the application. As you know by now, it was because of one large multi-center double-blind control study of about 5,000 patients per arm might not have a statistically persuasive evidence and that was the pivotal study for evaluation.

The virtual method used by the sponsor in the evaluation of the primary efficacy endpoint for the OASIS-2. Here I like to explain this virtual method graphically. First, let's focus on the left box. This is the current active-control trial.

We have the experimental treatment and we have the active-control treatment. If the estimated relative risk of the treatment over control and is 95 percent confidence interval limits are all less than 1, then treatment event rate is less than active-control event rate.

In that case, treatment effectiveness would help establish and that's a check mark. Due to the ethical reasoning, we may only be able to find some past trials in which the placebo arm was included for some time ago which is our right box.

The external data or historical trial or placebo controlled trials are the term we used which generally consist of more than one trial. If the effect or control relative to placebo can be ambiguously established, for example replication of the results, relative risk of the control to placebo and again is 95 percent confidence and everything being less than 1, then we have another check box there.

Then the comparison of the treatment versus the placebo would be quite clear and straightforward. Again, we have now the third check box.

Now, the problem we're dealing with here is what if the results was a question mark on the left box and a question mark on the right box? Can one legitimately evaluate the treatment versus placebo as

shown in the box at the bottom?

From our observation this is one of the objectives that the sponsors try to conclude. The theme of the virtual method is to directly answer the question of treatment being superior to placebo, the bottom box, by making a few assumptions and by some statistical properties if used appropriately.

So we have to talk about assumptions with this virtual method. First, and the most critical assumption, is that effective control in the historical data is identical to the effective control in the active-control trial. There is no sufficient data for verification of this assumption. It is very difficult, if not impossible, to replicate the effect of control relative to placebo in a current active-control trial without the concurrent placebo arm.

Secondly, for the mathematics to work out right, one needs to assume that the estimated relative risk of treatment relative to control obtained in the active-control trial is statistically independent from the estimated relative risk of the control relative to placebo gathered from potentially a few to many

historical trials called meta-analysis. It is assumed that the placebo control trials being included are clinically sounding and the statistical method for the meta-analysis used to estimate effective control is statistically valid.

If all the above assumptions are met, then this virtual method can be efficient approach used to show that treatment is superior to placebo. However, this virtual method can be very sensitive to departure from assumptions, especially if the effective control differed between the historical trials and the current active control trials.

As I mentioned in the beginning, progress this year has shown by simulation that when the control event rate in a current active-control trial increases just slightly compared to the control event rate in the historical placebo control trial, then the first positive rate of relatively concluding that treatment is superior to placebo can be large.

From our simulation studies it appeared that the first positive rate can be very large in the number of trials available for random effect which was

what the company used. Meta-analysis is not large. For example, even with ten trials the random effect meta-analysis can still carry a larger than expected false/positive rate.

In fact, in Biometrics 1999 the title of that inference in random effect metal-analysis. Follmann and Proschan from NIH also pointed out that when a number of trials is not large, random effect meta-analysis using normal approximation may not be valid for testing the effect of control relative to placebo.

What we are seeing in this particular application, first let me focus on the Oler, et al., application. As you know, the time is limited so my slides are actually cut into 1/3. I hope I can make the story continue.

I would like to here point out that the heparin plus aspirin, the active-control even rate, was not the same as that of the OASIS-2. First of all, the heparin even rate was 4.2 percent from the OASIS-2 trial.

If all the six trial estimate from the

Oler study is used, the heparin plus aspirin even rate was 7.9 percent, the six studies there. You can see that it was almost twice as high than that in OASIS-2. On the other hand, when the three blinded trial estimate is used, the heparin plus aspirin even rate was now 2.2 percent. These are the three blinded studies.

As far as application of the Oler six trials, it was shown that there were three blinded studies and three unblinded studies so here we show you when you pull together the blinded and if you just focus on the blinded results, you see that kind of difference. Now with the three blinded studies the 2.2 percent is actually half that of the OASIS-2 estimate.

So what does this tell us? These raises the alarm that we may not yet have the effect of heparin plus aspirin clearly established and that assumption of the effect of control in the active control arm being the same as the effective control in the historical trial may be very questionable.

Therefore, interpretation of comparison of

Refludan with aspirin alone is highly dependent on selection of studies from meta-analysis. Especially OASIS-2 did not conclusively reflecting being superior to heparin plus aspirin.

As you can see from this slide, on the right-hand box when using the six trial, as the sponsor did, you would get a relative risk of .64 and that risk estimate with interval will be used to derive the relative risk of Refludan versus placebo of .56 leading to a significant Refludan effect of p-value .014.

However, if the three blinded trials are used, Dr. Rashid, the FDA reviewer, and also Dr. Hock in 1997 of essence trial review, both pointed out that the relative risk of heparin plus aspirin versus the aspirin alone would have .78 relative risk. You can see the interval estimation now is much wider.

When such an estimate obtained from the meta-analysis is used. Relative risk of Refludan versus aspirin becomes .64 and that the p-value generated from Dr. Rashid and Dr. Hock was .095. The .095 here could be underestimated. When we actually

perform the simulation study, based on the scenario observed from the data itself, we found that the false/positive rate was likely to be doubled around .18 in our research.

The sponsor FRISC/FRIC study, there is actually a lot more story into it. It is actually a two-step process in getting the control relative to placebo. Since I have to skip a few slides, I hope I can explain better here. The two-step process here that we're talking about is we don't have the middle to be the active control. Here what we have is a D, the dalteparin, another treatment.

For these two studies the trial have about 750 patients per arm. One needs to be very careful in interpreting the result here. Let's look at the right box of the FRISC study first. This is just like the historical control trial we had before except that it is now placebo relative to treatment, not relative to active control.

Dalteparin clearly was shown to be significantly better in reducing the risk of death or MI, p-value about .001 so we have a check here.

Dalteparin prevent rate was 1.8 percent in the FRISC trial.

Now, let's look at the left box. The FRIC trial served as the current active-control trial comparing heparin plus aspirin, the active control, to the dalteparin, the treatment. This comparison would be valid if one could assume that the effect of dalteparin in the FRISC trial, which was 3.9 percent, is the same as that in the FRISC, 1.8 percent.

If one perform a simple test for the statistical significant difference or no difference on this dalteparin, the p-value was .018. This is exactly the situation we found from our simulation studies that false/positive rate of concluding that active-control is superior to the hypothetical placebo using such a virtual method can be very high.

Now, move to the Oler trial. As pointed out by Dr. Fisher in his manuscript, when the active-control trial show that treatment is superior to control and that the historical trial showed the control superior to placebo based on a large number of trials. Then the population differences between the

two type of trial will be of less concern.

Here in this Refludan NDA we don't have convincing evidence of Refludan being superior to heparin plus aspirin in the active-control trial. We don't have the convincing evidence of heparin plus aspirin being superior to the aspirin from just a few trials.

We do have differences among these small Oler at all trials. Concerns of assumptions might not be met. These are exactly the concerns that making the virtual comparison of Refludan versus aspirin alone difficult to conclude.

In summary I like to convey a few important messages. From the Oler et al. in addition to the dose regimen differences, definition of endpoint differences, trial design differences, small sizes of trials, number of trials which could be appropriately included for meta-analysis may be less than what is available.

Here we had heparin plus aspirin event rate deferred from that of OASIS-2 between using the three-blinded-trials scenario versus using the six-

trial scenario. Therefore, the first key assumption for a statistical valid approach of virtual method may have been violated.

Given all the uncertainty of the heparin plus aspirin effect seen in Oler et al. trials, should six or less than six trials be used for the meta-analysis especially the active-control trial seem to have a very weak evidence of concluding Refludan being superior to heparin plus aspirin.

As you saw from earlier slides, with the FRISC and FRIC trial if conclusion of heparin plus aspirin being superior to placebo can only be 50 percent chance of being incorrect, one may have severely overestimated effect of heparin plus aspirin. The question then becomes can such over estimate effect obtained from the FRISC/FRIC study be combined with Oler et al. trials.

Finally, the virtual method can be very efficient but we found that it suffers from departure from key assumptions of control event rate being the same between the active-control trial and the placebo historical control trials. Which, of course, we know

could not be unequivocally assessed from existing trials. The implication of this ought to be carefully considered, particularly in this NDA in which the active-control trial did not conclusively show Refludan is superior to heparin plus aspirin. Thank you.

DR. PACKER: Dr. Fleming.

DR. FLEMING: Dr. Wang, while you're still here, in our briefing report from the FDA on page 34 it was suggested that the FRISC and FRIC trials data that we were using were from non-randomized arms. Can you clarify what that is about?

DR. WANG: Okay. I am not the reviewer for this NDA but my communication with the primary reviewer is that they are randomized studies. Correct me if I'm wrong, Dr. Rashid.

DR. RASHID: Yes. FRISC and FRIC are randomized but we are comparing with the one arm from FRISC and the one arm from FRIC so there are two different arms of two different studies. They are non-randomized.

DR. FLEMING: I see. I'm going to try to

be fairly brief here. I'm acutely aware of time. There are a number of issues and Dr. Wang has mentioned several. As Lloyd Fisher pointed out, the critical challenge here is to be able to come up with studies that are going to be giving us a relevant estimate of what the active control's effect is.

We have been involved in active-control trials for a long, long time and I've always argued there are some critical ingredients required or assumptions or truths that have to be in place in order to be able to understand what the effect is of the intervention relative to placebo.

The first is the active comparator has to be a very effective regimen with a precisely estimated effect in the precise population in which the study is being done. That also means concomitant meds, doses, other things, patient characteristics, things that could influence outcome need to be comparable.

Admittedly to achieve that in the most satisfactory sense is an incredibly tall order and it's one of the reasons that active-control trials have been viewed to be less reliable in their

interpretation than a direct placebo control assessment.

A couple of things that I might want to turn attention to and they are somewhat related to Dr. Wang's presentation. If we go to page 28, table 4.1. Lloyd might have a slide to this.

This, Lloyd, is the table that gives the six studies that go into the Oler meta-analysis. The thing that strikes me at the beginning when I look at this is that the Holdright trial is dominating in terms of the number of events in this overview. In fact, it's an event rate that is 27 percent on heparin/aspirin remembering that what we're looking at in OASIS-1 and OASIS-2 are event rates of 4.2 percent and 4.8 percent. Presumably the Hold right analysis is looking at different time frame or different endpoint and Lloyd might clarify that while I go on here.

The other five studies are on the opposite extreme. They are very small studies with very low event rates so that you have a total of 13 events -- I assume these are death MI events from what Lloyd

said -- 13 events on the heparin/aspirin and 28 events on the aspirin if you're looking at this meta-analysis without including the Holdright data.

One of the first things that strikes me is that 13 events on heparin/aspirin gives you a 2.4 percent rate which is half of the event rate that we are seeing in OASIS-2. The data are what they are but it's interesting that the event rate is low there for what we would expect it to be and it's these data that are the basis of our trying to estimate what the heparin effect is.

It does raise for me one of the concerns, and we've already alluded to it, meta-analysis of the literature is what has been referenced as the way that Oler used to obtain these data. These are very small studies and if you had a very small study of this size and things went in the wrong direction, interestingly none of these go in the wrong direction.

In such small studies that's probalistically unlikely that none of them would go in the wrong direction. It just makes me wonder what else is out there that didn't get into the literature

that is an equally small experience that as a result legitimately wouldn't be viewed to warrant publication. Is this, in fact, an unbiased representation of the literature.

Other issues that have been addressed, and I'll just be quick on these, is the endpoint is all-cause mortality and MI. I actually agree with Lloyd. I think that's the best. It is slightly different from what we're using in the OASIS trials. I think the Oler data is over the period of treatment and what isn't clear to me is if we can even say this represents the events in these five smaller trial that would have occurred up through day seven.

Of course, as I think has been made clear, I have reservations about whether just looking at effects over seven days is adequate. There isn't evidence presented here to give us a sense of what was the effect of heparin. How much of this effect was sustained out to day 35 much less day 180.

Concomitant meds, these could be different and Dr. Wang is referring to these issues and Lloyd has already alluded to them as well. Issues that make

one a little bit uncertain about whether these estimates are able to be translated into what we would have expected in the exact population that was in place for the OASIS-2 trial.

The FRISC and FRIC studies if you turn to page 30 the data are presented there for these two studies. What is evident here is the critical study here is the FRISC trial, not so much the FRIC trial. The FRIC trial is telling us that dalteparin and heparin seem to be about the same.

The critical linkage to the placebo, so to speak, is the FRISC trial. In this trial the estimated rate of events is also really low. It's 1.8 compared to the FRIC trial where it's 3.9. One is left with some uncertainties as well here. You have very small numbers in FRISC. You've got 49 total events.

I agree with whoever else made the comment. The analysis of all of these meta-analyses for the putative placebo, the analysis that gives the most encouraging result is the FRISC/FRIC and it's really based on FRISC and FRISC is based on 49 events

where you have an event rate in the dalteparin/aspirin group which is less than half of what you get in the FRIC trial.

In a sense we say this variability is factored in and Lloyd is right about that. It is factored in because the methodology that he's talking about is, in fact, looking at if you want to compare A to C, you can look at A to B, B to D, D to C, and that gives you A to C and the variabilities are additive and they are factored in.

When one looks at the data as to whether it makes sense, there are some of these issues that Dr. Wang had brought up come forward and certainly raise some concerns. I guess ultimately one of the issues, too, that one has to think about, and it's a difficult philosophical issue, is the study was designed as a superiority trial.

It did not identify prospectively that it wasn't necessary to show superiority. It was adequate to show non-inferiority via a specific margin or according to a specific method where we would be using given trials as a way of assessing the effect of the

placebo against the active control.

If you had set out to do an active-control trial to show non-inferiority and you actually established superiority, we all accept that as being a fully appropriate conclusion. What is problematic is when you set out to show superiority and you fail to do so and then you acknowledge what may be true.

It's not necessary to show superiority. It's actually adequate to show non-inferiority, but then we're stepping back and using data. That may be out best attempt to choose those appropriate historical experiences that will represent the effect of this active comparator.

There are going to be necessarily judgments as to which of these studies are appropriate and which are not. It's very difficult when it's left with the sponsor to carry that judgment out because you know, in fact, what the results are going to be when you see these studies as you are deciding which of these studies to choose.

Ideally, prospectively one would have an independent group of people surveying the literature

without a specific interest, financial or professional interest choosing those studies that are the most reliable way of assessing what the effect of the active comparator is and proceeding forward.

Of course, even in that ideal setting the studies that you may have to choose from may be limited in terms of the reliability that they are going to be able to provide for this assessment.

My sense is that if the approach that Dr. Fisher has laid forward is methodologically very reasonable, the concern is what we can put into that approach, i.e., the trials that are available as the evidence that he is required to use in order to ultimately assess what the effect is of heparin. In fact, if it were this clear, i.e., if it was widely accepted that heparin was effective, is it, in fact, not labeled in this indication? It's an interesting philosophical issue in itself.

DR. PACKER: It's not but whether it would be labeled if an application were made is a separate issue. Clearly the agency does not rule on applications that are not before it.

DR. FLEMING: So, in essence, the concerns that I have is as you look at the most critical elements of these studies that are the basis of determining the effect of heparin, if you look at the Oler study, the data in terms of numbers of events are dominated by the Holdright trial that is completely out of line for what the event rate ought to be.

The remaining studies are all incredibly slow and give an aggregate event rate that is less than half of that that we have seen in the OASIS-1 and OASIS-2. Similar comments for FRISC which is the critical study for that particular. Bottom line is we're looking at OASIS-2 at a study that provides 714 events that's the basis of our understanding what the effect is relative to heparin and we are relying on 49 events in the FRISC approach.

And we are relying on if you put aside Holdright 13 events plus 28 or 41 when we're using the Oler approach. There's extreme concern about how reliable our estimates of heparin are with this approach.

DR. PACKER: Dr. Fisher.

DR. FISHER: I wanted to make a couple of comments. It's always tempting to get into a debate mode but we are here basically to work on data. First, I want to be sure I understand what the agency did. Your false/positive rate of 50 percent, you said there was one underlying control rate? Is that correct? The simulations? The reason I ask is unfortunately I've done this so recently it wasn't in the review document so it's a little hard to react in real time.

DR. WANG: The way we did the simulation study is to say here is the data that we observed. Given this is the likelihood of the truth, then what would be the probability of saying that treatment is going to be superior to the placebo, the aspirin given that there really is no difference. Yes, we do utilize the data information to try to simulate the data as it is.

DR. FISHER: I don't quite understand. That means that the data would show the difference to say we simulate under the null hypothesis with the likelihood -- as I understood it, I'll only make one

point that I think is a fallacy both addressed by the FDA and by Tom. To me what they were going on and on about these rates and the trials is precisely -- precisely why people use odds ratios.

If you look at the aspirin data, for example, that's how you get consistency. You don't compare the rates in the trials. You compare the odds ratios or the relative risk and that is very important because the populations are never quite the same and this is the one thing that makes totally using historical controls so difficult.

DR. FLEMING: There's no debate about using odds ratios. I'm very comfortable with that. If we go to page 28, if you have that slide, is it, in fact, true if you look at the Holdright data that we're looking at, an event rate of 27 percent?

DR. FISHER: I haven't computed the event rate but we can put up -- let me see if I find the -- why don't you put up slide LF-23.

DR. FLEMING: The debate isn't about whether the odds ratios --

DR. FISHER: Not the actual values. The

individual studies are behind you. If you go to the next slide, there's a plot and, as you can see, the Holdright data is the majority of the data and the small studies have much wider confidence intervals. That's why, of course, the relative risk is much closer to the Hold right data than a lot of the other data points.

DR. FLEMING: Lloyd, we want to make sure. The issue at hand here isn't whether the Hold right is saying the relative risk is of the same order of magnitude as the other studies. The issue is the Holdright data is based on what is hidden there, the fact that the baseline event rate in Holdright is, I believe, 27 percent. In the aggregate of the other five studies, it's 2.4 percent. Is that, in fact, true? It is true. And how is it 27 percent in the Holdright study? Is that, in fact, death MI at day 3 to 7?

DR. YUSUF: None of this is death MI.

DR. FLEMING: That's not what Lloyd said.

DR. FISHER: Yeah, this is. It is death MI.

DR. FLEMING: It's certainly relevant to know. We should be talking about the same endpoints over roughly the same time period in order to be able to use your method appropriately.

DR. FISHER: I can give you the time periods for the individual studies. It was six days, five days, three to four, three to four, three to four, two and five to seven so about five to six days is the average whereas our endpoint was at seven days. As I mentioned, I didn't go back to the end of therapy to make it more comparable because that was more favorable.

DR. FLEMING: Is there any explanation? Is it surprising to anybody that we're seeing a 27 percent event rate?

DR. YUSUF: Tom, there's no explanation why the Holdright absolute event rates are different from the others. Having said that, whenever we do meta-analysis in different areas there is a huge difference.

The second thing is just the calculation you did, if you take out Holdright which is the

outlier in that, you said it's 30 versus 28. The odds ratios will be lower and the confidence limits will be tighter. If Lloyd were to do the same calculations excluding Holdright, the effect sizes will be bigger and the p-values will be more extreme. I'm sure the p-value of 0.06 will be well less than 0.05. In a sense what Lloyd has done is more conservative than if you take Holdright out.

DR. FLEMING: What we have -- and the committee can look at page 28 -- what we have are six studies. There is not a single study in this group that provides a substantial amount of data with an event rate that is remotely close to what we are seeing in the OASIS trial. I worry about the interpretability of what is base in Holdright. I have serious concerns about how to interpret that, 27 percent in the heparin arm.

If you pool the other five, the big concern that I have isn't that those are individually invalid. They give us a totality of 13 events. These are exactly the types of experiences that you would expect could readily have not been published.

DR. FISHER: But although there are other concerns as has been expressed, one can also make the argument fairly strongly based on FRIC plus FRISC alone throughout all of Oler.

DR. FLEMING: And the critical study there is FRISC because that's our linkage, what we are really crying out for here.

DR. FISHER: No, you're saying it's critical because that has the big non-one estimate.

DR. FLEMING: No, Lloyd. It's because what ultimately we have to do is we have to get a comparator to ask for alone and that is what FRISC is providing.

DR. YUSUF: You raise two issues, Tom, which I would like to respond to. The first is whether these trials are biased in any way. That is a very hard one to answer but I can answer it. We've done three things to look at it not because of this presentation, because we have a paper coming out in the Lancet where we've done a meta-analysis of all the unfractionated heparin trials and all the low-molecular weight heparin trials.

All we found was 100 more patients in the unfractionated heparin trials. In doing this we wrote to everybody who did unfractionated heparin trials. We wrote to every company that had unfractionated heparin. We also wrote to the Cochran database. We did as an exhaustive literature search as is humanly possible. The second point I wanted to make --

DR. FLEMING: My concern is getting away from a literature search.

DR. YUSUF: That's why we wrote to people. The companies that did the trials, the Cochran database, and people that we knew were interested in unstable angina asking them, "Do you know if a trial was missed?" Several of you know that is the approach we take. It takes years to do that but we really did that and we couldn't honor extra data. This doesn't mean I can guarantee there aren't trials out there. This just means we did the best humanly possible and it doesn't alter this.

The second point is the event rates does not invalidate -- variable event rates in different trials does not invalidate the estimates that you

derive from meta-analysis. For instance, within a given trial, you can have low-risk patients with a one percent event rate and high-risk patients with a 10 percent event rate and you calculate an overall treatment effect because the odds ratios are transportable.

DR. FLEMING: That's what you have to assume. You have to assume that the overall effective intervention is independent of many other factors that are strikingly influencing event rates.

DR. YUSUF: And where we have a lot of data, for instance, we have the data with beta blockers. We have the data with aspirin. We have the data with cholesterol lowering. Lots of areas where you do have good data, that assumption --

DR. FLEMING: But we don't have the data with heparin. You've just indicated we don't. The critical question at hand here is heparin. Is, heparin, in fact, providing a 10 percent, 20 percent, 40 percent reduction. That's the question at hand. Not aspirin, not anything else.

DR. YUSUF: Tom, I'm talking for general

principle, the general principle being absolute event rates don't invalidate the meta-analysis or the estimates within the totality of a single trial because different subgroups can have different event rates. We all agree we wish we had more data on infractionated heparin. We are in this unfortunate situation, difficult situation, where clinicians are absolutely convinced that unfractionated heparin should be used. We did pull 500 centers before we started this trial. Can we do this trial with this placebo? Unanimously not one center said we could do it versus placebo. Whatever the reason, the people are convinced this works and the modest amount of data that there is, which is not ideal by any means, is what you have in front of you, and is supported.

DR. FLEMING: What you're describing is, in fact, the very common and unfortunate but classical limitation that we encounter as we attempt to do putative placebo assessments. It's exactly as you say. Very often we're in this circumstance.

DR. YUSUF: Tom --

DR. FLEMING: The fact that there are, in

fact, no other data doesn't, though, allow us to say the data that are here are more reliable than they otherwise would be. The critical limitation of a putative placebo argument is that you've got to come up with an estimate that is reliably predicting what the effect of that putative placebo would be in the population and if you see an event rate that is five-fold or eight-fold larger than in your trial, it's immediately clear that the circumstances of the other trial are very different. You are having to assume that the odds ratio effect of heparin in that setting would be like what you have no data on which is the odds ratio in your setting for the effect of heparin.

DR. YUSUF: That is an assumption that we have to make like a tautology. One little point, Tom, just to point out. It's the page 28 table you pointed out. Holdright had an unusually high event rate but that is a trial that showed the least treatment effect. We took the rest of the data, the number of events of 13 versus 20, on approximately similar numbers of similar people in the autumn group. Yes, you immediately point out they are tiny numbers but

that's all we have.

DR. FLEMING: Tiny numbers and now with a very low event rate lower than the OASIS trials.

DR. YUSUF: Yes, but, you see, we agreed in principle the event rate does not effect the treatment effect size across most treatments that we've been able to examine.

DR. PACKER: Let me try to do the following. I think that the committee has heard and understands fully well what the issues are and it is unlikely that we will be enlightened further by discussions on this issue. What I would like to do is ask Dr. O'Neill for his comments on it because that would be, I think, helpful to our deliberations.

DR. O'NEILL: I think what you've heard over the last hour, hour and a half, is a discussion of a method that Lloyd Fisher has proposed for imputing a placebo. There are two aspects to that method. One is relying on meta-analyses and various strategies for the meta-analyses which includes which studies go into those meta-analyses.

I think you've heard from Tom Fleming that

there is a concern that there is a fair amount of heterogeneity in sample size as well as background event rates among those studies. How they all got in there is your guess. They are from the literature and it's well known that lots of studies don't get into the literature. If you are negative, you don't get into the literature. That's the point Tom was trying to make.

The other point is the fact that the imputation strategy separate from the meta-analyses has an extremely strong assumption. What you've heard from Sue-Jane Wang is an effort that has been going on at the FDA ever since the "imputed placebo strategy" has been thought about to deal with what is a tough problem. We have a lot of concerns that no one has gotten it right yet.

In this particular instance this method hasn't gotten it right is an extremely strong assumption. The assumption is that everything is the same and would be the same in this current study as it was in "the historical meta-analyses trials." I think it's pretty apparent that Tom Fleming has pointed out

that there is a lot of differences in heterogeneity in the studies. That's the bottom line.

Sue-Jane has said when there is heterogeneity, you're false/positive rate is very high. So the issue then is you can't believe any of these p-values that you've been seeing. They can be inflated dramatically. How much we don't know but this is very early in the first and second stages of what I would call this imputed placebo strategy effort.

We're in the second inning of a nine-inning game. This is a methodology that is being proposed and there are so many unknowns. There are more questions than answers. To make a major decision on the basis of this, that's not to say that it's not a worthwhile effort but there are a lot of things that I think have been pointed out that empirically justify the concerns.

You need to think about why people are analyzing in the literature heterogeneity and meta-analyses. They take the very simplistic approach. While Salim might say that the treatment effect is

independent of the control rate, I don't think so.

There's a lot of effort around in meta-analyses which show that your treatment response is related to what your background event rate is. We've seen in this collection of the three studies of the Older meta-analyses or even within the context of the OASIS-1 and OASIS-2 so differences in the event rates.

What Sue-Jane Wang was saying is the inference on this imputation strategy is extremely sensitive to that. I think empirically there is enough evidence for that. FDA had done a little more than was presented and, in the interest of time, not all the slides were gone through.

You have to realize this is tough sledding. This is not simple stuff. The material that Lloyd Fisher presented in the application needs a lot of thought. We put a fair amount of thought into it and we have a lot of concerns and I think you have seen part of the concerns from Sue-Jane Wang and that's what the bottom line is.

DR. PACKER: Dr. Koch, we'll ask you to respond. Please, we are desperate for time so we'll

ask you to be to the point.

DR. KOCH: Yes, I will be to the point. It's responsive to something that Dr. Califf asked. He asked whether there were any sensitivity analyses done. Yes, there were sensitivity analyses done but they were done by a different method. They were done by basically asking the question that had aspirin been the control group in the OASIS-2 study, what is a reasonable number to expect as the additional number of people with death or MI in OASIS-2.

To do that we assumed different values of relative risk for heparin versus aspirin. The conservative estimate that we used was in the vicinity of .8 top .85 at the higher end of the confidence limits that Dr. Fisher showed.

We also made the assumption that anybody who had a failure on heparin would have also failed on aspirin as well. We then used the event rate on heparin to estimate a conditional probability of failing on aspirin given that you did not fail on heparin. We used a lower-bound confidence interval on the heparin rate when we did that.

We also calculated a lower-bound on the number of additional aspirin type patients who would have failed had aspirin been the comparator. It would have been at least 25 to 35 and p-values that you get when you do that are below 01.

Obviously, if you make stronger assumptions about how good heparin is, the results get stronger and this methodology can be shared with the FDA if there is an interest in this as an alternative approach. It was mainly done to simply verify the kinds of information that we were getting from the meta-analysis and the putative placebo analysis that Dr. Fisher presented.

DR. PACKER: Marv, quickly.

DR. KONSTAM: Well, I was just going to ask about the sensitivity analysis because I think the situation that we're in is that the community is practicing in a way that is not condoned by the FDA. The data that's been shown to us I gather represents the entirety of data upon which we can estimate the degree to which heparin, in fact, is acting. With all the caveats of the problems with that data, I think it

helps me in figuring out how I'm going to come down on this to really see what our point estimate of heparin effect is influences the value of our drugs. I don't know if it's worth showing a slide of that.

DR. PACKER: I have to take the chairman's prerogative and simply say that there is a sensitivity analysis in the documents which have been presented to us. Is that not correct?

DR. KONSTAM: No. We haven't seen a slide of it.

DR. PACKER: Oh, we haven't seen a slide of it.

DR. KOCH: There is a slide that the sponsor prepared with a somewhat different kind of sensitivity analysis. What I described was a different way of doing the sensitivity analysis that I did independently which shows basically the same thing.

The point is if you're willing to accept on the basis of what you saw from FRISC/FRIC and Oler that a reasonably conservative estimate of the relative benefit from heparin is a risk ratio of .8

moving up towards .85, then there's different ways in which you can combine that with the OASIS-2 study to produce p-values that start moving down below 01 and you just have to decide.

DR. KONSTAM: In fact, Gary, you've already got it. It's in the OASIS-2 analysis. Basically just look at the confidence interval for the relative risk and see and inferiority analysis if it excludes what you consider to be where the placebo would reside.

DR. KOCH: Yes. Or if you're interested in the superiority to aspirin, you simply multiply the confidence interval by .8 on both sides.

DR. PACKER: Marv, I just want to clarify one thing. I don't think that the FDA takes any specific position on the efficacy of heparin so that it's not that physicians are practicing or not practicing the way which the agency would condone.

DR. KONSTAM: All I said is it's not condoned. In other words, the FDA has not indicated that it's effective therapy.

DR. PACKER: I think that the only thing

that one can do is take the data that exist with heparin and we have seen that data presented. The limitations of the analyses that have been presented have already been described by many individuals.

It is the only data that exist and the question that we need to address and in part intuitively is whether the limitations which are known to accompany the kind of analyses are of sufficient concern to us that they would weaken an argument that lepirudin is effective had it been compared to placebo. In other words, the limitations that are -- I think, Lloyd, you agree with the limitations which have been presented. Is that correct?

DR. FISHER: Yes, yes. None of us can generate more data or data that were acquired other than how it was. That is certainly true.

DR. PACKER: I can see actually no philosophical or mathematically important differences in the two views which have been presented. It is really up to us to determine whether the assumptions which are inherent in the method that Lloyd has presented are of sufficient concern to us to effect

conclusions regarding the efficacy of lepirudin versus placebo. Is that fair?

DR. FISHER: In that the estimated magnitude of the estimates are so far off. I'll mention briefly what I mentioned before. Behind you on the screen, the estimation of the percent of the estimated heparin effect preserve with the confidence intervals.

This doesn't directly affect that but you can mentally slide things down quite a bit and you'll still look good relative to the estimate of heparin. Now, you have to decide if that heparin estimate has any validity or, in your own mind, what you think is going on.

DR. PACKER: We are not going to become smarter.

Tom, you're going to get the last word.

There is no mechanism of becoming smarter today. The data that we have are the only data we have and the assumptions that are inherent in the model have been described and outlined and agreed to by all concerned. Tom.

DR. FLEMING: I'm just concerned that we haven't discussed safety.

DR. PACKER: We're going to do that right now. Can we present safety, please?

DR. LUZ: Since patients treated with antithrombotic agents are known to be at increased risk of suffering hemorrhagic adverse events -- sorry, I missed that slide. My talk will be structured as follows. First, I will give you an overview of the safety data collected and the definitions used in the OASIS studies before I turn on to discuss the individual findings for bleeds, strokes, and other adverse events.

Due to the known increased risk of bleeding in patients treated with antithrombotics, the key focus of the safety evaluation in the OASIS studies has been on the occurrence of minor and major bleeding events.

A second focus has been on the occurrence of stroke. In particular, hemorrhagic stroke. Both major bleeds and strokes were essentially adjudicated by the blinded adjudication committees of the studies.

Consistent with the short half-life of the drug and the short duration of treatment in the trials, the focus of both the safety evaluation and this presentation will be on the initial seven-day period.

The OASIS study protocols prospectively define major and minor bleeds. According to these definitions, major bleeds were all those bleeds that were fatal, life-threatening in the opinion of the investigator, bleeds that required surgery or transfusion of at least two units of blood or blood products, or those that again in the opinion of the investigator were permanently or significantly disabling. Minor bleeds were all those that were not major.

Before CCC, the coordinating office of the trial in Hamilton and blinded the study, they recognized that in a number of cases investigators had specified life-threatening as the only criterion of major bleed without any objective evidence to support this classification.

In particular, many of these bleeds were

not fatal, not intracranial, nor did they require surgery or transfusion. Therefore, for the analyses CCC introduced a new objective definition of life-threatening bleeds. That includes all bleeds that are fatal, intracranial, required surgery, or transfusion of at least four units of blood or blood products. This definition has been adopted by Aventis for our own analyses.

Stroke was defined in the OASIS study protocols as the presence of new focus neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours. Three types of stroke were differentiated; hemorrhagic stroke, ischemic stroke, and stroke of uncertain type.

Importantly in the analyses of bleeds, both hemorrhagic and uncertain stokes were counted as intracranial bleeds in order to avoid any potential underestimation of the frequency of intracranial bleeds.

I will now turn to discuss the bleed findings first from OASIS-1 and then from OASIS-2. This slide gives you the most important bleeding

findings from the OASIS-1 study. As you can see on the left-hand side of the slide, there was a clear and dose dependent increase in the rate of minor bleeds from 10.6 percent in the heparin group to 16.3 percent in the low-dose lepirudin group, and 21.5 percent in the medium-dose lepirudin group.

In contrast, there was no difference in the occurrence of major bleeds and the absolute rates of major bleeds were low in all three treatment groups. This is also reflected if one looks at the subcategories of nonlife-threatening and life-threatening major bleeds which all occurred at low and similar frequencies in all three treatment groups.

This is the same presentation for the OASIS-2 study. Again, there was a highly significant increase in the rate of minor bleeds from 4.5 percent to 7.7 percent. You will note, though, that the absolute incidences were much lower than in the OASIS-1 study.

Although there was a similar relative increase in the incidents of major bleeds that also reached the level of statistical significance, the

absolute rates of major bleeds were low and, in fact, as low as in the OASIS-1 study.

As you can see on the right-hand side in the right half of the slide, the entire difference in major bleeds was accounted for by nonlife-threatening major bleeds but occurred at a frequency of .3 percent in the heparin group and .8 percent in the lepirudin group.

In contrast, there was no difference between the groups in the occurrence of life-threatening bleeds but were observed at a frequency of .4 percent in both groups.

This is a break-down of major bleeds at seven days by the categories that were provided in the data collection forms. As you will note, the incidences of fatal bleeds, intracranial bleeds, and bleeds that required surgery were, in fact, low and similar in both groups. Of note, among the five intracranial bleeds, there were four uncertain strokes and only one confirmed intracranial bleed that was observed in the heparin group.

Most of the major bleeds were managed with

transfusions of at least two units of blood and there was a statistically significant difference between the groups with the higher incidents observed in the lepirudin group.

Similarly, there were appreciable differences between the groups in the occurrence of bleedings that in the opinion of the investigator were permanently or significantly disabling or life-threatening.

Looking at the leading sources or locations of bleeds, you will note that the leading sources that also accounted for most of the difference between the two groups were gastrointestinal and hematuria. The relatively low rates of surgical and puncture site related bleeds should be interpreted on the background of the relatively low intervention rate during the infusion.

Among the other major bleeds that are not further specified here, there is a total of three retroperitoneal bleeds, two in the heparin group, one in the lepirudin group, and no intraocular bleed.

With respect to minor bleeds, the leading source was puncture site related bleeds. Here there was no difference or the incidents were similar between the two groups. Across the vast majority of all other sources of minor bleeds the overall pattern that showed an increased risk of minor bleeds in the overall population was also reflected in the subgroups.

We also performed a substantial site of subgroup analyses that were all prespecified in the statistical analysis plan. The subgroup analyses were done on hemorrhagic adverse events as opposed to bleedings. Hemorrhagic adverse events included obviously all bleeding events but in addition also events that were not bleedings themselves but associated with a certain risk of bleeding. In particular, false vascular aneurysms.

Over all the pattern of hemorrhagic adverse events across the subgroups was reflective of the overall pattern in the total study population. There were, however, two subgroups with disproportionately increased rates of hemorrhagic

adverse events, namely patients with a baseline creatinine of more than 1.5 milligrams per deciliter and patients weighing less than 50 kilograms.

These are the findings. As you will see, while there was no appreciable difference in the incidence of hemorrhagic adverse events in the heparin group between the subgroup levels for baseline creatinine, lepirudin patients with a high baseline creatinine had, in fact, a disproportionately high rate of hemorrhagic adverse events.

The same observation can be made for weight where there were only minor differences for heparin but, again, a disproportionately high rate in lepirudin patients weighing less than 50 kilograms.

As I pointed out earlier today, patients were to be excluded from participation in the trial if they had renal insufficiency as assessed by a creatinine level of at least 2.0 milligrams per deciliter. If at any point during study infusion elevated creatinine levels were found, the infusion dose was to be reduced by 50 percent starting at levels of 2.0 and to be terminated with levels

exceeding 2.5 milligrams per deciliter.

There was no weight adjustment below 50 kilograms in the trial so the adjustment was only made in the range between 50 and 100 kilograms. Based on the subgroup findings that I just presented, we now conclude that obviously a dose adjustment would be needed in patients with elevated baseline creatinine starting at a level of 1.5 milligrams per deciliter and the weight adjustment should cover the entire weight range including low body weights.

We've also investigated the potential impact of warfarin, indirectly assessed the impact of warfarin on the overall study results. You've seen a similar presentation in Dr. Yusuf's talk. This is a comparison of the overall study results with the results in patients who did not receive warfarin. First for minor bleeds in the top half of the part and then for major bleeds in the bottom part of the slide.

As you can see, the difference in the risk ratios was, in fact, very moderate with the 95 percent confidence intervals overlapping widely. At least the

data would indicate that the additional warfarin did not substantially increase the risk of bleeding in lepirudin patients.

Beyond seven days both in the period between eight and 35 days and 36 to 180 days the extent of bleeding was considerably lower than during the first seven days and there were no appreciable differences between the groups in any of these two periods.

In the following I will be discussing the stroke findings again starting with OASIS-1 and then moving on to OASIS-2. These are the stroke findings from OASIS-1 at seven days on the left-hand side and 35 days on the right-hand side. You will note that the number of strokes and the incidences were very low and there were no differences between the treatment groups.

In OASIS-2 at seven days the overall stroke rates were relatively low and almost identical in both groups. Similarly, there were no differences in the occurrence of hemorrhagic stroke, ischemic stroke, and stroke of uncertain type. Importantly,

there was no single hemorrhagic stroke in the lepirudin group in both OASIS studies during the first critical seven days.

At 35 days there was a slight imbalance in the overall stroke rate between the two groups with a slightly more strokes observed in the lepirudin group. The difference did not reach the level of statistical significance though. However, there were contrasting effects on subcategories of stroke that I will explain to you in the following.

Hemorrhagic strokes were observed less frequently in the lepirudin group than in the heparin group, the difference being statistically significant. Similarly, ischemic strokes were observed more frequently in the lepirudin group than in the heparin group, and again there was a statistical significance associated with the difference.

These findings are currently unexplained given that in the period beyond seven days there was no difference between the treatment groups in other hemorrhagic events, and given that during the same period there was no difference between the groups in

the occurrence of other ischemic events, namely cardiac ischemic events. It is difficult to explain these findings.

If one compares the findings for ischemic stroke from the OASIS-2 study with literature reported data that are available from the GUSTO-IIb study looking only at patients who did not present with ST elevation at baseline and the PURSUIT study, it becomes clear that the .7 percent rate of ischemic stroke observed in the OASIS-2 study is consistent with the findings from these other studies.

In contrast, the .3 percent rate observed in the heparin group of the OASIS-2 study is surprisingly low against the background of the literature reported data.

In the following I will very briefly discuss the findings for other adverse events. This is just a summary slide indicating that there were no differences in nonhemorrhagic events at seven days between the two treatment groups and for serious nonhemorrhagic adverse events. If anything, the rate was slightly lower in the lepirudin group than in the

heparin group.

Reassuringly given that lepirudin is a heterologous protein, there were no differences between the groups in nonserious or even serious allergic reactions.

In summary, at seven days there was excess in minor and nonlife-threatening clinically manageable major bleeds in the lepirudin group. There were no differences in life-threatening bleeds, no difference in stroke, and no difference in the occurrence of other adverse events.

At 35 days there was again no or only a slight difference in the occurrence of total stroke. However, there were contrasting effects on subcategories of stroke that occur in the unexplained. There were no differences in the occurrence of other adverse events at that time point. Thank you for your attention.

DR. PACKER: We'll begin questions with our primary reviewer, Dr. Borer.

DR. BORER: You had approximately just slightly less than, I guess, 100 patients in each arm

of the study who underwent coronary artery bypass grafting after the infusion was begun -- after either infusion was begun so there are about 200 patients total. I don't know how many of those patients were operated on within 24 hours of cessation of the infusion. I would like to know that.

Then I would like to know what the perioperative mortality rates were in the patients who were on lepirudin versus on heparin, the whole group or the 100 versus 100, and for those who are operated on within 24 hours of stopping the infusion. I would like to know the blood products used in those two groups as well.

I would like to know how many patients were brought back to the operating room for bleeding. Not complication but for a post-op bleeding in the two groups, if you can compare them.

DR. LUZ: Let me start with the last part of your question. As you saw in the breakdown of sources of major bleeding, there were only eight versus seven surgical bleeds.

DR. BORER: No, no. I'm not asking about

surgical bleeds. I'm not even sure you captured the data I'm asking about, but once somebody went to bypass grafting, I assume they were censored. Is that correct?

DR. LUZ: Let me first show you the data that we have on PCI during infusion. 026, please. This is just a flowchart to show you how many patients underwent PCI or CABG during study infusion. If you just focus on the bottom part of the slide, there is a very small number in both groups that actually underwent CABG or PCI during infusion of active study medication.

This slide summarizes the findings for these patients. It's a bit crowded and complicated. I have tried to walk you through that slide. For both heparin and lepirudin you have three columns. First, the events in all patients, then events that occurred before the intervention, and events that occurred after intervention.

The top two rows give you the incidences of CV death MI and CV death MI refractory angina. To

focus on this first, one can see that the total that the overall incidents of both endpoints was higher in the heparin group than in the lepirudin group. The same observation can be made both for events that occurred before intervention and after the intervention. Now, if one moves on to discuss safety, the first and most important observation that one can make is that there were no major bleeds in any of these patients.

The second point is that there were, in fact, only minor differences in the incidences of minor bleeds. In fact, the incidences of minor bleeds were higher overall in the heparin group than in the lepirudin group. Again, this mild trend was observed both for events for and after the intervention. It's a small database but it is all we have during infusion.

DR. BORER: What is the intervention?

DR. LUZ: Pardon me?

DR. BORER: Can you define intervention for me? The intervention is the angioplasty or the bypass graft?

DR. LUZ: Yes, it's either CABG surgery or PDCA.

DR. BORER: Do you have data to answer the question I asked. That is, to compare the 100 patients that were operated on after lepirudin versus the 100 patients that were operated on after heparin.

DR. LUZ: No, I don't have the data.

DR. BORER: Okay. I think that those data should be made available to the FDA because --

DR. LUZ: We'll be glad to.

DR. BORER: -- it's exactly in that population that we are now seeing important problems with other clot active agents that are being used for acute coronary syndromes.

DR. PACKER: Joann.

DR. LINDENFELD: The overall rate of the angioplasty or coronary angiography in the first three days of the study during the infusion was what? Very low.

DR. LUZ: It was just the 100 patients so about --

DR. LINDENFELD: Again, just as we have

concerns about bleeding. The most common cause of bleeding, of course, is intervention and this had a very low rate of intervention. I think we just have to be aware that we'll see substantially more bleeding if there is more with more interventions as we would see in the states.

DR. YUSUF: (Inaudible. Off microphone.)

DR. CALIFF: I think Joann's point is relevant to U.S. practice that these data are not very relevant because intervention is almost always done the first 48 hours and that makes it difficult.

DR. LINDENFELD: And we know that the rate of bleeding if it is higher will be substantially higher with an intervention.

DR. CALIFF: Whether that's the appropriate treatment pattern or not is a different issue.

DR. PACKER: Ileana.

DR. PIÑA: In the FDA review that we've received, there is a listing of adverse events resulting in discontinuation of infusion. It seems that the hemorrhagic events are twice as many in the

lepirudin group. Are those hemorrhagic -- but you've concluded that there were no excess major bleeds. Is that part of your going back into the documents and finding that some of the events that were classified as major bleeds were indeed not?

DR. LUZ: No. The determination of whether a bleed was major or not was purely based on the information that was collected on the major bleed form. We had prespecified criteria that the investigators had to check and depending on whether or not there was a check mark, the bleeding was reported as major and, therefore, further adjudicated or not.

DR. PIÑA: To me a hemorrhagic event that leads to the discontinuation of the infusion in my estimate would say that the investigator felt that it was significant enough to stop the infusion. Then I think that the follow-up to Jeff's point that when you do have bleeding with this agent, what do you give? Do you give fresh/frozen plasma? Do you give products? Do you give whole blood? What do you give? You've got time before your half-life has dropped.

DR. YUSUF: The most common thing was just

to stop the infusion. That's what people did. The next most common was give blood. In no case in the whole study was ultracentrafication needed, although that was one of the things we told people. Everything was handled by giving blood or stopping the medication.

DR. LUZ: In fact, the important point is in the vast majority of cases the discontinuation of infusion per se was sufficient because no transfusion was needed. The overall frequency of transfusion was in the range of .4 percent. The early discontinuations were obviously much more frequent.

In fact, we believe that no difference in the occurrence of life-threatening bleeds might have to do with the early discontinuation that in cases with minor bleeds or ongoing bleeds could be stopped simply by terminating the infusion.

DR. PIÑA: And were any of these hemorrhagic bleeds people who received thrombolytic therapy or people that ended up going to interventions? Do you have that data?

DR. LUZ: We have very few patients who

concomitantly received thrombolytic agents. The vast majority of patients who suffered bleed did not receive thrombolytics.

DR. PACKER: Rob and then Marv.

DR. CALIFF: Two questions. One is if you just take needing one or more units of blood transfusion in the two groups, what does that look like? Any transfusion?

DR. LUZ: Well, in fact, I think we have only two cases where only one transfusion was given in the vast majority. This makes sense from a medical point of view there were at least two transfusions.

DR. CALIFF: We have those numbers. There's an excess of transfusion in the --

DR. LUZ: Yes.

DR. CALIFF: And the second question what would the recommendation be for someone who needs to undergo urgent bypass surgery in this circumstance?

DR. YUSUF: (Inaudible. Off microphone.)

DR. CALIFF: So you stop and wait four to five hours to go to surgery.

DR. YUSUF: This is a matter of great

concern at the beginning, especially at our center. Our IRB held up our protocol. Then the chairman called Eric Toppel and I think talked to Chris Granger as well. Then we came up with the strategy that all you do is wait four to five hours.

DR. PACKER: Marv.

DR. KONSTAM: You know, looking through the briefing document, I understand there are two sets of data with regard to life-threatening bleeds. I'll just say my understanding and you tell me if I've got it wrong. There was an investigator driven definition of life-threatening bleed and then you redefined life-threatening bleed so the data came out two different ways. But if you stick to the original investigator driven definition of life-threatening bleeds, there were 23 in the lepirudin group and 12 in the heparin group for a p of .089. Is that right?

DR. LUZ: Perhaps we can look at the data and I can try to shed some light on that. 079. This is a breakdown of bleedings that were reported as life-threatening by the investigator. I see you just pointed out there were 23 such cases in the lepirudin

group and 12 in the heparin group.

Applying the objective definition of life-threatening, the counts were nine in heparin and seven in lepirudin.

DR. KONSTAM: Can I stop you? When did you come to that definition? The objective definition. When did that appear?

DR. LUZ: The definition was introduced when the investigator group in Hamilton before unblinding the study --

DR. KONSTAM: Before unblinding but they knew there were a lot of bleeds going on. In other words, yes before unblinding but they had already --

DR. LUZ: The overall incidents of major bleeds, as I pointed out, was as low as in the OASIS-1 study so from that point of view there was no reason to be concerned.

DR. KONSTAM: Right, but you knew that you had 35 cases that had been designated life-threatening bleeds. You didn't know that?

DR. YUSUF: No. I'll tell you how this

happened, Marvin. This happened about six months or so before the end of the study when the statistician came to me and I wasn't aware of what was happening, not the event rate or nothing, and said, "Look, we've got several people that are calling events life-threatening bleeds. They didn't get any IV fluids or blood. They didn't have an intervention. They didn't have anything and they didn't have lepirudin, hematoma, nothing. What should we do?"

I said we should have an objective measure not knowing what it will turn out to be. We had an objective measure put in which is you need to have either hemodynamic instability or the drop in hemoglobin by more than five or needing allotropes or needing a lot of blood transfusions or needing an intervention. I had absolutely no idea what the overall event rate was on the blinding and I didn't know what had happened later.

DR. PACKER: Dr. Farrell who is the FDA medical reviewer for the FDA.

DR. FARRELL: I just wanted to focus us. I was afraid we were going to get off the subject of

ischemic strokes. When I looked at that, there's a definite difference between days eight and 35. If you are not in favor of lepirudin and if you actually look and subdivide that into weeks, the majority of the strokes occur between days eight and 14. This may be a drug effect. It's not true for the heparin group.

DR. LUZ: It would be difficult to explain it. Given that during exactly the same period the incidents of coronary ischemic events were identical in both groups, there was no indication of other ischemic events ongoing. It seems surprising that the drug should have a specific cerebrovascular effect that causes ischemic strokes.

DR. KONSTAM: The designation of ischemic stroke was by the investigator. Was there always confirmation that there was not a bleed involved?

DR. LUZ: Yes. In 90 percent of all cases the diagnosis was confirmed by CT or MRI and centrally and blinded adjudicated. In the only six cases where no CT or MRI was done, the diagnosis was uncertain stroke. That was confirmed by the adjudication committee. Actually, the adjudication committee

confirmed 70 of the 74 reported strokes.

DR. YUSUF: (Inaudible. Off microphone.)

DR. KONSTAM: Right, but there were a far greater number of strikes that were designated ischemic than there were designated hemorrhagic bleeds.

DR. YUSUF: The deltas.

DR. KONSTAM: I understand.

DR. PACKER: Okay. I would like to -- I see there are no other questions. We have a real need to complete this meeting by 4:00. I hope we can do that. I have asked Dr. Hirsh to markedly curtail his presentation. His original presentation had 26 slides for risk of benefit which, in all honesty, Jack, probably sets an all time record as far as the experience of this committee. You'll get extra credit for every slide you skip.

DR. HIRSH: Okay. Thanks very much. Let's go to the next slide. In this presentation before going to the meat of the presentation, I'll just briefly review the current antithrombotic treatments for acute coronary syndromes.

Again, I'll just hit the highlights. There's been this discussion about heparin plus aspirin being more effective than aspirin alone. I think the evidence is strong that heparin plus aspirin is more effective than aspirin alone. The debate is just how much more effective is it.

As you know, in enoxaparin, a low molecular weight heparin, is more effective than heparin and it was approved by this committee based on the triple endpoint of all-cause death, myocardial infarction, and refractory angina. It was approved on the basis also of the putative placebo. There are two of the lepirudin studies. The OASIS-1 and OASIS-2 have been shown to be more effective than heparin on the basis of all-cause death, myocardial infarction, and refractory angina.

Two other low molecular weight heparins have been studied. Neither are more effective than heparin and one fragment was approved on the basis of a placebo control study and glycoprotein-IIb for antagonists plus heparin as being compared with placebo and heparin and both of them were approved.

Now, to go onto the key issues with lepirudin and acute coronary syndromes is that, and we've heard this many times, although the primary endpoint for OASIS-2, which is the double endpoint of seven days, was only borderline significant at p=0.086. I believe the evidence is persuasive and that hasn't changed. These slides were made before I heard the presentation and I still believe this, that lepirudin is more effective than heparin and I believe the evidence is compelling that lepirudin is more effective than placebo.

This is based on the two studies with the triple endpoint at seven days, OASIS-1 and OASIS-2, both significant risk reduction shown here.

On the pooled analysis of OASIS-1 and 2 for the double endpoint of seven days, which was significant.

On the analysis that Lloyd Fisher did on the putative placebo where lepirudin was superior to putative placebo and was highly statistically significant.

Now, Dr. Yusuf has discussed the

consistency within class of the OASIS studies. What I would like to do is discuss the overall consistency and point out that lepirudin -- the data with lepirudin are consistent with similar data from GUSTO-IIb which evaluated desirudin.

This evaluation is based on OASIS-1 and 2, lepirudin, GUSTO-IIb with desirudin. The endpoint was all-cause death or myocardial infarction at or close to the end of treatment. As you'll see on the next slide, the RRR was 26 percent which was highly statistically significant for the combined analysis.

This shows you the more detailed analysis of those studies. I would like to point out that OASIS-1 and 2, GUSTO-IIb and, of course, the combined OASIS-1, 2, and GUSTO-IIb were all statistically significant for the endpoint of all-cause death or MI close to or at the end of the treatment period. We've got to use this to compare this with the other forms of treatment.

This hasn't been discussed yet so I would like to spend just a little bit of time on this. This is the discussion of the net clinical benefit with

lepirudin.

The evaluation of net clinical benefit, we used pooled data from OASIS-1 and 2 using an integrated endpoint to find all-cause death, myocardial infarction, disabling stroke, and life-threatening bleed. This integrated endpoint captures the most serious efficacy and safety outcomes.

What this shows is that 7.6 of 1,000 patients treated did better with lepirudin than heparin for the quadruple endpoint, all-cause death, myocardial infarction, disabling stroke, and life-threatening bleed. This was statically significant.

The integrated endpoint was expanded to add all bleeds and add refractory angina. That' is shown on the next slide which shows with the expanded integrated endpoint, the benefit in favor of lepirudin was 10.6 patients per 1,000 patients treated.

Dr. Yusuf discussed the durability of benefit for OASIS-1 and OASIS-2. This is a discussion, the durability of benefit using the integrated quadruple endpoint. That is, the net clinical benefit.

As I mentioned, we used pooled data from OASIS-1 and 2. What you'll see on the next slide is the results 72 hours, seven days, 35 days, and 180 days. As you'll see, the effect was durable.

Dr. Yusuf has shown this slide. Just concentrate on the numbers in the circle which is the actual risk reduction. You can see there is neither loss nor gain over the complete period of the study.

To move to my last point which is a comparison of the relative efficacy and safety of hirudin with two new classes of antithrombotics that have been approved, low molecular weight heparin specifically, enoxaparin, the glycoprotein IIb/IIIa antagonists.

Now, these comparisons were indirect and they have the limitation of being indirect but I believe they are informative. Just to point out again that hirudin and low molecular weight heparin were compared with an active-control heparin where the glycoprotein IIb/IIIa antagonists were compared with placebo, both groups receiving heparin.

The outcome you'll see that is being shown

is the all-cause death of myocardial infarction at or close to the end of treatment period. This is common to all the studies.

This table shows the relative risk of the p-value for the comparison of all hirudin versus heparin, for enoxaparin versus heparin using the double endpoint at or close to the end of treatment, for all low molecular weight heparin versus heparin, and for GP I put IIb/IIIa antagonists versus placebo. The effect is significant for these three.

The reason it's not for all low molecular weight heparin versus heparin because in two of the studies, as you saw -- well, you saw one of them but in two of the studies, one with FRAX heparin and one with fragment, the low molecular weight heparin was no different than heparin. Therefore, the relative risk was brought close to the unity when those two were added to the enoxaparin.

This shows the more detailed analysis. You've already seen this with the significance for these four including the essence in the TIMI-11B data both of which cross the point of unity. The Antman

meta-analysis at eight days is significant. And this shows the FRIC and the FRAX.I.S. data. The point of this slide is that the order of magnitude of benefit seen in the pooled analysis with the hirudin studies is very, very similar to that seen in the Antman meta-analysis.

This shows the same data for hirudin but now comparing it with the glycoprotein IIb/IIIa. I would like to concentrate particularly on the comparison of the pooled data with the various studies with hirudin and at 72 hours for the all-cause death myocardial infarction and for the Kong meta-analysis. Again, the risk reduction is of the same order of magnitude.

One of the concerns with hirudin has been bleeding. This is a summary of the major bleeding rates in the OASIS-1 medium dose, OASIS-2, GUSTO-IIb, the low molecular weight heparin studies I showed, and the glycoprotein IIb/IIIa antagonists studies I showed.

This, again, just points out that there was a significant increase in bleeding with hirudin in

the OASIS-2 and GUSTO-IIb. This is the GUSTO-IIb, patients only without ST elevation, those not treated with thrombolytic therapy.

The other point I would like to make is that the order of magnitude of bleeding is similar when one compares the three studies and compares the four studies with low molecular weight heparin. In three of the studies with glycoprotein IIb/IIIa antagonists there was an increase in bleeding with the test drive compared with the control.

These are my concluding slides. Although the primary endpoint for OASIS-2, which was cardiovascular death, myocardial infarction at seven days, was only borderline significant. I still believe that the evidence is persuasive that lepirudin is more effective than heparin and I think it's very persuasive, indeed compelling, that lepirudin is more effective than placebo.

Within each OASIS study there's a consistency of benefit across different endpoints and the different time points. The effects are consistent across both OASIS studies and data with lepirudin are

consistent single data from the GUSTO-2b study with desirudin. There's enormous consistency. This provides a totality of data.

The risk reduction with lepirudin is of the same order of magnitude of enoxaparin. It is also the same order of magnitude as the GP IIb/IIIa antagonists.

As you've heard, there is an absolute increase in major bleeding with lepirudin which is small and similar to that seen with GP IIb/IIIa antagonists. From the net clinical benefit, the integrated clinical endpoint, the increase in bleeding is more than offset by benefit from serious efficacy outcomes.

So at the end of the day I still believe that lepirudin represents an important addition to currently available antithrombotic agents for treatment of patients with acute coronary syndromes. Thank you.

DR. PACKER: Thank you very much, Dr. Hirsh. Questions? If not, the committee will proceed directly to the questions that are before it. I'm not

going to read the introduction but I will go through questions 1 through 6. We have absentee votes from four members of the committee and we'll begin with our primary reviewer.

The first question asks whether refractory angina is an acceptable component as it is defined and assessed in the OASIS-2 trial. We'll begin the voting with Dr. Borer.

DR. BORER: Yes, I believe it is. First of all, I think that in the OASIS-2 definition intervention was a part of it so I think the question may be slightly incorrectly worded but it doesn't matter. Whether it did or didn't, most of the patients who had an angina endpoint had an intervention and I just don't believe this is an issue. I think that the definition of angina is acceptable and that it is an acceptable component of the endpoint.

DR. PACKER: Does anyone -- we need to go through this so we'll just start from Marv. Do you want to say yes or no?

DR. KONSTAM: Yes.

DR. FLEMING: Yes.

DR. LINDENFELD: Yes.

DR. CALIFF: Yes, but a comment that this endpoint needs a higher level of statistical certainty to be acceptable because it's less compelling than irreversible endpoints.

DR. DIMARCO: Yes.

DR. PACKER: And yes. The vote of Dr. Graboys is no, Dr. Grines yes, Dr. Piña no, and Dr. Armstrong yes. The total vote is nine yes and two no.

Question No. 2. Has adequate evidence been presented to demonstrate that the heparin regimens used in the OASIS trials were effective in the study population (patients with unstable angina or acute MI without ST segment elevation)? We have discussed this at great length. We need to vote. Dr. Borer.

DR. BORER: Okay. Intuitively I think heparin is likely to be better than placebo. I fully support the use of historical data for creation of comparisons to evaluate the efficacy of new therapies

when you can't do placebo control trials anymore.

However, I am very concerned that the evidentiary base for the putative placebo here is unacceptably weak and I have difficulty saying that because it's in contra distinction to what Dr. Hirsh said and there's no one in the world who is more highly respected in this area than he is. Nonetheless, I would have to vote no. I don't think adequate evidence has been presented to demonstrate that the heparin regimens were effective.

DR. PACKER: Okay. And we'll begin with John on this side. We'll just go through the vote.

DR. DIMARCO: I'll agree with Jeff that the evidence isn't great for heparin but I think it's going to be really impossible to do a heparin/placebo trial so I think we're stuck with what we have and what we have is clinical practice so I will say this is the standard regimen, this is standard use clinically, and there is some evidence in support of it so I would say yes.

DR. PACKER: Okay. We'll leave it at that. Rob.

DR. CALIFF: I say yes also. The question to me is not whether heparin is effective. It's how effective is it. I think it's hard to tell how effective it is but to me all the trials go the same way.

DR. PACKER: Joann.

DR. LINDENFELD: I would say no. I'm just not sure I could say specifically that heparin is effective on the basis of the data we've seen.

DR. PACKER: Tom.

DR. FLEMING: Milt, I'm adjusting to the world of this advisory committee. On other advisory committees I don't get pinned to yes and no and as a statistician it's awfully hard to make this dichotomous. I will give you an answer but let me precede it by saying that the OASIS study was a wonderfully conducted study providing a large amount of data giving us considerable insights about the relative efficacy to heparin. The cliche is you can't make silk out of a -- I would have to say the analysis by Dr. Fisher was on target for what could be done with the data that are available.

DR. PACKER: We shouldn't confuse issues here. This is not a question about the agent which is the target of this NDA. This is a question about heparin. I just want to clarify that.

DR. FLEMING: I understand. I understand. To finish the thought, the evidence as it has been provided to us about heparin is inadequate. Not because of the statistical methodology but because of the available data. In essence my answer is no, the data do not adequately demonstrate that the heparin regimen was effective in essence, in my view.

Historical data and clinical insight would have to establish that the effect is on the order of 10 to 12 percent at 35 days and it would have to be based on that experience. I can only respond to the data presented to us so my answer would be no.

DR. PACKER: Okay. Marv.

DR. KONSTAM: I'm going to vote yes but I'm going to also say that I'm lowering my standards to do so and it's in the context of the vote of public opinion that the medical community feels overwhelmingly that heparin is an effective agent in

this setting and that handcuffs the trials that can be done.

Of the data that were provided, I would say that the FRIC and FRISC combination are probably more convincing than the Oler meta-analysis. I will say under other circumstances that level of data would not be sufficient for me to say this but in the present context I'm going to vote yes.

DR. PACKER: I'm going to vote no. I just want to emphasis that I do believe that heparin works but the question does ask has adequate evidence been presented which leads me to vote no. I'm not certain that my vote is incompatible with those who have voted yes.

The votes of Dr. Graboys yes, Grines yes, Piña yes, Armstrong yes. The final vote is seven yes, four no.

Third question. Do the data provide adequate evidence of the effectiveness of Refludan for its proposed indication? We'll begin again with Dr. Borer.

DR. BORER: Again, intuitively as I said

about heparin and placebo based on the data we've seen, intuitively I think that lepirudin is more effective than heparin. I think the active comparison is highly suggestive but because of my concern about the putative placebo, I think that by itself it's not really sufficient to support a reasonable conclusion.

It doesn't say it's not better but a reasonable conclusion. It's a single trial. It's smaller therapeutic effect than was expected. There are some safety concerns that haven't been fully evaluated. I am concerned that OASIS didn't support its primary hypothesis but this by itself really wouldn't necessarily cause me to withhold an approval recommendation if all the other data were compelling.

I don't think all the other data are sufficiently compelling and, therefore, I don't think it's appropriate to set the precedent that approval should be provided based on a single sort of marginally significant trial of a new drug versus an active comparator when the active comparator hasn't been shown rigorously to be better than placebo, or at least acceptably better than placebo. I don't think

that we've reached the standard that I would set for this particular drug from this particular trial.

DR. PACKER: Okay. Dr. Borer's vote is no. Which side did we start on the last time? I'm sorry. John.

DR. DIMARCO: As I read the new indication, there's nothing in there that states that it is superior to heparin so I would vote yes.

DR. PACKER: Rob.

DR. CALIFF: I'm going to take 20 seconds on a soapbox or maybe a little longer. I've got all the pluses and minuses here. This is a very difficult one for me. On the plus side we've got two studies going in the right direction. You only have to believe that heparin is a bit better than placebo to buy the putative placebo argument. I believe it is.

The complete systematic overview of all the hirudins that Dr. Hirsh sneaked by in the last few minutes is pretty compelling, I think. We are dealing with a leading cause of death and disability. I'm worried that the standard for this in heart failure are getting so high that it's going to discourage drug

development in these areas.

Looking at what it takes to get drugs through other committees and the FDA, this is an incredibly high standard. We need better agents for this condition particularly with the combinations that need to be given and this drug is already approved for heparin-induced thrombocytopenia. It would be a funny situation to say that a drug should be used in place of heparin when you produce thrombocytopenia but there's no reason to use the drug which is kind of the conclusion that we'll be coming to. Finally --

DR. PACKER: We see that.

DR. CALIFF: Well, I mean, it's kind of dumb. Then finally --

DR. PACKER: We see lots of dumb things.

DR. CALIFF: So then finally there would be no surprises, I think. There is a lot of data and nothing surprising except for the ischemic stroke issue has really come out of this whole discussion.

On the minus side, the primary study, the heparin overview is pretty weak. We would all agree and wish it was better. I'm particularly concerned

about publication bias. There is an excess of bleeding. The treatment is dependent on renal function and we've learned a lot in the last year about the difficulty U.S. physicians have in understanding creatinine clearance and the problems that might arise.

The study is not very relevant to the U.S. practice. There's no African Americans and there's almost no coronary intervention. This is really around the border for me but I think I would have to vote yes on this and it's pretty subjective. I could go either way but I think I have to vote yes.

DR. PACKER: Joann.

DR. LINDENFELD: Rob said it well. For all those same reasons I'm right on the fence, too, but I think I would vote yes.

DR. PACKER: Tom.

DR. FLEMING: For the information that I was giving in my previous answer, the effect with the OASIS study is establishing about a 12 percent reduction in death MI at 35 days. In fact, it had achieved what it had been powered to achieve. The

study itself could well have carried the day.

If, in fact, we could be confident, highly confident that heparin itself provides about a 12 percent reduction in death MI at 35 days, then I would believe this is convincing data. The evidence has not been presented to be that convincing.

Rob points out, of course, the high number of patients that we would need to see in order to provide clear evidence, for example, at a seven or 35-day time point. Of course, the reality for that is this is a clinically very important issue but it's also one where we have to recognize we are only preventing a small fraction of the total events and that's the reason that it's taking such a large study to be able to sort out whether you're having a small effect or no effect.

Because, as I indicated in my answer to No. 2, the data here don't provide clear evidence that establishes that heparin itself is providing roughly a 12 percent reduction in death MI at 35 days, my vote is no. I believe that evidence would have to be in hand to make it yes.

DR. KONSTAM: As Rob indicated, we have this tough situation where essentially the entire medical community practices in a way that has not been acknowledged based on hard data, I guess, by the FDA that it is effective. Nevertheless, that is the situation and we have to make a decision whether that situation is going to handcuff any additional progress or we can figure out a way to make things move on.

When I look at this DNA, the heart of the DNA is the OASIS-2 trial. Looking at the primary endpoint as well as all other endpoints and all time points, I'm most impressed by the right sided confidence interval which is right about one in a 10,000 patient trial. I feel this trial is fairly convincing for at least equivalence to heparin.

Then we have to come back and say do we believe heparin works or not. As I indicated in my answer to the previous question, the medical community is voting with its feet overwhelmingly that it works and I believe the data that was presented here today at least supports that and so, therefore, I'll vote yes.

DR. PACKER: I think that Rob summarized it well. It's really a matter of judgment as to how you weigh all the factors. I think that the way that I would weigh the factors would probably go more towards Tom concerns and I would vote no.

The votes for Dr. Graboys no, Grines no, Piña no, Armstrong no. The votes are seven no, four yes.

No. 4, do you have safety concerns regarding Refludan for this indication, bleeding complications, etc. Jeff?

DR. BORER: Well, I think there are issues that need to be better defined. Personally, as I've made clear during the discussion today, I think we need to know what complications we can expect, or rather how to handle the follow-on therapies that are likely to be used in practice, particularly bypass grafting, so I think those data need to be put together.

I'm concerned about the excess of strokes in the eight to 35-day period, particularly eight to 14 days. I can't explain it. It doesn't really seem

to fit into my understanding the pathophysiology but that doesn't mean very much because often we don't understand the way drugs work. I would like to see that better defined so, yes, I think there are some safety concerns here that need to be explored further.

DR. PACKER: So that's a yes. We'll begin with Marv.

DR. KONSTAM: I'm concerned about the bleeds. I think at the dose used we have bleeds clearly in excess of what we see with heparin and I'm concerned that the bleeds that were considered by the investigators to be life-threatening bleeds seem to be significantly more frequent than with heparin so I am concerned about those things.

The ischemic stroke issue also is concerning. I'm confused by it because I don't have any explanation for it but I think that is something else to be a little concerned about.

DR. PACKER: Tom.

DR. FLEMING: Yes. Just a quick comment. Marv has indicated similar perspectives. The major bleeds and the ischemic strokes are the issues that

strike me as of greatest concern and this is somewhat related to the next question. There really are two relative comparisons for safety as well. If we're looking at just deciding what the relative safety is to the active comparator, then it's the safety comparison that we see in the clinical trial.

On the other hand, if we're thinking efficacy is against the putative placebo, then we also have to think of the safety experience against what the safety experience would be of the putative placebo. We have to add in those additional safety experiences that we think are due to the active comparator.

DR. PACKER: Okay. Rob. Oh, I'm sorry.

DR. LINDENFELD: I have additional concerns, particularly when there is a much higher rate of intervention as we have in the states.

DR. PACKER: Rob.

DR. CALIFF: I would vote no on this but for two reasons. One, there's a whole bunch of other hirudin data from angioplasty trials and others that I know about that wasn't presented here. Secondly, I

think you know what you see is what you're going to get which is a modest excess of bleeding in 20,000 or so patients. That's a much better database than most other treatments we have but the whole committee hasn't seen all the data.

DR. PACKER: John.

DR. DIMARCO: Other than the first word, I would say yes, I have safety concerns for exactly the same reasons that Rob just mentioned he didn't. I think there's probably going to be a price to pay with a drug like this and bleeding is going to be the side effect and people are going to have to be concerned about it.

DR. PACKER: My vote is yes. All absentee votes were yes so the vote on this is 10 to one. Fifth question. Given the data from the OASIS trials, do you believe the benefits of Refludan exceed its risks for the sponsor's proposed indication? Why don't we pause there and, Jeff, why don't you lead off the vote.

DR. BORER: Well, I've already indicated that I don't think the benefit has been compellingly

demonstrated and, therefore, obviously, I can't say that it exceeds the risk. Do you want --

DR. PACKER: That's sufficient. That's sufficient. Okay. And, Marv, why don't we start with you.

DR. KONSTAM: Yes, and in the dose that was used in OASIS-2.

DR. PACKER: Why don't we go yes and no because it will just make life easier. Marv is yes.

DR. LINDENFELD: Yes.

DR. PACKER: All right. Tom.

DR. FLEMING: Do I believe benefits exceeded the risks? No, I don't believe it's been proven adequately that benefits exceed the risks and, again, a reminder that if we are thinking of that against the putative placebo, we have to be thinking of all of the risks that are associated with the intervention and not just the increase relative to the active comparator.

DR. PACKER: Joann?

DR. LINDENFELD: Yes.

DR. PACKER: The answer for Joann is yes.

Let me just make sure.

DR. CALIFF: Milton, I vote yes. I've got to catch a plane.

DR. PACKER: John.

DR. DIMARCO: I'll vote yes.

DR. PACKER: My vote is no. Graboys' vote was no. Grines vote no. Piña's vote no. Armstrong's vote no. It is seven to four no. Six is not relevant and the remainder of five is what further studies would one advise. I'm not certain how one would address that question. I think that is really for the sponsor to propose based on all discussions and concerns that have been expressed.

Any other comments?

DR. BORER: I would just like to make one point here. I don't believe and some other members of the committee suggested they didn't believe that the benefits of heparin were clearly demonstrated. I would certainly believe that there is no evidence to suggest that heparin is worse than placebo.

If somebody wanted to do the kind of comparison that was just done, and this is a difficult

study to do, if somebody wanted to replicate these data, I think that would be a perfectly reasonable thing to want to do.

DR. PACKER: There being no further comments, we are adjourned.

(Whereupon, at 4:09 p.m. the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: 90TH Meeting of the Cardiovascular and Renal Drugs Advisory Committee

Before: DHHS/FDA/CDER

Date: May 2, 2000

Place: Rockville, MD

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