DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

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90TH MEETING

TUESDAY,
MAY 2, 2000

The committee met at 9:00 a.m. in the Masur Auditorium of the National Institutes of Health, Building 10, 900 Rockville Pike, Rockville, Maryland, Dr. Milton Packer, Chairperson, presiding.

PRESENT:

Milton Packer, M.D., Chairperson
Robert Califf, M.D., Member
John DiMarco, M.D., Member
Marvin Konstam, M.D., Member
Thomas Graboys, M.D., Consumer Representative
Ileana Piña, M.D., Member
Joan C. Standaert, Executive Secretary

PARTICIPANTS:

Paul Armstrong, M.D.
Jeffrey Borer, M.D.
Thomas Fleming, Ph.D.
Cindy Grines, M.D.
Joann Lindenfeld, M.D.

FDA

Ann Farrell, M.D.
Florence Houn, M.D.
Robert O'Neill, M.D.
Thomas Permutt, Ph.D.
Mushifiqur Rashid, Ph.D.
Lilia Talarico, M.D.
Sue-Jane Wang, Ph.D.

SPONSOR REPRESENTATIVES:

Lloyd Fisher, Ph.D.
Jack Hirsh, M.D.
Gary Koch, Ph.D.
Matthias Luz, M.D.
Salim Yusuf, D. Phil., M.D.

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9:00 a.m.

DR. PACKER: Good morning. I'd like to call to order the 90th meeting of the Cardiovascular and Renal Drugs Advisory Committee. This is the second day of a two-day meeting and we will ask Joan Standaert to read the conflict of interest statement for this morning's session.

Joan.

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

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interest and firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

Dr. Udho Tadani has been excluded from

participating in today's discussion and vote concerning Refludan.

Further, in accordance with 18 U.S.C. 208(b) full waivers have been granted to Drs. Cindy Grines, Ileana Piña, Robert Califf, Jeffrey Borer, Marvin Konstam, Milton Packer, and Paul Armstrong. Copies of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office located in room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Drs. Jeffrey Borer, Robert Califf, and Cindy Grines have interest which do not constitute financial interest within the meaning of 18 U.S.C. 208(a) but which could create the appearance of a conflict. The agency has determined notwithstanding these interest that the interest of the Government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Jeffrey Borer, Robert Califf, and Cindy Grines may participate fully in all matters relating to Refludan.

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

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

That concludes the conflict of interest statement. I would like to make just one public service announcement. The management of the auditorium has asked me to remind individuals that no food is permitted in the auditorium and that you are to please take all your papers and belongs with you when you leave. Thank you.

DR. PACKER: Thank you very much, Joan. The topic for today is NDA 20-807/S-004, Refludan or lepirudin. The sponsor is Aventis Pharmaceutical Company. The indication that is being pursued is as an anticoagulant in adult patients with acute coronary

syndromes.

In the matter being brought to the committee today, the Cardiovascular and Renal Drugs Advisory Committee is acting in a consultant capacity to the Coagulation Drug Products Division and consequently this is not an unusual occurrence. We have acted as a consultant committee when there is a major cardiovascular indication which is being pursued even outside the Division of Cardiovascular and Renal Drugs.

Without any further ado, we'll ask the sponsor, Aventis Pharmaceuticals, to being their presentation. I'm so sorry. It is traditional to ask whether there is any public comment. There being no public comment, with due apologies I'll ask the sponsor to begin their presentation.

DR. LUZ: Good morning, Mr. Chairman, ladies and gentlemen. I'm Matthias Luz, the global project leader and global clinical manager for the lepirudin or Refludan at Aventis.

It is my pleasure to come before this committee today along with my colleagues to share with

you the results of the OASIS studies and discuss the use of lepirudin in unstable angina or acute MI without ST elevation. More shortly, acute coronary syndromes or ACS.

The agenda will be as follows. In my introductory talk I will give you a brief overview of the regulatory history and principal pharmaceutical properties of the drug, introduce the rationale for its use in ACS, and briefly review several aspects of the clinical trials that are of relevance to the understanding of the presentations and interpretation of the results.

Next Dr. Salim Yusuf will present the clinical efficacy data of the OASIS studies. Dr. Yusuf is a Professor of Cardiology at the McMaster University in Hamilton, Canada, and the chairman of the OASIS steering committees.

The next speaker will be Dr. Lloyd Fisher. Dr. Fisher is a Professor Emeritus of Biostatistics at the University of Washington. He will discuss how lepirudin might have fared had we been able to compare lepirudin plus aspirin versus aspirin alone as opposed

to heparin plus aspirin.

We view this comparison as an integral part of the submission since first the U.S. regulatory standard for the approval of new drugs is that the new drug has to convincingly be placebo and, second, heparin is not approved in ACS.

I will then be presenting the clinical safety data. Finally, Dr. Jack Hirsh will summarize the clinical evaluation. Dr. Hirsh is a Professor of Medicine also at the McMaster University in Hamilton, Canada, and the chairman of the OASIS-2 Data and Safety Monitoring Board.

For the discussion of specific statistical aspects, we also have Dr. Gary Koch who is a Professor of Biostatistics at the University of North Carolina, and Dr. Larry Roi who is the project statistician for lepirudin available.

I will be available to moderate questions as needed.

Refludan was approved in the United States in March 1998 for the treatment of patients with heparin-induced thrombocytopenia and thromboembolic

complications. Since then the drug has also been approved in Canada, all 15 countries of the European union, and 15 further countries.

Post-marketing experience is available from an estimated 5,000 patients worldwide. Specific information has been collected through an extensive two-year drug monitoring program in the European union that involved approximately 1,300 patients and constitutes the largest prospectively collected database in heparin-induced thrombocytopenia. Importantly, the dose used in HIT is identical to the dose that is proposed for the new indication.

Based on the findings of the OASIS studies, we propose that the following new indication be approved. Refludan as indicated for anticoagulation in adult patients with acute coronary syndromes, ACS, unstable angina or acute MI without ST elevation.

In this setting Refludan has been shown to decrease the rate of CV death or new MI combined double endpoint, as well as the rate of CV death, new MI or refractory angina combined triple endpoint. Of

note, the two endpoints mentioned were the primary and key secondary endpoint of the OASIS-2 study that forms the principal basis of this submission.

The rational for use of lepirudin in ACS is derived from the pathophysiology of the disease and the pharmacological properties of the drug. Acute coronary syndromes are caused by plaque instability or rupture leading to activation of blood coagulation. This, in turn, leads to complete or partial exclusion of the coronary arteries.

Thrombin has been identified as playing a key role in the pathogenesis of ACS. Hirudin as the most potent and specific thrombin inhibitor known can, therefore, be expected to have a great potential in drug therapy of ACS.

Natural hirudin is produced by the saliva glands of the medicinal leech. Lepirudin is a recombinant hirudin that is derived from transfected yeast cells.

This slide summarizes and illustrates the most important mechanistic differences between heparin as an indirect thrombin inhibitor and lepirudin as a

direct thrombin inhibitor. Let me walk you through this slide.

In the top right-hand part you see a very schematic presentation of a thrombin molecule with the catalytic or active site, the heparin binding site, and the fibrin binding site. Lepirudin binds to both the active side and the fibrin binding site of the thrombin molecule.

Since its affinity thrombin is higher than that of fibrin, it is able to find to thrombin even in the presence of fibrin. Therefore, both fluid phase and clot-bound thrombin can be inhibited by lepirudin. In contrast, heparin binds to the heparin binding site of thrombin.

In the presence of fibrin, thrombin is held in a tight turnery complex with heparin and fibrin. In this situation heparin in the active heparin AT-III complex cannot access the heparin binding site of the thrombin molecule. Therefore, clot-bound thrombin is prevented from inhibition by heparin.

The clinical pharmacology of lepirudin was

extensively discussed in the original application for HIT. This slide just briefly summarizes the key pharmacokinetics features. After IV administration, the drug is rapidly distributed to the extracellular compartment. Clearance occurs mainly by the kidneys, the terminal half-life ranging between 0.8 and 2.0 hours after IV infusion. Of note, consistent with the primary elimination pathway decreased renal function leads to a prolonged half-life.

The basis of the submission or the OASIS-1 and OASIS-2 studies, in particular the 10,000 patients that OASIS-2 study. The entire program additionally involves two small early Phase IIa feasibility studies that were submitted with the original application for HIT and will not further be discussed during today's presentations.

In the following several slides, I will review the active heparin that was used as the control in both OASIS studies. The U.S. regulatory standard and preferred control is placebo. Although no active drug except aspirin) was approved for use in ACS before the OASIS studies were conducted, heparin was

randomized heparin controlled registration studies, namely the ESSENCE study and TIMI-11B study, comparing enoxaparin with unfractionated heparin, the FRIC study comparing dalteparin with unfractionated heparin.

You will note that the initial bolus was almost identical in all studies. The TIMI-11B study used the weight-adjusted bolus that at the average weight of 75 kilograms yields almost the same dose as in the other studies.

Similarly, the infusion doses used in these five studies were, in fact, very close to each other the OASIS studies marking the upper end of the tide range.

In my last slide I will briefly review the approach to the primary analysis in the OASIS-2 study. Aventis specified Modified Intention to Treat analysis as the primary analysis in the statistical analysis plan prior to unblinding of the study.

The protocol specified in Intention to Treat analysis as primary, and the ITT has had emphasis in FDA review. Therefore, for the purpose of today's presentation, we will focus on the ITT

findings and, in addition, provide some MITT findings.

You will find the ITT findings also in the appendix to your briefing documents. Importantly, as Dr. Yusuf will show in his presentation, there are no appreciable differences between ITT and MITT findings. This is not surprising because among the 10,141 patients enrolled in the OASIS-2 study, the MITT analysis only excludes 61 patients who did never receive study drug and two patients who received study drug but did not have a seven-day assessment.

Thank you for your attention.

DR. PACKER: Before proceeding, let's see if the committee has any questions. We'll begin with our primary reviewer, Dr. Borer

DR. BORER: I'd like to go back to the pharmacokinetics that you presented. Let me preface my question by telling you why I'm asking. Several drugs have been approved in the last couple years for treatment of patients with acute coronary syndromes and they are all very potent antithrombotics of one sort or another, generally platelet active.

All were approved with the kind of kinetic

information that you've presented here and no more. The result has been that in the percentage of patients, and in your study it's 1.9 percent of patients receiving lepirudin that go emergently to by-pass grafting, the surgeons were left totally unprepared for what then transpired which often was major bleeding.

You list no bleeding complications in the surgical patients. We may want to discuss that later on when you get to your safety section, but at least I would like to know now more about kinetics. You have the terminal plasma half-life here. Can you tell us something about the binding kinetics with thrombin? Over what period of time after the drug is stopped will there still be an antithrombotic effect?

DR. LUZ: The binding between hirudin and thrombin is essentially an irreversible binding so there will be a continued effect. At least that is the assumption in the plaque. With new thrombin generated, this will certainly play a minor role after the elimination of the drug.

DR. BORER: So over what period of time is

the aPTT still abnormal? And over what period of time is the bleeding time abnormal? What period of time are patients at risk from excessive bleeding or abnormal bleeding once the infusion is stopped?

DR. LUZ: The aPTT usually returns to normal levels within five to six hours which is consistent with the half-life of the drug.

DR. CALIFF: I'm sorry. Doesn't that depend on renal function in a very strong way?

DR. LUZ: It certainly depends on the renal function. That's why I say usually in patients with normal renal function with the half-life going up. With impaired renal function one can also expect that the aPTT levels would remain elevated in these patients.

DR. BORER: If there was persistent elevation or if somehow we found that there was a proclivity for abnormal bleeding even though the aPTT has begun to come down, is there an appropriate antidote, an appropriate regimen to use? For example, give fresh/frozen plasma or whatever. I mean, what would you do if you had to perform an emergency

operation?

DR. LUZ: To answer your question very specifically, there is no specific antidote available. There have been various attempts to reverse the hirudin action including certainly the use of fresh/frozen plasma or facta concentrates. There is no well established concept to reverse the action. Ultimately, the only way to remove the drug from the circulation would be that the patients undergo hemodialysis.

DR. BORER: Okay. We may come back to this in the safety issues but I would like to at least flag this as an issue now.

DR. PACKER: Maybe we should also take the opportunity now to have the committee discuss a little bit the heparin dosing. We probably will not have a better time than now to do so. All the discussion moving forward will probably focus on other issues.

The sponsor has utilized two different -- slightly different heparin dosing in OASIS-1 and in OASIS-2 and the meta-analysis by Oler also used a variety of heparin dosing regimens.

The two regimens in OASIS-1 and OASIS-2 titrated the aPTT from 60 to 100 seconds. I would like to get some discussion in the committee as to the validity or advisability of the heparin dosing is one of the questions that is being posed to the committee.

Rob, can I start with you?

DR. CALIFF: Well, I guess it would be useful to get the sponsor's point of view on what the best interpretation of the best heparin. I think there are two issues here and I know we're going to come back to this multiple times throughout the day.

One issue is how does the heparin dose used in this study compare with what is going to be used in the systematic overview to generate this putative placebo. The other question is what the right heparin does. I know that the new guidelines recommending a lower heparin does and what is in these studies. It might be useful to hear your point of view as to whether you think this dose use as a control is actually too high.

Let me just say I haven't been involved in this field for quite a while. It seems to me the dose

you picked at the time you did the study was the dose that the experts recommended. I don't think there's an argument about whether the dose you picked at the time was one that would have been picked by most people in the field at the time. The question now is now that the trial is over how do we interpret it in the light of new information.

DR. LUZ: Well, there are several aspects. First, as I showed, the average dose given in the OASIS trial was right in the middle of the range that was used in the Oler meta-analysis. It also compares in a tight range with the regimens used in other registration studies using heparin as a control.

If you expand this comparison to studies that use heparin in addition to other drugs or had heparin aboard in some way, you'll find that the range is exactly the same. There is no difference.

Second point is that the actual guidelines that were in effect at the time when the OASIS studies suggested an even higher dose consisting of 80 units per kilogram for the bolus and 18 units per kilogram an hour before the infusion. We were, in fact, below

that range.

The third point is that the GUSTO-IIa study suggested to some degree that 1,300 units might be too high. We stopped below that with the dose regimes in the OASIS studies.

The fourth point might be that with the weight-adjusted regime that was used in the OASIS-2 study, you might expect that patients having a bigger body weight would have higher rates of bleedings because they received more heparin as compared to a fixed dose of 1,000 or 1,100 unit regime. This, in fact, was not found in the OASIS-2 studies. The bleeding rates in patients below and above 75 kilograms were identical.

Apart from that, and Dr. Jack Hirsh could perhaps elaborate on that further, to the best of my knowledge there is no established dose response relationship for heparin that has come out of a randomized trial looking for clinical endpoints.

DR. CALIFF: I think that is true. On the other hand, study after study in the last three or four years has found that patients who do have aPTT

greater than 70 to 75 seconds not only have a higher rate of bleeding but a higher rate of ischemic events.

Again, I'm not questioning the choice of the dose at the time it was done. What I'm trying to do is get some perspective on how we look at it now that we have a lot more information about heparin.

DR. HIRSH: Rob, can I comment on that? Actually, I know of no new information since the initial trial was commenced that is at variance with the dose that was selected. There were two problems. One is that the bleeding has tended to occur in patients treated with thrombolytic therapies. Is that not the case?

DR. CALIFF: I think there is a much higher rate of bleeding with thrombolytic therapy but even in the nonthrombolytic looking at the TIMI trials and all the GUSTO trials. Above about 70 seconds there's a pretty dramatic up-slope to the bleeding risk. Also the surprising increase in ischemic events which none of us expected to see but it's been replicated in about four large trials.

DR. HIRSH: I think that the most robust

way of looking at heparin is the case rather than the PTT. The PTT is very tremendous. The PTT is like the prothrombin time to the INR so that you may have got it in some of the studies but depending on the reagent, a PTT of 60 to 100 would be the same as 40 to 70 with other reagents. This has been well published. I think that the best way of looking at it would be dose rather than PTT because, as I said, the PTT varies so much.

DR. PACKER: But, Jack, you would say this dose is one that you would recommend today?

DR. HIRSH: Yes, based on the data I didn't see any reason why not.

DR. PACKER: But the dose is to be titrated to adjust the PTT.

DR. HIRSH: Yes, that's the standard approach, to adjust the PTT. It's a very inexact approach because unlike the prothrombin time, although attempts have been made to standardize the PTT, those attempts have not been widely used. The fruits of those attempts have not been widely used.

If you can recall back to the days 15

years ago when people using a prothrombin time instead of an INR, that's where we stand now with the PTT. That's why I say I think if one was to look at the best way of comparing dosing regimes, it would be based -- there are three things to look at: the bolus, because that's going to have an early effect because there's always an overshoot; the continuous infusion; and the PTT.

I think of those three the PTT is least reliable. To say that if you go beyond a certain PTT you are going to run into trouble would be the same as saying if you go beyond a certain prothrombin time, you get into trouble. We know that a prothrombin time with a reagent with an ISI of, say, 2.7, the INR would be about 13 compared to an INR of about three prothrombin time with an ISI of 1.

DR. CALIFF: So the point you're making is that the PTT is not a standardized answer. There are multiple.

DR. HIRSH: That's why I think that PG is not standardized. The bolus dose is standardized, the continuous infusion is standardized. It's reasonable,

I think, based on local hospital practice to adjust the dose because you're not going to get a very, very precise --

DR. CALIFF: But so as not to mislead people, you're not saying that if you give a standardized dose that biological anticoagulant activity is going to be the same from patient to patient.

DR. HIRSH: No, it's not. It's going to be highly variable.

DR. CALIFF: Right. So there are two factors here. One is the biological variability of what happens to heparin when it gets in the system, and the other is that we have a lousy test to follow it. Two sources of variability.

DR. HIRSH: So to answer the question, I think that to go back to the original question, whatever dose within the range that was shown that was selected would be reasonable and it would be hard to argue that one dose is better than another dose.

DR. PACKER: There has to be a relationship between dose and bleeding. There is a

relationship between dose and bleeding events.

DR. HIRSH: Definitely.

DR. PACKER: Okay. Paul.

DR. ARMSTRONG: Jack, just before you leave, let me be clear. You would advocate a nonweight-adjusted bolus and an infusion as was articulated in OASIS-2 and a PTT target that was the same as in OASIS-2, or would you adjust the PTT target differently now in the light of current information and guidelines or not? I want to be clear.

DR. HIRSH: I'd certainly use the bolus version, the continuous infusion. I think it's reasonable to use a lower dose in the very light and a higher dose in the very heavy but weight is a fairly weak predictor of response to heparin.

When it comes to the PTT, if the mean dose that was used was the same in the various studies, then the PTT response that was -- or the target PTT was a reasonable target PTT if anything was a little higher than would be currently used but certainly not lower. To answer your question, I would probably go a little lower now except knowing that the mean dose

of heparin that was used in the study was really quite low, I don't think they ever shot with PTT.

DR. PACKER: Marv.

DR. KONSTAM: I would just like to know in OASIS-2 what was the frequency of measuring the PTT? How often was dosage suggested?

DR. LUZ: As per the protocol, it was to be measured six to eight hours after start of the infusion and at least once daily thereafter. I think the average number of measurements was in the range of six.

DR. PACKER: Any other comments? I think part of the reason we're having all this discussion is that both of the major trials being presented by the sponsor are active comparator trials against the drug which is not approved for the indication which is being presented and for which a dosing regime that optimizes efficacy and safety has not been established and remains a moving target. I think that it's part of the struggle that we will face today in trying to decipher risk to benefit relationships.

Okay, you can proceed.

DR. LUZ: Let me introduce Dr. Salim Yusuf, the chairman of the OASIS-1 and 2 steering committees.

DR. YUSUF: Mr. Chairman, ladies and gentlemen, on behalf of the OASIS Investigative and Steering Committee it's my pleasure to share with you the results of the two OASIS trials. OASIS stands for the organization to assess strategies and ischemic syndrome.

It's a program of research that consist of three parts. All three in patients with unstable angina or acute myocardial infarction without significant ST elevation.

The first part evaluates the relative efficacy of hirudin versus unfractionated IV heparin and this involved two studies, the OASIS-1 study and the OASIS-2 study. It also involved the concept of prolonged antithrombotic therapy with warfarin as the standard therapy on top of aspirin as subsidies of these trials.

A third component looked at the clinical course and practice patterns in multiple countries and

data have already been published from 8,000 people from six countries and there are ongoing attempted in several other countries.

This is the design of OASIS-1. The study group involved people with unstable MI without ST evaluation, unstable angina or MI without ST elevation. Patients were randomized to three groups, unfractionated heparin, low dose of lepirudin, and a medium dose of lepirudin.

By the statement you would probably recognize there was meant to be a high dose of lepirudin as well. However, as we were just about to embark on this program, the data from GUSTO-IIa was published and there was concerns of safety at a higher dose of hirudin so it was dropped.

The study included 909 patients. There were three major endpoints that the study focused on: cardiovascular death, myocardial infarction, and refractory angina as a composite. The same composite but stopping at refractory angina and the same composite on cardiovascular death or myocardial infraction.

The most important endpoint in the study was considered to be the first one simply because it was the highest event rate and because sample size is calculated based on this. Although this endpoint is clinically the most relevant, the number of events were expected to be very few in this pilot study.

The study was a randomized partially study. Therefore, we ensured a number of steps to ensure there is an unbiased evaluation of the outcome the key component of which was central randomization and central blinded adjudication.

These were the doses used. The low dose of hirudin involved a bolus of .2 milligrams per kilogram followed by an infusion of 1 milligram per kilogram per hour for 72 hours. The medium dose involved a bolus of .4 milligrams per kilogram per hour followed by an infusion of .15 milligrams per kilogram per hour for 72 hours.

The infractionated dosing regimen was as described by Dr. Matthias Luz so that in those over 60 kilograms 1,200 units an hour was used and those under 60 kilograms a lower dose was used, 1,000 per hour.

Both regimens were given for identical periods of time of 72 hours. The target dose adjustment was aPTTs in the range of 60 to 100 seconds.

Aspirin was recommended in all patients at a dose of 325 milligrams a day during hospital stay, but thereafter there was flexibility in the dose of aspirin used.

The next three or four slides will give you key aspects of both OASIS-1 and 2 that are essentially common. The patients were entered within 12 hours after the onset of pain. They were randomized to either treatment for 72 hours. There was a second randomization in a subgroup of people eligible for the warfarin component that occurred between 12 hours and seven days so this is a partial factorial design.

Warfarin was then given for three to six months as the standard therapy. The primary comparison for lepirudin versus heparin in both trials on all endpoints was at seven days and the duration of follow-up in the program as a whole was six months.

These are the definitions of the various

events that were used in OASIS-1 and 2. They were identical for most events and only different for one event to a small extent based on our experiences in OASIS-1.

Cardiovascular death is the same definition that we've used in all trials. Death was considered to be cardiovascular if it was proven cardiovascular or the cause was unknown, only those deaths that were proven to be non-cardiovascular were called non-cardiovascular.

New myocardial infarction was defined within the first 24 hours as requiring all three; new clinical symptoms, new enzyme elevation, or ECG changes. After 24 hours any two out of the three criteria were acceptable, either new clinical symptoms or enzyme changes or ECG changes.

These are the definitions of refractory angina used in both trials. Refractory angina was defined very stringently. Patients had to get typical new chest pain despite optimum medical treatment defined as being on aspirin or another antiplatelet agent and then on at least two anti-anginal

treatments, one of which had to be IV nitrates.

There had to be new ECG changes that indicated ischemia. In addition to that there had to be an urgent cardiac intervention and it was defined as either thrombolytic therapy for an impending infarction or urgent intervention that is taking the patient rapidly to the cardio cath needing PTCA, CABG surgery or, as I said, thrombolytic therapy, or the insertion of an intra-aortic balloon pump. Or for those centers where facilities for cardio caths were not available, transfer for intervention in an urgent fashion to one such center.

Later on I'll point out to you the overwhelming majority of these patients did, indeed, have an intervention after discharge and before seven days and later as well hospitalizations for angina with ECG changes and admission to an ICU or CCU was accepted also as a criteria.

This was double-up because in OASIS-1 there were one or two cases that we noticed and so in a larger study in order to capture these events, the definition was expanded. Again, the majority of these

people had interventions as I'll show you later.

This is the definition of severe angina. Severe angina was very similar to refractory angina except that the need for intervention was not there. It meant again typical chest pain despite medical management, plus new ECG changes.

I should point out that several trials that have been used as the basis for regulatory approval actually included this definition as refractory angina at least in part. In a sense the definition of refractory angina in OASIS is stricter, or at least as strict as the strictest there is in the literature.

These are the baseline characteristics of patients in OASIS-1. First, the randomization was deliberately unequal in a ratio of four is to three is to three so that 371 patients were randomized to infractionated heparin, 271 to lepirudin low dose, and 267 to the medium dose.

You will notice from this all of the baseline characteristics are balanced. About 2/3 were men. The mean age was 64. The mean weight was 78.

The majority of people came in with unstable angina. Only 13 percent were admitted into the trial with an initial diagnosis of myocardial infarction without ST elevation and the majority had abnormal ECGs, and the mean time to randomization was about 6.7 to 7.9 hours.

These show other key historical aspects. Again, these are balanced between the three groups. Myocardial infarction was seen in about 40 percent, previous revasculization procedures in about 30 percent, hypertension in about just under half of the people, 20 percent had diabetes, and 67 percent had a history of previous strokes. These baseline characteristics are in general similar to what you would observe in most randomized trials of unstable angina.

Now, because this was an open trial, we carefully monitored treatments other than the allocated treatments. You will see the overwhelming majority of patients received aspirin as per the protocol. The use of nonstudy heparin prior to randomization was similar.

The use of nonstudy heparin after

randomization was, if anything, lower in the median-dose lepirudin group compared to the unfractionated heparin group with the low dose being in between. Thrombolytic therapy was used in three percent of those with unfractionated heparin and looks slightly lower in the other two groups.

Beta blocker use was 76 percent here, 73 percent in the low dose, and 71 percent in the medium dose. Nitrate use also showed a trend towards less use in the medium dose. Calcium channel blocker use was balanced, as was ACE inhibitor use also was balanced. There is no evidence that the group in the hirudin groups got more aggressive pharmacological therapy that was not part of the protocol mandated regimen.

These are the data on aPTT over the first 72 to 96 hours. The blue is unfractionated heparin and because of the bolus, and as described in numerous studies, you get an initially higher level with heparin than with the hirudins. Orange is the low dose and the yellow is the medium dose of hirudin. And you can see that these two doses, the medium dose

and the unfractionated heparin, for what it's worth had a similar aPTT, whereas the low dose had a slightly lower aPTT.

These are the main efficacy results of OASIS-1. The composite of cardiovascular death, myocardial infarction, refractory angina, as well as severe angina which is the main endpoint, showed a dose dependent reduction so that it was 15.6 percent in the unfractionated heparin group, 12.5 percent in the low dose group, and 9.4 percent in the medium dose hirudin group. The difference between this and this is statistically significant. A test for trend is also statistically significant.

The same results were obtained for cardiovascular death, myocardial infarction, and refractory angina. You will see 6.5 percent, 4.4 percent, and 3.0 percent. The difference between unfractionated heparin and the medium dose is nominally significant. Again, a trend towards lower rates for cardiovascular death and myocardial infarction was also observed compared to unfractionated heparin.

The next slide indicates that during the treatment period we would have expected almost all or the majority of benefit to emerge. Indeed, that was the case. You will see the differences in the quadruple endpoint. In the triple endpoint, and on cardiovascular death and MI trends emerge entirely during the treatment period with little further benefit beyond that.

The next slide shows you the components of these and this on cardiovascular deaths represents very few events, one or two per group. When you look at more frequent events, myocardial infarction is a dose dependent relationship. Refractory angina, at least for the medium dose, there is a reduction. And for sever angina there is a dose dependent relationship. At least these three components contribute to the differences in the composite outcome.

These are the data on long-term follow up. You will see for the three sets of composite endpoints the early differences between heparin and the two doses of hirudin persist in general up to six months

and you will see that for the composite refractory, and you'll see that for the composite with cavuvast cadet and myocardial infarction. There is new evidence that after three days of therapy the --

(Whereupon, off the record when the recording stopped and information was lost. Back on the record at 9:56 a.m.)

DR. PACKER: This would be a good time to open the discussion of OASIS-1. Open for discussion. We'll begin with our primary reviewer, Dr. Borer.

DR. BORER: Salim, I have several methodological questions that probably are easy to deal with that weren't clear to me from the book that we were given, not in any particular order.

How was the patient variation and response to warfarin resolved, or was it? As I understood the protocol, everybody got 10 milligrams initially by mouth and then three milligrams a day and there was no monitoring of pro time or INR to titrate the dose. First, am I correct in that?

DR. YUSUF: There was monitoring. First, let me tell you in OASIS-1 nobody was randomized

before three days because there was concern on bleeding or putting a new drug and warfarin together. The mean time to randomization was about six or seven days so it was well after the hirudin was given.

The second is there was monitoring of INRs frequently. I think it was daily for the first three days and then less frequently. I don't remember the exact regimen but it was done.

DR. BORER: Was the dose then varied in response to the INR?

DR. YUSUF: Yes, the dose was then varied.

DR. BORER: I see. Okay. That wasn't clear to me. The severe angina and refractory angina endpoints are based on a case report form?

DR. YUSUF: Yes. Also one other thing. Each of the things we were interested was documented. We asked for all the ECGs. They were read centrally. We asked for the discharge summary and they were also looked at.

DR. BORER: Okay. My recollection reading through the reports of OASIS-1 and OASIS-2 was that at least in OASIS-2, which I'm not asking about now,

there was the potential for missing the angina events in patients who didn't have a completed seven-day report because the forms then would only capture mortality and myocardial infarction. Was this true also in OASIS-1? Was there potential for missing the angina events in people who did not have completed form at seven days or seven-day complete reports and did that happen? I mean, were there incomplete reports?

DR. YUSUF: I think there were about -- actually, at seven days we had complete follow-up in OASIS-1 in all the patients. I have a backup slide but it shows we have complete data at seven days in everybody. In OASIS-2 we have missing data on seven in each group. That is 14 out of 10,000 people for that outcome.

DR. BORER: Okay. We'll get to OASIS-2 later but I was more concerned about OASIS-1 now. After the initial period of hospitalization, aspirin dose was variable. Did you make any effort to analyze the follow-up data based on aspirin dose? Was aspirin a confound or do we not know?

DR. YUSUF: After seven days we didn't try to do that. Before seven days, as you can see, almost everybody got it so you couldn't do a stratified analysis.

DR. BORER: The Inclusion of patient into the warfarin follow-on, that did not include the entire population, did it? You know, we can talk all day about biases and such but I would like to hear just what you have to say about the potential for selection bias that might have confounded OASIS-1 based on the use or non-use of warfarin.

DR. YUSUF: I think the first thing was not everybody was eligible for warfarin. For instance, if they had bleeding on hirudin, physicians would give -- or heparin, physicians would be reluctant to use it.

Second thing we found given that OASIS-1 was done in North America was that there was a considerable reluctance on the part of physicians to randomize people to warfarin so that only about 35 or 40 percent eventually got randomized. Now, the people who got randomized turned out to be a lower risk group

than the people who didn't.

People who had refractory angina and had an intervention, the physicians thought they had fixed all the problems so they never got randomized to that. In the end from a trial point of view, the warfarin part did not help us because we weren't able to answer the warfarin question and what we learned is physicians don't like using warfarin.

The key thing is warfarin was started around five to six days in OASIS-1. By the time you get an effective INR, it's beyond the seven days so it's unlikely to have any effect. We've also done stratified analysis so it was balanced. The few people who got into the study was balanced by the three randomizations and the results stratified or adjusted did not make much difference to the results.

DR. BORER: What was non-study heparin in the heparin group?

DR. YUSUF: Non-study heparin was if at any stage -- okay, there were two. First, before getting into the trial some patients could have been in heparin and then when they get randomized, they go

to the randomized therapy so that's one.

The second is at the end of 72 hours some physicians wanted to continue heparin longer, given antithrombotic therapy longer so then when we stopped it, they used it for a longer period of time, usually a couple of days more.

DR. BORER: Did you make any effort to analyze the results based on whether non-study heparin was added on or not?

DR. YUSUF: As I showed you, it was added on less in the medium dose hirudin.

DR. BORER: One final question that I have. You indicated -- and this is just so I can get clear here. I'm not making a qualitative statement. You indicated that the main endpoint was the quadruple endpoint. That's what you were looking at at seven days. Is that something that was determined before the study or is that something that was determined after the results were in?

DR. YUSUF: Well, what happened, I mean, is as follows. We did not clearly expect in a 900 patient study divided three ways to get overwhelming

results so we said here are the three composites. We have high power on this composite and we said these are the three endpoints that we're interested in.

We knew we had very low power on cardiovascular death and MI. We had some power on refractory angina. For the one endpoint that we calculated was the first one. We didn't say one is primary, one is secondary, and one is tersary. Implicitly, that was the order in which one assumed it would be the case.

DR. BORER: Thank you.

DR. KONSTAM: Can I follow up on that?

DR. PACKER: Yeah, Marv. Go ahead.

DR. KONSTAM: I'm still not sure. Let's start with the severe angina endpoint. That was specified in the protocol as something you were going to look at?

DR. YUSUF: Absolutely.

DR. KONSTAM: And when you say that -- you mentioned that the selection or endpoint retrospectively might be rationalized on the basis of the way you performed the power analysis. What was

the power analysis exactly performed on?

DR. YUSUF: It was performed on the quadruple.

DR. KONSTAM: It was specified in the protocol that the power analysis was done on the quadruple?

DR. YUSUF: Yes.

DR. KONSTAM: At seven days?

DR. YUSUF: At seven days.

DR. KONSTAM: That's also --

DR. YUSUF: It's in the protocol.

DR. PACKER: Ileana and then John.

DR. PIÑA: Salim, how many patients were actually on heparin at the time of their admission before the randomization occurred? I would assume that some patients came in with chest pain and they were automatically put on heparin. Was there any adjustment time stopping the heparin and starting the randomization drug? How was that handled?

DR. YUSUF: I think about approximately 29 or 30 percent, if I'm remembering the slide, were on heparin before they got into the study and the

instructions that we gave people is as soon as you get the telephone randomized allocation, switch to the study medications.

DR. PIÑA: So just make a change?

DR. YUSUF: Yes. And we did document that it did happen. Obviously there may be a five or 10-minute delay but it happened very rapidly.

DR. PIÑA: And that includes the bolus?

DR. YUSUF: Yes. Well, okay. That's a good question. If you were on previous heparin, the bolus was skipped.

DR. PIÑA: Do you think that could have affected that early increase in PTT that you saw with the heparin group on the graph?

DR. YUSUF: Well, if you were on heparin, the bolus was skipped so that wouldn't account for it but it's the other people that you get that so the remaining 2/3 is where you get that peak. You're right, Ileana.

DR. PIÑA: Did you collect aPTTs in the group on heparin before they were randomized? In other words, you knew where they were before they got

randomized?

DR. YUSUF: Yes. It was a requirement of the protocol.

DR. PIÑA: Another one of my confusions is the severe angina, refractory angina, because it sounds like the different is really a matter of the physician judgment at some point where intervention is required.

DR. YUSUF: That's right.

DR. PIÑA: Do you have a sense of how many patients were initially classified as severe angina that went on to become refractory? In other words, they had the intervention? When did you capture that or did you capture that?

DR. YUSUF: We captured it but for this analysis that I'm presenting to you, the most severe first event is what's counted. No, that's not true.

The first event is what's counted within seven days, but then for the triple endpoint the most severe is counted so for the quadruple endpoint if severe angina occurred and then somebody had refractory angina and the same patient had an MI and

then died, in the analysis you take the first one. For the triple endpoint you don't worry about severe angina and for the double endpoint you don't worry about a minor event unless there were clinical important events that occurred earlier.

DR. PIÑA: One last question. When you randomized after the seven days either to warfarin or standard, what was standard?

DR. YUSUF: Standard was everybody received aspirin so standard was no treatment. Ho warfarin.

DR. PIÑA: Aspirin and nothing else?

DR. YUSUF: Yes. Well, beta blockers.

DR. PIÑA: Oh, yeah. The additional medication but not anticoagulant.

DR. YUSUF: Sure.

DR. PACKER: John.

DR. DIMARCO: Salim, patients were randomized in the emergency room. Is that correct?

DR. YUSUF: Sometimes in the CCU.

DR. DIMARCO: Okay. Wherever the event occurred. Were they pain free at the time of

randomization?

DR. YUSUF: Some were and I think, what is it, 60 percent had pain. We have the data and we've looked at it. It was approximately half had pain and half did not have pain at the time of randomization with a plus of 10 percent.

DR. DIMARCO: What I'm curious about is in the patients who, you know, you have 10, 12, 13 percent who have MI without ST segment elevation and one of your endpoints is new MI, how did you distinguish between those two? Did the pain have to go away and then they had some pain free interval and then they had recurrent pain?

DR. YUSUF: New ECG changes and new enzyme elevation.

DR. DIMARCO: Well, the enzymes would have still been up from the first --

DR. YUSUF: Yes. The first 24 hours, John, is very complex to diagnose. I agree with you. That was a challenge to do that.

DR. DIMARCO: I'm just curious how you did it exactly.

DR. YUSUF: First they needed new pain in the first 24 hours.

DR. DIMARCO: So the pain had to go away?

DR. YUSUF: Had to go away and you needed new pain and it was meant to be more than 20 minutes. Not just a little bit of pain requiring nitro but more than 20 minutes. Then they needed new ECG changes. Then you needed further elevation in the enzyme which is if it was already elevated, a further 20 percent increase.

Then a committee looked at all of this blindly. The majority of new MIs did not occur after the first day. You could see that from the curves that I showed you.

DR. PACKER: Tom Graboys.

DR. GRABOYS: Just to follow up on that, were you able to obtain triponen levels on any of these patients?

DR. YUSUF: At the time we did the study, triponen was not commonly available in Canada. In fact, I don't think any of us had triponen. We talked about it.

DR. PACKER: Rob Califf.

DR. CALIFF: There are a lot of interesting things about this presentation and I know they will keep coming up again and again. First of all, just in terms of discussion within the committee, I think that the way you've handled this is about as well as it can be done. Issues in the first 24 hours are almost impossible to sort out.

I would point out that this is a population without ST elevation so they typically don't have six or eight hours of pain. That would be highly unusual so the recurrent pain is a little easier here than it is in an ST elevation population where frequently the discomfort won't go away for eight, 10, 12 hours.

The enzymes are almost impossible because if they are up to start with in the first 24 hours, trying to really sort that out is difficult so we are probably missing a lot of recurrent events in the first 24 hours just because you don't have a clean way of sorting it out, nor will triponen be helpful because once it's up, it's up for a long time. There

are some really complicated and difficult issues here.

One of the things about what you've done here is proposing to combine OASIS-1 and OASIS-2. I know we're going to get into more.

DR. PACKER: Right. We're going to get into this.

DR. CALIFF: So hold off on that?

DR. PACKER: Hold off on that.

DR. CALIFF: All right. Then I'll go to my last point which is the refractory angina definition. I'm not aware of a plain way to do this because any way you look at it, it's pretty subjective. In terms of what you did with the sites, did you only look at cases where the sites called it an event and then you adjudicated it? Or did you go back and actually review every record for things that might have told you there was an event that the site wasn't picking up? If you did the latter, how did you really go about that?

DR. YUSUF: We did both. We obviously took the events reported and then we adjudicated it centrally. In 45 percent of the patients across all

sites a monitor was sent out to scan the charts to see if there were any events missed. It wasn't done 100 percent. I was done in approximately half the people.

DR. CALIFF: What did you find in that 45 percent? Were the sites missing events?

DR. YUSUF: The company did it so they know the answers to that.

DR. LUZ: There were no previously unreported events of death, MI, or refractory angina. There were a total of four severe angina events, three of which occurred before day seven, two in the heparin group, one in the low dose lepirudin group, and one additional severe angina event up to 35 days that was considered in the medium dose lepirudin group.

DR. YUSUF: At seven days it is 410. Is that right, the missed event? 210 severe angina.

DR. CALIFF: Just to clarify, this is OASIS-1 that we're talking about?

DR. YUSUF: OASIS-1.

DR. CALIFF: That seems almost too good. I've never seen monitoring that would pick up so few differences with a site.

DR. YUSUF: I don't know.

DR. LUZ: In addition, one should perhaps mention that the FDA has inspected one of the OASIS-1 clinical sites and did not detect any previously unreported events during the hospital phase.

DR. PACKER: But this is worth asking about because in every trial that this committee has seen, including trials that are double-blind, the audit process picks up a higher frequency of discrepancies, routinely picks it up.

It's just part of the expected process of looking at the difference between what is reported on the case report form and what actually may or may not occur at a site. Can you describe the audit procedure that was followed in OASIS-1?

DR. CALIFF: Nothing I feel compelled to add. I mean, our work which shows if you had two clinicians looking at the same patient at the same time, you wouldn't have agreement that was quite this high. This is difficult but I think it would be worthwhile to go through it.

DR. YUSUF: I mean, I've told you what I

now, Milton. I think there is one thing, though. Our definitions and our forms match identically which is important. Our definitions are pretty stringent. I know severe angina is the least stringent of the three but you can always pick up interventions if you carefully chart it.

Since the need for intervention is a key part of refractory angina, I doubt that we truly missed refractory anginas because of the audit. And with MIs, too, we had very clear definitions and people had to meet them.

The other thing is we asked them to send us every enzyme value in every patient centrally so sometimes if a center said this is not an MI and scanning it centrally we found an enzyme pattern that was typical, we went back centrally and asked them, "Are you sure this is not an MI? Send us the case charts." And we scanned that.

In a sense, what you would normally do at a site audit we did it by fax centrally because of the way we managed the trial.

DR. CALIFF: I think the key thing here is

a requirement for intervention was part of the definition.

DR. PACKER: But not for severe.

DR. CALIFF: For refractory but not for severe. Right.

DR. PACKER: But I'm still confused. We're dealing with a putative primary endpoint that is driven primarily by severe. That constitutes most of that endpoint.

DR. YUSUF: That's partly true, Milton, but also when you look at the composite with refractory angina without severe angina, you get the same dose dependent relationship and the difference between unfractionated heparin and medium dose heparin is -- medium dose hirudin is nominally significant. It's a consistency.

DR. PACKER: I understand but we're still -- I'm still confused by this. It is a true statement that most of the endpoint that includes severe angina is driven by the episodes of severe angina.

DR. ARMSTRONG: It looks like it's about half, Milton.

DR. PACKER: About half. Right. But the delta is driven primarily by the delta on that component.

DR. ARMSTRONG: About half.

DR. YUSUF: On that endpoint, yes. But if you take the CV death MI refractory angina, it's really driven by both MI and the interventions.

DR. GRABOYS: The delta is 23.

DR. YUSUF: I'm sorry, Tom?

DR. GRABOYS: At day seven the delta is 23 when you include severe angina, 16 when you don't, and when you just look at death MI it's 11.

DR. YUSUF: Okay. So they both contribute to it.

DR. PACKER: Can you tell us more about the audit and what was done and how it was carried out?

DR. LUZ: What was actually done was that in the patients that were randomly selected, the case record form was 100 percent verified meaning that each and every entry made into the case record form was reconciled with the medical charts. In addition, the

medical charts were screened to see whether there were any additional entries that were not captured by the case record form.

One point that you might want to be aware of, we're talking about a study of only 900 patients and a relatively small overall number of events. The four severe angina events are, in fact, a certain percentage. One certainly has to put this into perspective with the overall number of events and that it's maybe not this surprisingly low.

DR. PACKER: When you say the charts were screened for events, the patient's record, charts were screened for events, what -- and the criteria that were used by the auditors were the criteria, the definitions, that you showed us today?

DR. LUZ: Essentially, yes. Of course, the monitors were not medical doctors that were able to really make an assessment whether this is refractory, severe, or recurring angina. What they were looking for was each and every event that was marked to be ischemia or whether there was an ECG indicative of ischemic changes.

DR. PACKER: And that these were monitors that were employees of Aventis?

DR. LUZ: Yes.

DR. PACKER: And they were unblinded?

DR. LUZ: Well, they were as unblinded as the trial was.

DR. PACKER: This is an unblinded audit?

DR. LUZ: The trial was unblinded with respect to the comparison of heparin versus lepirudin and it was blinded within the lepirudin doses and the audits were done exactly the same way.

DR. PACKER: I'm just wondering.

DR. YUSUF: Can I make a --

DR. PACKER: Salim, I'm just wondering how much comfort we can take from an audit carried out by a sponsored where the auditor knew the identify of the treatment.

DR. YUSUF: Can I make two points? The audit consisted of really two parts. One part is every single enzyme value in every patient had to be sent to us documented in the form and then that was reviewed without knowing the allocation. That is

unbiased.

The second thing was the -- there are two other events they are looking for. I agree that severe angina could well be a little soft when somebody is looking at it at the center. The second part is refractory angina needed an intervention and that is a hard one to be biased on. It's a pretty hard one.

All the enzymes, B at the CCC reviewed blindly. MIs we would have definitely picked up. I believe the refractory anginas we picked up. I agree severe angina, that question that you raised, we'll have to think about.

DR. PACKER: I think it would be hard to feel reassured here that we're having a treatment effect on a putative endpoint driven by severe angina which is the most subject to interpretation in an unblinded trial where the investigator knows who's getting what, audited by company employees who are aware of the treatment assigned. I'm not reassured.

DR. CALIFF: Milt, you certainly pointed out the flaws in a phase to experience which was

designed, I think, to understand what an appropriate dose would be to take into Phase III. We're not cynical enough to believe that -- I just want to say this.

We're not cynical enough to believe that most investigators would alter the results or somehow in a cynical way try to make the treatment look better than it really is. It's just not as good a methodology as a blinded study. We're also not saying that company employees would alter records typically. Are we?

DR. PACKER: I'm just saying that you generally find what you look for.

DR. CALIFF: So the bias is not easy to quantify. I think you would agree with that. Wouldn't you, Salim?

DR. YUSUF: Well, I think on CV death MI and refractory angina it's very unlikely there was material bias. I agree with Milton that there is a certain concern of potential bias on the severe angina component. I hope most people think that is a reasonable position.

DR. PACKER: I wanted to ask one issue --

DR. FLEMING: Before leaving this point, just to quickly comment, Rob, the issue could certainly, though, be that chances or subconscious views of what the profile would be of a known intervention could influence decisions for when you would perform other interventions. So in a trial where the physician judgment influences the occurrence of the endpoint, the lack of blinding could, in fact, enter in.

DR. CALIFF: And it could work either way, though. Couldn't it? For example, if the nurse was really scared about this new experimental treatment and knew the patient was getting it, the patient might be watched more carefully.

DR. PACKER: I wanted to ask Tom to pursue this but let me see if I understand correctly and just for clarification purposes before turning it over to Dr. Fleming. There was no prespecified primary endpoint in this study. Is that correct?

DR. YUSUF: We did not put the word primary against any of the three endpoints. As I

said, there was one endpoint on which we calculated our calculation.

DR. PACKER: I just want to make a -- endpoint that you calculate power is not necessarily the endpoint that one spends alpha on. One has all sorts of opportunities to power on endpoints which are not the primary endpoint. It's actually occurring to an increasing degree.

I'm trying to figure out that you had in the absence of a prespecified primary endpoint and in the absence of a statistical plan, one had three possible endpoints examined at three different times across three different treatments. How does one know what is the critical p-value to examine any of these endpoints?

DR. YUSUF: I think a point to note is there were only three endpoints and they were all specified to be looked at one time point. The others were consistency analysis. The long term was consistency to see you don't lose the benefit. The early one was to see when does the benefit emerge.

Really there were three analyses and I

think in this context we are looking at three that are concordant. All three that are concordant. There is really no statistical way to analyze what three events that are highly correlated and they are concordant. It is reassuring that for all three endpoints the pattern of the results is identical.

DR. PACKER: Tom, any questions?

DR. FLEMING: No.

DR. PACKER: I'm sorry, Joann.

DR. LINDENFELD: That's okay. The creatinine cut off for OASIS-1 was 2? Is that correct?

DR. YUSUF: Can you help me, Matthias? Was that right?

DR. LINDENFELD: I guess in follow-up to that, I wonder if we could see what the average creatinine was or how many there were that were 1.5 to 2.

DR. YUSUF: It's about 97 if I remember. You know what I mean.

DR. LINDENFELD: Right. The point I'm getting at here is we're going to come --

DR. YUSUF: We don't know that now, Joann.

DR. LINDENFELD: We're going to come back to this problem of how to use the drug with renal insufficiency and I think we're going to need to know that for both studies and to just maybe look at the patients in that upper creatinine range if we have any.

DR. LUZ: We can use the analogy with OASIS-2. Both studies specified in the protocols that patients would have to be excluded from participation if they had know renal insufficiency as assessed by creatinine level of 2.0. The creatinine level was not required to be available at the time of randomization. In OASIS-2 we had about five percent of all patients that had a level that was higher than 1.5. Very few that had more than 2.0

DR. YUSUF: And I think, Matthias -- sorry, Joann. Matthias will show you data, at least from OASIS-2 by creatinine.

DR. LINDENFELD: Okay. Good. A second question I have is about pro times for INRs. The published paper says the warfarin was started within

12 to 24 hours but it was actually started later. Is that right?

DR. YUSUF: Yes. There were two phases. One was where it was started well after the infusion because the company was concerned.

DR. LINDENFELD: In the publication it says in Phase II it was started 12 to 24 hours after treatment.

DR. YUSUF: After treatment. So after three days?

DR. LINDENFELD: After three days. And do you have INRs? I recognize that --

DR. YUSUF: Yes.

DR. LINDENFELD: Between the two treatment groups?

DR. YUSUF: The target INR was in the first trial 1.5 to 2, very low INRs. In the second trial 2 to 2.5. Now, I don't remember what was achieved by seven days but the vast majority was subtheraputic. That was one of the problems we found because, remember, you started on day three to day four and by seven days the vast majority we weren't

dosing.

DR. LINDENFELD: I just wondered if there was any difference between the two groups, heparin versus --

DR. YUSUF: No, there wasn't.

DR. PACKER: Paul.

DR. ARMSTRONG: Salim, our briefing notes suggest that severe angina was added in Phase B and not present in Phase A so I presume there was a protocol modification. They also suggest that the definition was two episodes of recurrent angina as opposed to one of which one required ST segment change. Can you just clarify that for me?

DR. YUSUF: Matthias, can you clarify? You're right, Paul, there were some changes between the first phase and the second phase.

DR. LUZ: You're right with both points. Severe angina was introduced before the second part of the OASIS-1 study took off and was actually introduced by the investigators group before knowing the exact results.

DR. YUSUF: And, in fact, well before

then.

DR. ARMSTRONG: So the planning must initially have occurred without recurrent or what you call severe angina as part of the analysis plan and then that analysis plan must have been modified when that diagnosis was incorporated in Phase B. Then how was that diagnosis established in retrospect in Phase A?

DR. LUZ: All patients who had recurrent angina were reajudicated by the blinded adjudication committee again.

DR. YUSUF: And all the recurrent anginas, which is a broader basket, were reported and we had required them to fill out whether there were ECG changes, recorded all the enzymes and the interventions so the committee was able to do it.

DR. ARMSTRONG: My second question is to further explore the issue of MI in the first 24 hours. As I understand it. it was either/or on enzymes or ECG changes in association with what was perceived by the investigator to be clinical symptoms. Can you clarify for me what the ECG definition of an MI was as opposed

to refractory ischemia in that similar time point and what component of the MIs were established by an ECG criteria alone?

DR. YUSUF: The ECG criteria in the first 24 hours required ST elevation or persistent ST depression of more than 2 milliliters which wasn't there previously along with the symptoms. My recollection, and these analyses could be done but I don't have it right now.

My recollection is the majority of events that the adjudication committee classified were pain plus ECG because despite the fact we had enzymes for the first 24 hours. Just like Rob said, it was hard to interpret. I was not involved deliberately in the adjudication committee. It was run by Cam Joiner totally independent of Hamilton.

DR. ARMSTRONG: So the new ECG changes for refractory ischemia by contrast would be characterized as what?

DR. YUSUF: ST depression, ulteen version, or transient ST elevations.

DR. ARMSTRONG: And, finally, 13 percent

of the patients had an MI on admission as their qualifying event which would be substantially lower than a number of other large trials of a similar syndrome. Any comments in relationship to that frequency which is often 45 percent of the population?

DR. YUSUF: I don't know, Paul. Obviously it depends on the trial you look at. I mean, some trials like the GUSTO trial, you're right, had more people but I think there was an attempt to have so many people with MI without ST elevation.

We had no such attempt. We also did a large registry, as you know, and this is approximately in that ballpark. Right now we are running CURE and this isn't the same ballpark. I think it may be the way we've defined the entry criteria.

DR. ARMSTRONG: Thank you.

DR. PACKER: Marv.

DR. KONSTAM: Salim, there were three treatment groups, right? How many comparisons across those three groups were you intending to make?

DR. YUSUF: Well, we were really intending a dose-dependent analysis to look at whether there

were trends. And we were intending to look at the extremes versus the -- you know, the two extremes.

DR. KONSTAM: Well, I mean, the p-values that you showed us. For example, for the quadruple endpoint, I see a p-value of .018. What is that p-value?

DR. YUSUF: This is between the two.

DR. KONSTAM: Right. So this is between two of the groups. This is between the heparin and the high dose.

DR. YUSUF: And if you do one for trend, it's also significant. I don't remember the exact p-value. If you do an analysis of variance, it is significant. Then you go to the next step of finding out where the p-value comes from. It's like a second step procedure.

DR. KONSTAM: No, but the .018 is just --

DR. YUSUF: The extremes.

DR. KONSTAM: I mean, would you suggest there ought to be a correction of that given the fact that you are also comparing the low dose to heparin?

DR. YUSUF: There are problems in trying

to do a correction and here is the way. The first analysis when you have three doses is you look for trends. Once that is significant then you are exploring where that p-value for trend comes from so it's like a dependent analysis. I know where you're getting at. This is not sort of doing multiple analyses and then choosing the best p-value.

DR. KONSTAM: Maybe Tom will comment. I think the problem that we're going to have in trying to use this study as support for OASIS-2, one of the problems is we have multiple endpoints, multiple time points without really clear prespecification of a primary endpoint or time point in the protocol. Then we have three groups so there's lots of p-values. I guess, you know, it would be helpful to sort of get some feeling for how meaningful any one p-value is.

DR. FLEMING: Just to briefly comment, there are many issues and I'm awaiting the presentation of OASIS-2 before getting into them because it will be easier to address them globally but just one brief comment.

This analysis, as I understand, this

choice of this endpoint wasn't based on a predetermined idea that this was the most clinically relevant. Salim has already pointed out this is the endpoint that was going to have the most events and it gave you in a small screening trial at least some opportunity to have power on something.

This isn't even an endpoint that's in the labeling indication so there is a paradox right there in terms of is it important and is it significant or not. I guess I'm not worried in determining whether it's significant or not because there are so many other issues that are limiting the convincingness of this result in the total context of what we have.

DR. KOCH: Gary Koch, University of North Carolina. As was stated before, there was no formal analysis plan so all that one can do is to talk about what hypothetically might have been done. In a study of this type normally you would test the high dose against placebo first which would be the medium versus placebo. That's a comparison that is emphasized.

If that's significant, you then step down to the lower dose versus placebo. The other method

sometimes used is called the Hawkberg Method for multiple comparisons. With that method if both doses beat placebo with p less than 05, you get both doses. Otherwise, you test the dose with a stronger p-value at 025.

On the four-way endpoint you could say from a post hoc hypothetical perspective it would meet it. You could also say the study was powered for the four-way endpoint. You get a favorable result for the four-way endpoint, you step down to the three-way endpoint taking away the severes. You get a good result on that, you take away the refractories and step down to the other.

Hypothetically one could have said that had a rigorous analysis plan been written for this study, it might have emphasized the p-values that were shown. No such plan was written and so you just have to interpret these as a way of looking at the data and weight them as you consider appropriate.

DR. YUSUF: I think Tom's comment is appropriate. This is a study that was really designed to help us go to the next step and we have these

results and these p-values and, as you know, we didn't decide at that stage to claim victory. We wanted more data.

DR. CALIFF: But just to -- I mean, Gary stated the typical way it might be done but it's also true, isn't it, that depending on what you believe ahead of time, you could design an analysis strategy for the same problem that might emphasize one or another comparison and segment the total.

DR. YUSUF: I can tell you what we did. You're right. There wasn't a preanalysis plan but we did a thing for a three-way analysis which you do. That's the basis statistics. I've learned when you have three groups you test that across the three groups. Once that's significant, then you explore where the significance comes from. Maybe a more elementary approach. One little clarification. There is only one time point that was really specified when we do that.

DR. CALIFF: Another point I wanted to make was what Dr. Koch described might be the most often used approach but one could, for example, put

all your emphasis on the high dose comparison. It's hard to know unless it was written down.

DR. KOCH: That's what I said in this particular case. If a plan would have been written, it would have put all the emphasis either on a trend test or on the comparison of the medium dose versus placebo both of which are identical in this case.

In this study that is all the more likely hypothetically because a high dose was considered and then was abandoned before the study was implemented.

One could say hypothetically that if there was a dose that the investigators believed was going to have the most action, it was going to be the medium dose. Again, all of this is hypothetical.

DR. YUSUF: I think the key thing is that the aim of this part of the study, Milton, was to help us design the next study.

DR. PACKER: I just want to make sure that we have adequate clarification on Paul's comment. Has an analysis been done on the -- I think you stated, Salim, that the original sample size of OASIS-1A and 1B combined was based on the quadruple endpoint, the

quadruple endpoint, however, being recurrent and not severe angina. Has an analysis been done of the endpoint that you stated was the original endpoint for a basis of power calculations?

DR. YUSUF: Milton, in an ideal world we would like to think that trials are sort of designed as so much power and then so much endpoint. In this case what happened is we were allowed to only study so many people so we then backed up and said this is what power we had in this endpoint.

The recurrent angina part of it we found was a mish mash of so many events that we could not get objective documentation. We recognize that in the first 50 to 100 patients. We said recurrent angina is something we can't place much emphasis on. So at that stage we always knew we would go for 900. Then we looked at this and said if we had severe angina with these event rates, this is what our power would be.

But, Salim, in all fairness, and I don't want to belabor this issue, we can all appreciate very much that you only had 900 patients and that was fine but it's a difference to say that you had a chance to

only study 900 patients compared with the statement that there was a prespecified quadruple endpoint defined in a specific way in the original protocol that was the basis of the claim that that was the primary endpoint.

DR. YUSUF: That wasn't stated in the protocol that recurrent angina is a quadruple. Is that right, Matthias?

DR. LUZ: Yes.

DR. YUSUF: No, it wasn't stated the way -- I may have given you the wrong impression. Recurrent angina was not stated as a primary endpoint.

DR. PACKER: According to the FDA review, the clinical markers were a recurrent angina refractory, angina subsequent MI and cardiovascular death.

DR. YUSUF: All four were collected as was also collected in OASIS-2. They were collected. Four endpoints were collected.

DR. PACKER: Okay. I think we've beaten this to death. Why don't we go on to OASIS-2.

DR. YUSUF: Okay. Can I have the next

slide and have a minute to breathe. The next two parts of the presentation will be on the results of OASIS-2. Then the third part is an analysis showing you the consistency of results between OASIS-1 and 2.

The OASIS-2 patient population was identical to that in OASIS-1. In contrast to OASIS-1 two things were done. First, it was a double-blind study, and, second, we only focus on medium dose lepirudin versus the active control of unfractionated heparin.

10,141 patients were randomized. The primary endpoint was cardiovascular death or new myocardial infarction at seven days. Only one key secondary endpoint was identified. There were others identified but they were called other endpoints so the key secondary endpoint was the composite of cardiovascular death, new myocardial infarction or refractory angina at seven days which we've discussed for OASIS-1 and which was nominally significant there.

Other endpoints were the double and the triple endpoints, that is, these two endpoints, at the end of 72 hours which was the end of treatment. The

point of doing this was to look at biological coherence and see if the results emerge during treatment.

Then it was also done at 35 days to see if we had lost the treatment benefit. Revascularization procedures by seven days was also one of the three specified endpoints. Adjudication was again central and blinded.

There were the par calculations. Based on OASIS-1 and a large registry that we were running, we anticipated at seven days an event rate of 5.5 percent in the heparin group. If we observe this, then we would have 90 percent power to show a 25 percent risk reduction compared to heparin, or 80 percent power to show a 22 percent risk reduction.

We also did par calculations for slightly higher event rates and slightly lower event rates and we were comforted that if we got an event rate of five percent, we still had a reasonable trial.

For the second re-endpoint again, par calculations were made at 8.7 percent for the composite. These were the relative risk reductions

that would be detected at an alpha value of 0.01.

However, we observed a lower cardiovascular death and new MI rate of only 4.2 percent compared to 5.5 percent, almost 20 percent lower for the primary endpoint and also for the second re-endpoint it was 6.7 percent which is 8.7 percent. This seriously compromised the power of the study.

These were the regimens. The lepirudin dose was identical to the medium dose used in OASIS-1. Unfractionated heparin was very similar and, as Matthias Luz pointed out, instead of a fixed infusion rate per hour, it was slightly modified to be a weight adjusted dose but the mean dose happened to be very close to what was used in OASIS-1.

The same aPTT was started and the same recommendations for aspirin and, as before, the majority of patients received an anti-platelet drug.

The first trial was entirely done in Canada. This trial was a global study with patients from North America, Western Europe, South Africa, Australia and Israel, South America, and Eastern Europe representing a broad range of clinical

practices.

Again, the baseline characteristics are similar between the two randomized groups. As before, about 60 percent were men, mean age was 64, unstable angina was about 88 percent, almost identical to the first study. Abnormal CG was seen in 90 percent and the mean time from pain to onset of randomization was just over six hours.

These are the data on key historical aspects and, like before, about 40 percent had a previous MI. The proportion of people who had a previous revascularization procedure was slightly lower than the first study which was entirely done in North America. All other factors were very similar. About half were hypertensives, about 20 percent were diabetics, and about four percent had previous strokes.

These are the data on aPTT. As before in OASIS-1 during the first 12 hours the aPTT values were higher with unfractionated heparin and then lepirudin caught up and then they were both within the established range of 60 to 100 seconds during the rest

of the infusion period.

These are the primary efficacy analysis. The primary endpoint was cardiovascular death and myocardial infarction at seven days. There was a 16 percent risk reduction which was a p of 0.086 which is short of our prespecified 0.05 but came close.

A second re-endpoint was cardiovascular death, myocardial infarction, and refractory angina prespecified at seven days and there was an 18 percent risk reduction that is nominally significant and came very close to a prespecified 0.01.

These are the data to look at internal biological coherence which is again prespecified in the analysis plan so that at the end of 72 hours the entire difference between the two groups emerged so there is a 24 percent risk reduction at the end of treatment which is nominally significant. On the triple endpoint there's a 22 percent risk reduction that is nominally significant and you can see these two results are approximately the same in relative risk reduction. That was also true of the analysis at seven days.

These show you the time to event analysis which was prespecified in the protocol and as published in the paper. You will see the curves diverge for the first three or four days and then they remain absolutely parallel for the next few days indicating no evidence of an early rebound that has been of concern with antithrombin therapy.

Again, for CV death, myocardial infarction, and refractory angina the same pattern of the difference emerging in the first three to four days and the curves remaining parallel on this slide up to seven days.

These are the data on each of the individual components at seven days and at 72 hours. At both time points you will see numerically there are lowering rates of cardiovascular death, myocardial infarction, and refractory angina so that for the primary the prestated key second re-endpoint each component contributes to the difference observed.

Now, we further have provided in this slide key descriptors of what we mean by refractory angina. Cardiac catheterization only was in 49 cases

in the unfractionated heparin group and 55 in the lepirudin group and it was not different.

However, there was a difference in the rates of PTCA, 29 versus 15. CABG surgery 18 versus 15. Need for urgent thrombolysis and transfer to a tursery center for intervention.

I will show you in a minute that the majority of these people indeed had intervention. After being discharged, a few people were rehospitalized with unstable angina and this was part of the prespecified definitions and this was lower. You will see there is a clear difference in those with ECG changes, i.e., objective data, and no difference in those without objective data.

In the next slide I will show you details of those who were transferred from centers without cardiac catheterization facilities to those that had it, 53 versus 34. Before this judge at that same rehospitalization all but one in each group had an intervention. Before midnight after the day of pain onset, 31 versus 20 difference. Later during the hospital stay 21 versus 13 and no intervention was

done in one patient each.

I don't have a slide on the data on rehospitalization but we've just looked at the results to see what happens to the rates of intervention in them. If you give me a minute, I'll tell you what it is. Out of the 14 people here and eight people here, in these 14 people 12 had an intervention, and in these eight, seven had an intervention. The majority of the difference in refractory angina in the OASIS-2 study stems from the description of refractory pain, new ECG changes, and an intervention.

These are the data on any interventions. The previous was urgent interventions. These are on any interventions at seven days. You will see there's a 16 percent risk reduction which is nominally significant. The entire difference in that comes from differences in the rates of PTCA.

This is a summary of the results on the prespecified endpoints at seven days which was the primary point of evaluation. There is a reduction or lower rate of cardiovascular death on new myocardial infarction with the confidence limits just crossing

one.

There is a clear reduction in cardiovascular death, new myocardial infarction, or refractory angina and there is a similar order of magnitude of reduction of cardiac interventions of any kind within the first seven days. All of these point estimates are approximately the same.

The differences in these two are larger and emerge entirely during the treatment period which further adds plausibility to the differences observed here.

This slide shows you the data from 72 hours up to six months. The key point here is to show you that the differences that emerge in the first 72 hours persist right through up to 180 days. The difference of about .6 to .7 percent in absolute terms emerged early, 2.6 down to 2. During treatment is persisted out to seven days. It was about the same at 35 days and about the same at 180 days.

This indicates that three days of treatment whatever benefit is observed persist long-term and there is no evidence of loss of that benefit.

The next slide shows you the same data on the triple endpoint of cardiovascular death, myocardial infarction, and refractory angina is approximately a one percent difference a little less early, slightly greater at seven days, and it's about the same right throughout. Again, this indicates a persistence of the early benefit.

These are the data on non-cardiovascular deaths. There were no deaths in the first seven days classified as non-cardiovascular in both infractionated heparin or lepirudin. Between seven days and 35 days there were eight deaths in the unfractionated heparin group and three deaths in the lepirudin group that were classified as non-cardiovascular.

At 180 days there was a total of 30 versus 20 and these again indicate that this classification of using cardiovascular death in our analysis as opposed to total death certainly does not exaggerate the difference between the various groups.

The sponsor had prespecified in its analysis a modified intention to treat analysis which

excluded people who did not receive any drugs. You will see the difference between these two is only about 60 or .6 percent in this 10,000 patient population.

I have presented to you the intention to treat analysis which is what we as investigators publish. You will see the results are almost identical on the primary endpoint at seven days and at the second re-endpoint at seven days and the p-values are almost identical and hardly change. This indicates the robustness of the data and also indicates that the entire difference has emerged from the people who were treated.

As you know, in this part of the trial as well patients were randomized if eligible to the warfarin component. Only about 20 percent of the people received warfarin in this trial and it was balanced between unfractionated heparin and lepirudin.

These are the overall data showing the relative risk reduction of .84, whereas these other data on the non-warfarin patients, which is almost

identical, with confidence limits overlapping. These indicate that the randomization to the warfarin in no way affects, or at least in no material way affects the overall results of the trial.

This is the summary of the results from OASIS-2. In this trial lepirudin appears to be superior to unfractionated heparin. On the prespecified endpoints at the prespecified time of seven days there is consistency across all three endpoints. On the primary endpoint of cardiovascular death and myocardial infarction there's a 16 percent relative risk reduction with confidence intervals from -3 percent to 31 percent which is a p-value of .086.

On the second re-endpoint there is also a reduction on cardiovascular death, myocardial infarction, refractory angina, which is an 18 percent risk reduction. That is nominally statistically significant with confidence limits between three percent to 30 percent.

The need for any intervention is also reduced by 16 percent which is nominally significant. The differences in these two endpoints entirely emerge

during treatment, so at the end of 72 hours there's a 24 percent risk reduction on cardiovascular death and MI and a 22 percent reduction on cardiovascular death, myocardial infarction, and refractory angina that is nominally significant. Extended follow-up at 35 days and 180 days indicates preservation of absolute benefits. Now, about --

DR. PACKER: Salim, could you pause, please, and we'll open it up for questions on OASIS-2. I'll begin with our primary viewer Dr. Borer.

DR. BORER: Salim, I want to ask a couple of methodological issues and then a little bit about the data. First, I would like to echo what rob said. That is, in the first question I asked I am not in any way suggesting that anybody did anything inappropriate, but I would like to know how tight the blinding was in OASIS-2?

The reason I ask the question is that within out briefing documents it appears that some patients were begun in OASIS-2 on a therapy that they should not have received and that therapy was then changed after they had begun. How could they have

known after the wrong therapy was begun that it was wrong?

DR. YUSUF: What happens is -- and this is something we do in every trial including HOPE and the same thing actually happened in HOPE as well. People call in to a central number and they are given an allocation number, a package number, whatever it is. You know, a seven-digit number.

They could do one of two things. They could write the number wrong and take the wrong package. As soon as they randomize they access a page that has the information they gave us over the phone on patient identifiers and they write the treatment package as well.

Whenever there is a discrepancy between what's reallocated in our central computer and the centers which means they misheard the allocation, we immediately get back to the center and say, "You've chosen the wrong package. You must go back to the package that was allocated." Neither we, that is the staff who did it, nor the center knows what it is. It is simply based on the discrepancy between the package

number they wrote and the allocation number we gave.

DR. BORER: Okay. So nobody knew what was being given. They just switched packages. This, as I recall from the briefing document, and correct me if I'm wrong, the actual change occurred several days into the treatment.

DR. YUSUF: Sometimes the centers did not send us the fax. They meant to send it to us within 24 hours. Sometimes they took another day. Remember treatment is only for three days so you can't do anything. When we weren't able to change the package to the truly allocated package, the analysis is intention to treat. By that I mean what we intended centrally, not what they did there. In a sense, Jeff, it is sort of slightly, very slightly sort of diluting out any result.

Now, again, we don't know whether heparin -- they may have got heparin and we gave them another number that was still heparin, or whether heparin was switched to hirudin or vice versa. I have no idea because based on just the fact we wanted people to adhere to the letter of the law of the protocol.

DR. BORER: Okay. The point is that although now we know that they were switched from one to the other, they didn't know what they were switching from or two.

DR. YUSUF: Neither did we know. Neither did the staff know.

DR. BORER: I'd like to ask a little bit more about the potential for a warfarin-based confound. Here again, it seems as if there were far fewer patients included in the warfarin follow-on study or substudy than were expected or anticipated suggesting that as you described for OASIS-1 there may well have been some bias on the part of investigators to enter or not to enter patients.

That wouldn't necessarily -- that might concern me even though you showed a slide in which the results in patients with warfarin and without warfarin look fairly similar. Still, there could be a confound but in our briefing document, there were data presented from centers that were pooled that didn't have warfarin available.

Those data really looked very different,

to me at any rate, than the data that you showed us for with warfarin and without warfarin in that it looked as if the treatment effect was, at best, minimal in those sites where somebody couldn't be biased to giving warfarin or not giving warfarin because they didn't have warfarin to give.

Now, I understand this is a post hoc small analysis of a relatively small subgroup, but I would like to have those data shown if you have a slide of them or, if not, at least I would like you to discuss how we got to that result.

DR. YUSUF: Is this the one you mean? These are always --

DR. BORER: Yes.

DR. YUSUF: Okay. So you will see these are 2,000 people who were randomized to active warfarin standard therapy. This is the randomized part of the trial. These are the people that got randomized. These are the people with no warfarin available. These are the not randomized. No warfarin available was -- these are not by center, Jeff. At the beginning of the trial the sponsors weren't able

to secure warfarin and deliver it to the centers so we started. This not randomized is then the rest where a physician said "I've done a PTC or a cath or somebody bled or I don't want to put them into the warfarin part." Although we didn't make it optional, in the end that's what it turned out to be.

We have also done an analysis in two ways. I don't know, Matthias, if we have slides. We did an adjustment, you know, to see whether warfarin makes a difference and it doesn't. The second thing is this group was equally split between hirudin and heparin so that would not -- as you can see, these are the event rates but the ends are the same.

All of these the ends are the same and there is no obvious imbalance in baseline characteristics. In a way you could think of it like any other treatment like beta blockers being given. Some centers use it and some don't. When the ones that use it, they use it in some patients and they don't use it in others.

DR. BORER: You could think about it that way but as I look at the data, it appears that there

is a difference or a suggest of a difference among those who were given warfarin in terms of treatment effective versus those who weren't versus those in whom no decision could be made because it wasn't available. I just raise that as a concern. Obviously we can't resolve that.

DR. KOCH: Your concern is addressed by the p-value of .964 which you see which is comparing the differences of .7 percent, .4 percent, .4 percent, and .8 percent with one another. Although that is a low-power test, that is a test which is looking at whether the heterogeneity across those four groups has any realness to it. It's basically random.

DR. BORER: I'm sure that you're right.

DR. YUSUF: There's one other thing I can help you with if you don't mind, Jeff.

DR. BORER: Let me make just one point if I may. I feel uncomfortable saying this because I'm a cardiologist and not a statistician and you're a statistician so you know more than I do about this. I think it's unfortunate to suggest when a p-value doesn't make it, and this obviously is way off, but p-