DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

"Placebo in Hypertension Adverse Reaction Meta-Analysis" Study, a meta-analysis of more than 80,000 patients in placebo-controlled trials of antihypertensive medications, which evaluated the risk of irreversible harm in conducting placebo-controlled trials in patients with hypretension.

Wednesday, April 26, 2006

1:00 p.m.

The Ballrooms
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

William R. Hiatt, M.D., Chair
Cathy Groupe, RB, BSN, Executive Secretary

COMMITTEE MEMBERS:

John M. Flack, M.D., M.P.H.
David L. DeMets, Ph.D.
Thomas G. Pickering, M.D., D.Phil.
Ronald J. Portman, M.D.
Frederick J. Kaskel, M.D., Ph.D.
Steven D. Findlay, M.P.H.
Lynn Warner-Stevenson, M.D.
John R. Teerlink, M.D.
Robert A. Harrington, M.D., F.A.C.C.
Michael A. Lincoff, M.D.

NON-VOTING GUEST SPEAKERS:

Raymond Lipicky, M.D.
Dennis T. Mangano, M.D., Ph.D.
Sana M. Al-Khatib, M.D., M.H.S.

FDA PARTICIPANTS:

Robert J. Temple, M.D.
Norman L. Stockbridge, M.D., Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. HIATT: Thank you all very much for attending. My name is William Hiatt. I am from the University of Colorado and specialize in vascular medicine. I would like to first go around the room and ask that you introduce yourselves. Bob, we will start with you.

DR. TEMPLE: Bob Temple, I am the Director of the Office of Drug Evaluation I.

DR. STOCKBRIDGE: I am Norman Stockbridge, in the Division of Cardiovascular and Renal Products, under ODE 1.

DR. LINCOFF: I am Mike Lincoff, an interventional cardiologist at the Cleveland Clinic Foundation.

DR. HARRINGTON: Bob Harrington, interventional cardiologist, Duke University.

DR. TEERLINK: John Teerlink, cardiology, University of California, San Francisco and San Francisco VA Medical Center.

LCDR GROUPE: Cathy Groupe, executive

secretary for the committee.

DR. WARNER-STEVENSON: Lynn Stevenson, Brigham and Women's Hospital, cardiology.

DR. FINDLAY: Steven Findlay, Consumers Union and the consumer representative on the panel.

DR. KASKEL: Rick Kaskel, pediatric nephrology, Albert Einstein College of Medicine.

DR. PORTMAN: Ron Portman, pediatric nephrology, University of Texas in Houston.

DR. PICKERING: Tom Pickering, Columbia University, hypertension.

DR. DEMETS: Dave DeMets, University of Wisconsin, Madison, biostatistician.

DR. HIATT: Dr. Flack will be joining us in just a moment. Why don't we go ahead to the conflict of interest statement?

Conflict of Interest Statement

LCDR GROUPE: The Food and Drug Administration has granted general matters waivers to the special government employees participating in this meeting of the Cardiovascular and Renal Drugs Advisory Committee who require a waiver under

Title 18, United States Code, Section 208 which allows them to participate in today's meeting on the placebo in hypertension adverse reaction meta-analysis, (PHARM) study discussions.

All special government employees have been screened for their financial interests as they may apply to the general topic at hand. To determine if any conflict of interest existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants.

The following participants have been granted waivers: Dr. John Teerlink, Dr. Robert Harrington, Dr. Thomas Pickering, Dr. William Hiatt, Dr. Michael Lincoff, Dr. Ronald Portman, Dr. David DeMets and Dr. John Flack.

Waiver documents are available at FDA's dockets web-page. Specific instructions as to how to access the web-page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30

of the Parklawn Building.

Unlike issues before a committee in which a particular product is discussed, issues of broader applicability such as the topic of today's meeting involve many industrial sponsors and academic institutions.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

FDA would like to disclose that Dr. Steven Glasser has been limited to describing his role in the PHARM study and answering questions pertaining to it

With respect to FDA's invited guest speakers, Dr. Dennis Mangano has reported that he serves as a co-principal investigator with Dr. Raymond Lipicky on the PHARM project.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant's 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 product they may wish to comment upon.

DR. HIATT: Next will be the open public hearing section and I have to read this statement: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing section of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial interests that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a

company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

Does anyone from the public wish to make a comment?

[No response]

LCDR GROUPE: Just another note that Dr. John Neylan, our industry rep. will not be present. He notified us at the last minute that he wasn't able to attend.

DR. HIATT: Will there be any public comment today? If not, the topic of this afternoon's meeting is the use of placebo controls in short-term clinical trials of hypertension. I think the issues today have all been articulated in the background material.

I hope the committee appreciates the value of placebo-controlled trials versus active controls and why this is an important question. I think the issue will center on the assessment of risk. To discuss this we have three presentations and why don't we go ahead and get started with that? Oh, I am sorry, Norman, I skipped you.

Introduction and Background

DR. STOCKBRIDGE: That is just fine! As far as I know, there are only two meta-analyses that are pertinent to the discussion here. One of them is the one that Dr. Al-Khatib is getting ready to present to us. The other one is the one that Dr. Lipicky and his group did. So, I am looking forward to the discussion. Thanks.

Placebo Control in Short-Term Clinical Trials of Hypertension

DR. AL-KHATIB: Ladies and gentlemen, good afternoon.

[Slide]

First I would like to clarify, in the pamphlets that you may have picked up or received,

I am an electrophysiologist. You may have seen that. Some of you may be wondering why and electrophysiologist did a project on hypertension and I would like to inform you that this is a project that I did when I was still a cardiologist in training. I did this project back in 1999 and the results were published in Science in 2001.

[Slide]

So, when it comes to the use of placebo controls in any randomized clinical trial, the question always comes up as to whether it is ethical to use a placebo in that clinical trial. Sir Bradford Hill, back in 1963, said that the answer to this question will depend, I suggest, upon whether there is already available an orthodox treatment of proved or accepted value. If there is such an orthodox treatment the question will hardly arise for the doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing. Mr. Hill would be surprised actually to know that this question arises much more often than not.

[Slide]

What I would like to do in the next few minutes is to provide you with an overview of historical background of how the ethics of clinical research evolved, especially as determined by the Nuremberg Code back in 1948, moving on to the Declaration of Helsinki that was issued in 1964, and then the Belmont Report in 1979.

[Slide]

Then I am going to provide you with a very brief overview of the value of using placebo controls in randomized clinical trials, and how the use of placebo controls helps with randomization sometimes, definitely with blinding; go over the different types of controls and the importance of placebo controls and focus my attention primarily on the study that we did, where we intended to look at placebo controls in short-term clinical trials of mild to moderate hypertension.

[Slide]

So, the Nuremberg Code was issued in 1948 in response to the experiments of the Nazi doctors,

and the main features of the Code were that the voluntary consent of human subjects is absolutely essential; that in order to enroll patients in clinical research or any sort of experimentation risks cannot outweigh the benefits; and that animal experimentation should precede human experimentation. [Slide]

The Nuremberg Code specifically states that the experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

[Slide]

The Declaration of Helsinki was issued in 1964, and the main features of the Declaration were that medical care is different from medical research. It made it very clear that those two are different, and that study subjects should be assured of the best available treatment.

[Slide]

The Declaration states that in any medical study every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method.

[Slide]

The Belmont Report was issued in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It identified three basic ethical principles that continue to govern clinical research to date. Those principles are respect for persons, beneficence and justice.

The Report clearly states that persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. It moves on to say don't harm and maximize possible benefits and minimize possible harms.

[Slide]

So, with that background, I want to move on to talk about the randomized clinical trial. I don't need to convince any of you that the

randomized clinical trial is the most powerful experiment for assessing the effectiveness or the efficacy of an intervention. A prospective study comparing the effect of an intervention against a control, that is what a randomized clinical trial is.

[Slide]

Randomization is important because it takes care of selection bias and baseline characteristics that are known or not known to affect that the outcomes of interest are evenly distributed between the randomized groups.

[Slide]

Now, when you use a placebo control you are actually able to blind the research subjects and possibly their physicians so you protect the study from confounding by variables that develop during follow-up, and blinding prevents bias during data collection analysis assessment.

[Slide]

As you know, there are at least four different types of controls. There are placebo

controls. There is no treatment control. There is positive control and historical controls.

[Slide]

Many people value placebo controls for admittedly good reasons. Placebo controls offer a clear reference point and they increase the likelihood of attaining statistical significance with a smaller sample size, such that trials may be done more quickly and at a less cost.

[Slide]

But in order for an investigator to enroll a patient in a study where they might be randomly assigned to a placebo, the investigator has to have equipoise, which means equilibrium, meaning you don't know whether a treatment is better than another.

[Slide]

With that, I will move on to talk about placebo controls in short-term clinical trials of mild to moderate hypertension.

[Slide]

As you all know, hypertension is a very

common disorder. It is a risk factor for multiple ailments such as stroke, myocardial infarction, heart failure and, of course, premature cardiovascular death. In 1990 a review of 14 clinical trials of antihypertensive therapy showed that there was a 42 percent risk reduction of stroke with antihypertensive therapy; that there was 14 percent risk reduction of coronary artery disease; and 21 percent risk reduction in vascular mortality.

[Slide]

Following that, there were many trials, including SHEP and STOP-hypertension, that showed similar benefits in elderly patients, and since then the evidence has continued to support these findings.

[Slide]

So, we decided to conduct this meta-analysis to determine whether the use of placebo controls in short-term clinical trials of mild to moderate hypertension is safe and ethically appropriate.

[Slide]

We conducted a literature review from January of 1997 through December of 1998 and we only used the Medline database. In order to consider a citation for this meta-analysis, that citation had to be on a randomized clinical trial whose objective was to assess efficacy of an agent in the treatment of mild to moderate hypertension. It had to use placebo in any phase of the study, and it had to enroll non-pregnant adults. We arbitrarily prespecified a trial duration of 20 weeks or less.

[Slide]

Once we collected all these studies, we went through them and collected data on the duration and the location of the study; the number and type of patients enrolled; the type of antihypertensive medications used; whether IRB approval and informed consent were obtained; and the number of serious adverse events.

[Slide]

The serious adverse events that were of

interest to us were stroke, myocardial infarction, congestive heart failure and death due to cardiac events or stroke. Some people may argue that other adverse events may have needed to be included but those were the adverse events that we collected. Of course, when you are also reviewing papers it is hard to get to the bottom of all the serious adverse events. In general, those were the serious adverse events that were reported by the studies that provided complete safety data.

[Slide]

Safety data were considered adequate if the number and nature of adverse events were given for both the placebo and the active treatment arms.

[Slide]

Statistically, we used a maximum likelihood method to combine the estimates of risk differences. This method assumes a fixed-effects model. It is not a random-effects model. It requires numerical multiplication of the likelihood functions. Because we found that the event rates were pretty small, we decided to repeat the

meta-analysis by combining the studies using a Bayesian method.

[Slide]

So, 267 citations seemed to be eligible for our meta-analysis. After we looked through them really carefully we found that only 80 citations met all the eligibility criteria. Thirty-five studies used a placebo in a run-in period only and not in any other phases of the study. Two studies used placebo in the maintenance phase and 43 studies used placebo in the run-in period with or without the maintenance period, plus/minus the withdrawal period.

[Slide]

Here are the results. Of all the 80 citations that we found, 24 studies were done in the U.S.A. It was mentioned that IRB approval was obtained in 64 of these citations. Signed informed consent was mentioned to have been obtained in 69 of these studies. Adequate safety data were only provided by 25 studies, and those are the studies that were combined in the meta-analysis that we

did. You can see the split of which phases the placebo was used in for the different studies.

Before I present these results I want to mention, because I did not include it in any of the slides, that in the 25 citations that we combined in the meta-analysis different antihypertensive medications were used, including ACE inhibitors, calcium channel blockers, beta blockers and diuretics.

[Slide]

With regard to the serious adverse events in the two arms, you see that of the 4878 patients who received active therapy in our meta-analysis, only 2 people died. Of the 1604 patients who received a placebo, 2 died. The incidence of stroke was only 2 in the active therapy arm. No strokes were found in the placebo arm. Two patients in the active therapy arm had a myocardial infarction versus 3 in the placebo arm. Congestive heart failure was not reported as a serious adverse event in either arm. So, the total number of serious adverse events was 6 in the active therapy

arm and 5 in the placebo arm.

[Slide]

This graph shows the different studies that were combined. If you look at the pooled data here you see that the point estimate was zero in the sense that there was not a significant difference in the occurrence of these serious adverse events between the placebo arm and the active therapy arm.

[Slide]

When we repeated this analysis using the Bayesian method, we found again that the difference was zero and the worst-case scenario was 6 in 10,000 serious adverse events in the placebo arm compared with the active therapy arm.

[Slide]

So, based on these results we concluded that short-term exposure to placebo in clinical trials of mild to moderate hypertension did not seem to be associated with an increased risk of serious adverse events. But I also caution you that these results need to be interpreted only in

the context of these studies because many possible explanations could account for these findings.

First of all, we limited our analysis to short-term clinical trials of hypertension, only 20 weeks. If studies took more than 20 weeks they were not included in this analysis. We also limited this analysis to studies of mild to moderate hypertension with few co-morbidities. Most of those studies actually explicitly stated that sicker patients with multiple co-morbidities were excluded from the studies. Of course, in most of these studies patients were very closely monitored and they clearly stated that if these patients started all of a sudden to have high blood pressures that they couldn't control well, they withdrew those patients from the studies. So, with that in mind, this is the conclusion that we have. Thank you for your attention.

Committee Questions on the Presentation

DR. HIATT: Thank you very much, Dr. Al-Khatib. Could you stay for just a moment so we can clarify this because we will have some

questions to debate in a little bit about those particular studies--extremely helpful and informative.

The first question I want to ask you was I wanted a little bit more information on the upper end of this risk event rate. You quote 6 per 10,000. Is that over an average 2 months?

DR. AL-KHATIB: That is average of the 20 weeks, yes.

DR. HIATT: Then, that would be 36 per 10,000 per year.

DR. AL-KHATIB: Yes.

DR. HIATT: Which is 0.36 per 100 patient-years. Is that correct?

DR. AL-KHATIB: Yes, that is assuming that the risk stayed the same over the course of the year, yes.

DR. HIATT: Of course. That is an event of MI, stroke, death and heart failure.

DR. AL-KHATIB: Yes, correct.

DR. HIATT: What I am trying to do is understand the upper end of the absolute event rate

risk. I think that when we get to the PHARM study that is actually not that different for their upper end of the risk rate as well, and this includes a fourth component, which is heart failure, and PHARM just has three, MI, stroke and death. So, I think what we are talking about is roughly the same absolute upper boundary of risk. It is kind of roughly in the same range. That is my first question. I have more but go ahead.

DR. HARRINGTON: Sana, explain to me, most of these studies probably had no events in them whatsoever. How is the model handle when there are absolutely no events in the model?

Then, my second question--and maybe David can help as well--is in terms of the Bayesian analysis. My understanding of Bayesian statistics is that you have pre-hypothesis assumptions that go into the model. What assumption did you start with? Did you start with the belief that there was no difference between the treatments? Or, did you have some experience that gets entered into the Bayesian model that would assume that, in fact,

that null hypothesis was not true?

DR. AL-KHATIB: Those are very good questions. Vic Hasselblad actually was our statistician in this paper and I am pretty sure he can answer these questions much more than I can. But it was my understanding that, because there were many studies that did not have any events and the studies that had events had a very small number of events, our statistician felt that the Bayesian method is the way to combine the data.

Now, whether we went in with an assumption--if we had an assumption it was that we did not know. I think our assumption was that there was no significant difference between the two but I am not 100 percent certain. You would need a statistician to answer that question. I am not sure how--I mean, can you go in and not have an assumption like that and be kind of neutral? I am not sure.

DR. HIATT: It really adds to the denominator. Tom?

DR. PICKERING: Two questions. Firstly,

there are some placebo studies that are done on a background of active treatment. I assume these patients were on no other antihypertensive treatment at the time of these studies.

DR. AL-KHATIB: That is exactly right, yes.

DR. PICKERING: The other one was could you give us a bit more information about the level of risk in these patients, what sort of level of blood pressure are we talking about? You mentioned that co-morbid disease such as diabetes had been excluded. These were relatively low risk.

DR. AL-KHATIB: Yes, not all the studies actually excluded patients with diabetes. You know, the main co-morbidities that were excluded were if a patient just had a stroke or just had a myocardial infarction; if they are having ongoing angina or evidence to support that they have ongoing ischemia. Those patients were excluded from the trials.

DR. HIATT: The other kind of question I have is that we all know that long-term therapy is

clearly beneficial and we are wrestling with whether short-term absence of therapy causes risk. The question is there must be some point between very short-term and long-term where the benefit becomes manifest.

I think I know the answer to my question but I want to pose it anyway. Did you do a treatment by time interaction to find out--I think 20 weeks was your longest duration of therapy. Is there any point where these curves might start to separate? Probably you have no power to detect that but I needed to pose that question even if it somewhat rhetorical. Can you answer that?

DR. AL-KHATIB: No, that is actually an excellent question. You answered it. I mean, we really did not have enough numbers to kind of look and see. We did not look at time and events interaction. We really didn't have enough events. In all these people we only had 11. That was the total number of events, 5 in one group and 6 in the other. So, we actually did not look at that interaction.

DR. HIATT: You say you didn't look at it. I mean, I realize there is an event deficiency here and it is obviously a little bit late but, you know, you had enough events to tell us if the upper end of the boundary of risk was 6 per 100,000. So, you could make that statement. So, I would just pose the question that if there clearly is a point where risk starts to exceed benefit, can we even see that across 20 weeks in the aggregate? And, the answer is no. But if you dichotomize the population would you see any difference? Would 4 weeks be absolutely safe and maybe the end of the treatment window would not be? You don't know that?

DR. AL-KHATIB: We did not look at that, no.

DR. HIATT: And the upper boundary, is that a 95 percent confidence interval?

DR. AL-KHATIB: Yes.

DR. HIATT: What is the upper boundary?

DR. AL-KHATIB: Yes, 95 percent confidence interval.

DR. FLACK: I want to follow-up on Tom Pickering's question about severity. What was the average blood pressure and the range of blood pressures in these studies? It is a loaded question in part because you really can't tell how severe someone's blood pressure is just by looking at their blood pressure, in particular if they have been taking medicine and even withdrawn because there is contamination effect, but at least to get some estimate of what range of pressure we are talking about here when you say mild to moderate.

DR. AL-KHATIB: Yes, so that is a very good question. Just to kind of clarify, in a lot of those studies what they actually did--as you pointed out, those patients had been on their blood pressure medication and so there was a wash-out period and they used placebo in that run-in period. After that, if their blood pressure was in the range of, you know, 140 systolic, 145 is what I seem to remember from all the citations, they were considered to be okay to be considered for these studies.

DR. FLACK: I am going to put this out for the committee to consider--it is not really covered in this study but it is a problem in remotely done trials and there is even a corollary in newly done trials--one of the problems that you run into is when people enter these trials and they have a placebo wash-out period and some of the problems happen before they ever make it to randomization to active treatment or placebo. It is particularly problematic in trials that are not disciplined enough to say that we are not going to withdraw people from three or four drugs and take them and randomize them to placebo. Quite frankly, some clinical trials in the past have done that. This is kind of the tip of the iceberg because some of these folks are experiencing very substantial rises in blood pressure and potential problems before they ever get randomized.

The contemporary corollary of that is randomly allocating people to inadequate monotherapy. I can think of one major trial that compared valsartan and amlodipine where you had 7

or 8 percent of the people who had pressures over 180 systolic on multiple drugs and they ended up getting randomized to 80 mg of valsartan or 5 of amlodipine. And, then you start seeing events early on and then people jump on the bandwagon that what is really happening is that you have to control blood pressure early.

But I would argue that in part what you have to do is not take people off too many medications with severe blood pressure and destabilize them because 80 mg of valsartan will not keep pressure down as well as 5 mg of amlodipine. So, I think as we consider this one thing what we had better do is pay attention to the time period even before they are randomized, and some of these studies really need to do a better job of either starting with combination therapy or being able to accelerate it quicker because they are coming out now with this phony deal that you have to get pressure down quick.

What we find in our longitudinal data set is that the people in whom you can get their

pressure down quickly are at lower risk anyway, and there is a reason you can get it down quickly. It is kind of a response variable and they have characteristics, and if you can't get it down quickly, like albuminuria, obesity and target organ injury, they place them at higher risk and I think we have to be real careful about using that as some marker for you have to get it down real quick.

DR. HIATT: I think your comments are absolutely key, and particularly in the area around absolute risk coming into a placebo control. So, your point would be that if these patients that we are seeing here are relatively low risk you won't accumulate a lot of events. But if they were relatively at high risk even for withdrawal from medications, that may be a different unstable population.

DR. FLACK: Some of the patients who may have had problems never made it.

DR. AL-KHATIB: I mean, that is an excellent point because when we designed this research project one of the questions that we

raised was whether we can look at, okay, how many of these serious adverse events occur in the run-in phase, in the wash-out period. Unfortunately, most of those studies actually did not report the number of serious adverse events in the run-in period. So, that was very disappointing to us. We couldn't even look at it because the data were not there.

DR. FLACK: The reason I raise this is because if our objective is to say what is the risk for people participating in placebo-controlled trials, the withdrawal period, the wash-out period or even the period of inadequate monotherapy which you can at least capture is part of that risk.

DR. AL-KHATIB: Absolutely.

DR. HIATT: Yes, please?

DR. STOCKBRIDGE: There were 6 events on the active treatment group and 5 in the placebo group. There were roughly 3 times as many people--the denominator is 3 times as large in the active treatment group. How does it end up that the point estimate of the treatment effect is zero? Why isn't it on the order of about 3, 3-fold higher

among placebo?

DR. AL-KHATIB: I see your point definitely. I mean, I think it depends on the statistical methods that were used. The zero that you see was not the result of your taking this percentage minus this percentage. I mean, you are combining the data, and I think taking into account a lot of statistical things. The point estimate--we used the maximum likelihood method and then we used the Bayesian method. It wasn't just, you know, that we were taking the difference between two percentages. I wonder if Dr. DeMets can actually comment on those two methods statistically. I am not a statistician.

DR. DEMETS: Well, no one would accuse me of being a Bayesian so I am not sure I can elucidate that calculation but generally the question earlier was that probably some uniform prior was assumed to see if the data modified that in some way.

DR. STOCKBRIDGE: Do we believe the follow-up was the same in the active treatment

group and the placebo group? This was just the parallel placebo-controlled parts of the trials that were incorporated?

DR. AL-KHATIB: Of course, in a single study, in a single trial the duration was the same. But what you are saying is if you look at the aggregate of the duration of the active therapy patients versus the placebo patients, if that duration was equal? Is that your question?

DR. STOCKBRIDGE: I am looking for some other explanation, other than Bayesian priors that made the point estimate come out to be no effect.

DR. AL-KHATIB: We did not look at the aggregate, if that is your question. Of course, for the single study the follow-up time was the same but we did not look at the aggregate follow-up time for all the active therapy versus all the placebo.

DR. TEMPLE: Actually, I remember wondering about this when the paper was first published. It was 6 versus 5 and many more people on drug. The analysis is explained in the paper in

considerable detail but, of course, not being a Bayesian or a frequentist, I couldn't understand it. I don't know, Dave, maybe you might want to look and see what they said they did. It is displayed and described.

The other thing I would say is that I don't know about the trials you looked at but the trials that we eventually looked at were trials that were not done to discover anything so people weren't looking for people at high risk, or anything like that at all. It was just to show that the drug lowers the blood pressure. And, nobody would want to, in general, include anybody who was at risk so you wouldn't put those people into your trial. You would have to be crazy to do that. So, they are designed not to find out bad news and, you know, you don't want to not treat somebody who seems likely at risk. So, it is not entirely surprising that you don't see a lot of events in those people. It sort of is a good thing.

DR. HIATT: Part of the answer may be in

the distribution. It is clearly skewed. I mean, the point estimate says zero, but the left-hand side of the table for the active therapy is clearly skewed versus placebo. But I still don't understand it either. Are there other questions?

[No response]

Thank you very much. All right, I think we will move on to a presentation on the PHARM study, Dr. Raymond Lipicky.

A Report on the PHARM Study

DR. LIPICKY: Thank you, Mr. Chairman, members of the committee, Dr. Stockbridge and Dr. Temple, and people. It is my pleasure to present what Dr. Stockbridge said is my thing, which is mainly the Cardiac and Renal Drugs Division's thing, which was done by the Division of Cardiac and Renal Drugs while I was at FDA. My only principal responsibility since I retired is that I have delayed publication--

[Laughter]

--It is my fault entirely. So, this is all unpublished information.

[Slide]

It was a trial that had a lot of people with Steven Glasser who now is at Birmingham. We all know one another. And, the Ischemia Research and Education Foundation, Dennis Mangano, who actually funded the support services to be able to enable the thing to be done. And, a bunch of people at FDA that were principally responsible for collecting the data. All of the companies whose data this was were contacted formally and gave formal permission to use their stuff so there isn't data that is being presented for which there was no explicit agreement that it was okay to do so. It really was a collaborative effort that was led by no one. It just sort of happened.

What this was, it was blinded from original case report forms. I have to apologize up front. You will see from the typos, and so on, on the slides and the misspellings and my stumbling during the presentation, that this is a very carefully rehearsed program.

It was a meta-analysis of those things

that were reported as deaths and dropouts to NDAs or supplements to NDAs that came to FDA from the first knowledge of a placebo-controlled trial in hypertension which, I believe, was 1973 to something like 2002, which is when the database was closed.

It is 28 years of standard placebo-controlled antihypertensive stuff. Although we didn't review every protocol, didn't list all of the inclusion and exclusion criteria, Robert Califf characterizes these patients as people who could be run over by a truck and would get up and look for their tennis racket. So, these are basically pretty healthy people who have nothing wrong except that their blood pressure is high and they enrolled in placebo-control trials.

We know nothing about the wash-out period, zero; didn't look; know nothing about after the trial was over, zero. So, it is only during the placebo control trials from the day of randomization to the dropout that we know anything. There were 540 individual protocols that are

represented in the database, 86,000 randomized patients, 21,000 placebo and 64,000 on drug. And, the total thing was 12,657 patient-years of exposure. There are 42 chemical entities, 6 drug classes. And, there were 9636 events that were reported.

So, it is a pretty rich database and I have selected from this database some things that I will show you now; other things that are in more detail in the report to Dr. Stockbridge. Feel free to interrupt me at any time. I may be able to answer a question because this is obviously cherry-picked enormously. There is a lot of stuff in here that I am not going to show.

The mean age was 54 years; blood pressures 157/102 mean. This is just the dropout people so that this isn't the randomization thing. But at baseline, if you looked at the distribution curves for the blood pressures they were pretty much normally distributed. Some of the people who were brought into these trials were brought in for blood pressure cuff. Some were randomized because of

ABPM. We didn't care. They all had cuff measurements and they had measurements sitting and supine.

We had only a single primary endpoint, and that was the relative risk of dropping out of the trial if you were randomized to placebo. That relative risk was 1.33 with a p of less than 10 to minus 15. So, clearly, if you were randomized to placebo you had a better chance of dropping out than if you were randomized to drug. The other major thing was that if you looked at an index of irreversible harm, namely mortality, stroke and MI, the relative risk was 1.03--I guess I should have put a p value there--with relatively wide confidence limits.

[Slide]

On the whole, the reasons for dropout were administrative, lack of blood pressure control and adverse effects. So, the study found that people move, have intercurrent illnesses, have surgery and drop out for administrative causes. If they are hypertensive and they are not on antihypertensive

medications their blood pressure doesn't do well and if they are on drugs they have adverse effects. Bid deal! The thing that we are really interested in occurred very rarely. And, I can stop now because that is the whole story. Or, I can keep torturing you.

[Laughter]

[Slide]

The administrative other things were sort of standard, lack of blood pressure control. There were two components. They had therapeutic failure, and therapeutic failure was largely determined by looking at case report forms where people were dropped out--these were all dropouts--and determining that the only reason the patient was dropped out was because their blood pressure wasn't what one wanted it to be. It might have not been low enough; it might have been the same or it might have been getting bigger, but that was the major thing that you could glean from the case report forms when you were looking through them.

Hypertensive emergency is a misnomer, in

my judgment, where we made a big mistake in how we set up the trial that was intended to detect people who had new end-organ involvement and high blood pressure. Unfortunately, it said that diastolic greater than 110 or an increase in diastolic by greater than 10 was a reason for calling this hypertensive emergency whether people had troubles or not.

Adverse effects were two kinds, one we called other cardiac adverse effects and they were angioedema, edema, low blood pressure, nonspecific ECG changes, that kind of stuff. Other non-cardiac adverse events were basically laboratory abnormalities, headache, nausea and vomiting, and so on.

[Slide]

Indeed, all of this stuff was looked at for MI, stroke, death and unscheduled visits to the emergency room or hospitalizations were also tracked. So, all of that stuff was recorded.

[Slide]

Now, the largest single category were

administrative dropouts. That had a relative risk of 1.09, with a p of 0.031. Although that is the largest category, we recognize that that was not a primary endpoint. We only had one and we had a whole bunch of comparisons in this study. So, you will see in a later place that we will argue that if you wanted a p of 0.01 for all of the analyses we did, it ought to have a p of 10-6 if you do a multiple comparison thing. So, basically I think that this is a non-finding although, in fact, it says you are better off if you are randomized to drug.

Therapeutic failure shouldn't surprise anybody, p 10 -15. If you have hypertension and you don't get an antihypertensive your blood pressure doesn't do well. And, people who look after people tend to drop people from trials when that happens.

These two together are 62 percent, a surprisingly large number. All of the relative risks that are in the document that I supplied Dr. Stockbridge and on these slides are calculated from maximum likelihood statistics, the same as the

previous study. We also did standard Mantel-Haenszel and that turned out almost identical. The difference was in the second decimal place. So, there are no tricks here and there is no reason to wonder whether somebody did something funny or not.

[Slide]

It is interesting to look at the unscheduled visits, ER and hospitalization for the therapeutic failure and the other administrative dropout categories. The other administrative dropout categories have a goodly number of people who were hospitalized for surgery or carcinoma, were hospitalized for intercurrent illnesses, and so on and so forth.

It was sort of a surprising thing. I don't know why that is. There were a lot and it was much more than therapeutic failure. So, the question is what is the background rate for ER and hospitalization. Is it in the order of 4 percent or is it in the order of 1 percent? My best guess is that it is somewhere in the 1-2 percent range as

background, sort of standard background for this population and that things that were going on in the patients that were in the administrative dropouts I really don't understand. I don't have any explanation for that at all, and what I have proposed may be right or may be wrong.

[Slide]

You note that other adverse events and other cardiac adverse events both have relative risks that favor being randomized to placebo, and that there is a pretty healthy p value for that, and 10 -6 would be 0.01 so that is probably a real finding but there aren't very many events. Other adverse events--you know, I don't know whether that is real or unreal or whether that relative risk is there or isn't there but, in general, these two categories favor being randomized to placebo.

[Slide]

This is just words for what these other adverse events were and what the OC was so that you have a feeling for the kinds of things that those guys represent. That is just a crude summary of

some of the stuff.

[Slide]

Now, when you get to other adverse events and to other cardiovascular events you really start getting up into ER and hospitalizations of 10-12 percent. So, those were not of inconsequence. In fact, most of the hospitalizations in OC were for hypotension and, in particular for postural hypotension. So, these were events on blood pressure that were significant and that were not in favor of being randomized to drug.

[Slide]

Now, hypertensive emergencies--not too many events but way more events than are reported in the literature in any placebo-controlled hypertension study I have ever seen so this is just a crazy number of events that we found compared to anything that has ever been reported. It is hard to find hypertensive emergency in MRC and all that sort of stuff.

[Slide]

That was a pretty statistically

significant finding but, in fact, less than 25 percent of the patients that were in this category had in their case report forms words that were like some end-organ damage, retinopathy, or this or that, or the other thing. So, it is a grossly inflated number--real because some people did have newly appearing retinopathy. We did not go back, once we recognized our mistake which I will get to, and recollect everything. So, this is what we said we were going to do. This is what we found.

Now, the big deal was that this diastolic of greater than 110 was enforced. It was enforced by committee. We had committees to review all this stuff and, boy, you know, it was written so it got enforced. Increase of diastolic of greater than 10 was enforced by committee.

[Slide]

You can't see this, and that is the difference between OSX and NT. There is an image there I will guarantee you--

[Laughter]

DR. TEERLINK: If you double-click on it,

it will show up.

DR. LIPICKY: Double-click on the image?

DR. TEERLINK: But you have to do it in Power Point.

DR. LIPICKY: I see. Well, anyway, I can tell you what it says. It is a cumulative distribution curve of baseline sitting diastolic blood pressure. What it shows is that 20 percent of the population at baseline had a diastolic blood pressure greater than 110.

[Slide]

The next slide, which you also can't see, says that the supine diastolic blood pressure of greater than 110 at baseline was 20 percent. So, at baseline the greater than 110 was present in 10-20 percent of the population that was enrolled.

[Slide]

The next one and the next one you also can't see, which were change from baseline and, indeed, 20 percent of the entire dropout population had increases of diastolic blood pressure greater than 10 mmHg during the course of the trial.

So, that unfortunate clause of putting in numbers that were unrealistic--today hypertensive emergency is thought of in the 180 mmHg diastolic range--was a very unfortunate thing. It is a misnomer. It actually occurred but there is this spectrum of therapeutic failure and hypertensive emergency. We were not able to make the qualitative distinction that we wished to make although clearly hypertensive emergency patients were, in fact, hospitalized or had ER visits fairly frequently. So, it is not to be dismissed but it isn't what it appears to be.

[Slide]

Just to complete the spectrum, if you clear out stroke and MI, and so on, you start approaching 100 percent. So, this ER and hospitalization business has some meaning with respect to what the clinical impact of the dropout was. [Slide]

So, where are we then? What I have said is that if you look at it as a standard kind of curve, higher risk on placebo, higher risk on

treatment, all dropouts, higher risk on placebo--no question that that is true. That was the primary endpoint, no question about it. The hypertensive emergencies--I don't know how to evaluate that. We made a basic mistake. I don't know how we can correct that mistake. It was a real thing. The point estimate is lower. The confidence limits will be wider. I don't know how to do it.

The other cardiovascular things--10 -15, that is for real. The OAE, I don't know whether that is real or not and OT is not. The rest of it is clearly totally indeterminate, those being the point estimates and confidence limits. So, the things of most interest can't be answered.

If you look at irreversible harm, CVA, MI and death, 1.03 with those confidence limits, the upper limit being around 5 per 1000. This is relative risk. That sort of is the story.

[Slide]

Now, clearly, the impact of any of these things doesn't depend on the relative risk. It depends on the number of events. So, what we

looked at was the absolute risk of all of those things so that the absolute risk of OAE in terms of dropping out was like 18 patients per 1000 patient-years who dropped out because of that.

Then, there was another--I can't do the interpolations for other cardiovascular causes. Then, these were favoring drug, hypertensive emergencies, angina pectoris, etc. The net--the net was around 19 patients per 1000 patient-years. That is with administrative and therapeutic failure ignored. So, the net effect is that you are better off on placebo. If you eliminate hypertensive emergency your net effect goes out to 45 per 1000 patient-years--better if you are on placebo. So, this business of total number of events and the relative risk and what the absolute risk is really needs to be examined together.

[Slide]

Irreversible harm looks this way, a little better for death, a little worse for CVA and MI, and there is the sum for the irreversible harm. It is a little more than one per 1000 patient-years.

These are point estimates only.

[Slide]

Terrific! [Blank slide]. I am done. Questions?

DR, HARRINGTON: Ray, I just want to make sure that I understand the way that you did the analysis.

DR. LIPICKY: Oh, wait. Sorry, it came back, I am not done.

[Laughter]

DR, HARRINGTON: I will wait.

DR. LIPICKY: I don't know how that happened, the most important figures are missing. I guess I have to refer you to the handouts. I don't know why they are not there.

[Slide]

There are some three-dimensional graphs that are in the handouts. They really need to be looked at because I think they give the perspective of where things are. These are graphs of the absolute event rates in the control trials that exist in the literature, intervention trials in the

literature, that I was able to calculate the event rate per 1000 patient-years from. It represents around 200,000 patient-years of data.

On the X axis is blood pressure systolic. The sort of next X axis is the age, chronological age and those aren't linear scales; they are just there. Then, the incidence. What you can see are those little arrows in the lower left-hand corner that are the paired data that show the PHARM results in comparison to all these other trials. Does what I have just said make sense to you, looking at those?

[Slide]

So, what we have here is systolic blood pressure, chronological age and, unfortunately, these are not linear in their scaling. Then, event rate, incidence per 1000 patient-years, and these little arrows, which don't show, which would be pointing to this data pair here is the PHARM data for this systolic blood pressure and this chronological age. So, you can see that the older you are and the higher the systolic blood pressure,

the greater is all-cause mortality--I think without question; and that the PHARM results are entirely in keeping with all of the published early data--MRC and Australian trial, and so on and so forth.

[Slide]

Similarly, for non-fatal stroke this is PHARM, right here, and the older you are, the higher the systolic blood pressure, and the greater the absolute incidence of stroke is from intervention trials.

[Slide]

This is MI. This is PHARM data and this is the rest of the literature. You see that PHARM is entirely in keeping if you look at it in terms of blood pressure and chronological age.

[Slide]

I won't bother going through this. If you go through the diastolic blood pressure the same way things seem to be less orderly all the way through, although the PHARM data is here and you see that the PHARM data set contains the highest

randomized diastolic blood pressure of any of the trials that have ever been done--the lowest systolic and the highest diastolic.

[Slide]

Again, pretty disorderly with respect to all-cause mortality.

[Slide]

This is for stroke. Age is the biggest deal here. [Slide]

Now, that is what PHARM looked like, and you know that the 100,000 patient-year stuff from Peto [?] and Collins et al. by chronological age shows a nice continuous relationship for systolic and diastolic all the way through so there isn't any question about that. The PHARM data don't say that is not true but the PHARM data do say that, as far as it is concerned, it looks like systolic blood pressure is a more important parameter.

[Slide]

Then, this is the meta-analysis that Collins and Peto published which established additionally that there was some worthwhileness to

treating blood pressure. I want to point out that a lot of studies really individually did not find much.

[Slide]

So, the main thing I want to say is that 30 years and 590 trials have not yielded any data that even suggest that there is an increase in irreversible harm that occurs if you are randomized to placebo in short-term placebo-controlled trials; that the population represented by PHARM, in terms of its general incidence, is really no different from the intervention trials that have found a benefit.

[Slide]

And, I think that equipoise can be maintained for utilization of placebo in placebo-controlled trials short-term, and that 30-50 years from now someone ought to do this study again and find out if I am right. Now I am done.

Committee Questions on the Presentation

DR. HIATT: Thank you. Ray, if it would be all right, we would like to ask you a number of

questions.

DR. LIPICKY: Yes.

DR. HIATT: Let me clarify a couple of things. We need to know kind of the quality of the data and where it came from. This is all from case report forms. Is that correct?

DR. LIPICKY: That is correct.

DR. HIATT: The events that were being recorded really, in the estimation of the investigator or coordinator who filled out that case report form that said it was a non-fatal myocardial infarction or end-organ damage, occurred because you saw it on the case report form.

DR. LIPICKY: That is correct. If it was not on the case report form it would not have been seen. On occasion, what the investigator said on the case report form was not accepted as being the reason for dropping out. We had to make the decision of primary reason for dropping out and on occasion that reason that might have been stated by the investigator was not accepted. When that occurred that had to go through a committee, an

events committee, and about 15 percent of these events went to the events committee for clarification and, before it got recorded, it needed to have unanimous consensus that this was the event that caused the dropout.

DR. HIATT: But the primary data--you had no other source documentation--

DR. LIPICKY: No, sir, case report forms only.

DR. HIATT: I wanted to clarify that. The second question is--

DR. LIPICKY: There is a second limitation on that. That is, the companies in submitting reports say how many deaths and dropouts they had. Companies did supply case report forms de novo if they weren't contained within the NDA. So, if the company was in error with respect to how many dropouts they had, well, this whole thing is a can of worms.

DR. HIATT: I guess that gets to my other question. I realize that there is uncertainty but how many events could have been missed? Could you

have a non-fatal cardiovascular event and not have been dropped from a study and not have been counted in this database?

DR. LIPICKY: I can't disavow that. You know, people fear FDA really rather enormously, as I have learned, so the chances of that happening I would think are small but it could be. And, we did have some misclassification. I know of three examples that we didn't count because all of the checks that occurred didn't work quite the way they were supposed to.

DR. TEMPLE: I think Bill was asking whether someone could have had an MI and somebody decided to leave him on the drug so he doesn't show up as a dropout.

DR. HIATT: Right, that is what I am asking.

DR. LIPICKY: That is possible also.

DR. TEMPLE: Yes, but that would be a very strange thing to do.

DR. LIPICKY: It would be, yes, but it is possible.

DR. TEMPLE: You can't say no if nobody recorded it, didn't drop out and finished the study all the way to its twelfth week. You wouldn't recognize it.

DR. LIPICKY: Right.

DR. HIATT: So, just before we get into lots of interpretive kinds of questions, I just wanted to make sure I understood the nature of the data that we are reviewing. I guess in your judgment or estimation, we are seeing what you think are probably most of the major--

DR. LIPICKY: Well, I think this is clearly a subjective judgment, but from my experience at FDA, you know, this is about as pristine data as you can expect to see. Could there be errors? You bet. But it is probably as good as you can get.

DR. TEERLINK: Just to clarify, you are saying that if someone had a myocardial infarction it is an SAE, a serious adverse event?

DR. LIPICKY: Then we would not have it.

DR. TEERLINK: You would not have had

that?

DR. LIPICKY: Correct.

DR. HIATT: That was one of my later questions but I will get it out right now, so did you have an SAE database to look at as well?

DR. LIPICKY: No. Well, we had it but we didn't look at it because it took us 15 years to do this.

[Laughter]

DR. TEMPLE: It is a premise of our review activities that troubles for a patient are going to show up by having not been in the study anymore, with really very few exceptions. If someone has a stroke you don't leave them in a blood pressure study. That would really be a strange thing to do. If they go in a hospital, how can they be in a study anymore? They are in the hospital.

So, I must say, I think that is an extremely reasonable premise and is far better than any other data you have ever looked at if you read the literature, where you don't know what they are basing it on.

DR. HIATT: So, in this context then, the best surrogate for the overall risk in event rates probably is, indeed, dropouts.

DR. TEMPLE: That is the premise here, that you will find the trouble in the dropouts. Some of the dropouts aren't trouble, the administrative ones, but if there is trouble you will find it in the dropouts.

Just in case people don't know this, since 1985 the only case reports we get automatically are people who drop out of a study in association with something adverse. The other ones we can still ask for if we want them. Prior to 1985 we used to get every case report form and people mocked us for the trucks that backed up to the building, and took note of the fact that if you had to read them all you would have about, you know, a tenth of a second per page and they didn't really think we were looking at them. So, we focused on the place where we thought the trouble would be if there were trouble.

DR. PICKERING: I have a question relating

to your comment about the diastolic pressure being higher than in other studies. When this was starting there may have been studies where the only entry criterion was a high diastolic pressure. Is that information you have as to what the entry criteria were for these individual studies?

DR. LIPICKY: This was all diastolic blood pressure. Every protocol was diastolic blood pressure.

DR. WARNER-STEVENSON: I would just like to add my voice as well. While I think it is totally reasonable to take a patient out of a study who has a major adverse event, I also see patients who are not withdrawn from studies for adverse events.

DR. TEMPLE: Even like a stroke, do you think?

DR. TEERLINK: Yes.

DR. TEMPLE: I mean, not every adverse event.

DR. WARNER-STEVENSON: Certainly for an MI, I have seen patients who have been left in

studies.

DR. TEMPLE: Well, what is the rule for the study? Is it a study that is looking at outcomes including both MI and survival? Then you wouldn't because you are not supposed to.

DR. WARNER-STEVENSON: Well, I am not saying that these are things that are supposed to happen, I am just saying I am sure it does happen. I just don't know how often.

DR. LIPICKY: Well, I am sure it does too but I just want to reiterate that I think this is as pristine data as you have ever seen, not that it is foolproof nor that it does have everything.

DR. HIATT: For us to judge it any differently would mean that there must be some differential dropout or that the patients that weren't captured, that somehow it is going to bias us to assume that placebo is safe when it really is not. So, the issue really is--of course, it is incomplete but the issue is does it matter.

I wanted to get out the basis of the data for our discussion before we talk about

interpreting the data, and what I am hearing is that it probably is capturing most things in an unbiased way.

DR. FLACK: I have a couple of questions. What was the median time of follow-up in the studies?

DR. LIPICKY: I can't answer your question but let me put it this way, the median time to dropout for these dropouts was 28 days, almost regardless of what. I can't remember the plot of the cumulative thing but these trials were all three months or less, occasionally longer.

DR. FLACK: Three months or less? Okay. I also wonder if the risk is constant over time or if there is an interaction between treatment and time.

DR. LIPICKY: Yes.

DR. FLACK: And, it seems to me--

DR. LIPICKY: Time, calendar year?

DR. FLACK: Days, weeks, whatever.

DR. HIATT: The question is, you know, is the risk--

[Multi-member discussion]

DR. LIPICKY: There is an answer to one of the questions perhaps. We did an analysis of does it matter to the event rate as to whether it was 1973 or 2002. The answer to that question is no, things went up and down, and so on. Now, did the event rate follow a linear pattern during the course of the trial or some other descriptor? I think all of the curves that I have seen of this data would suggest that it was linear over the course of time in trial. DR. FLACK: And one final comment, and you picked up on it in your last statement there, I think there is a message probably as to what our tolerability ought to be for placebo-controlled trials in regards to baseline blood pressures even of short duration in this data set. I mean, if you look at those baseline blood pressures, in particular the systolic ones, you start getting over 170. This goes back to my point about withdrawing people with too severe hypertension and even putting them in short-term trials. I think there is a message here

that, you know, we have to take a lesson from. It would probably come from a subgroup analysis and the thing you are going to see as an investigator is going to be the baseline blood pressures. But we need some guidance for that by blood pressure as well as some combination of age and blood pressure where the risk even for short-term placebo-controlled trials is just unacceptably high.

DR. LIPICKY: Well, there is a suggestion from the graphs I showed that if you set the upper age at 55 and the systolic pressure at 150, you would be way down in the lower part of the event rates that were inconsequential.

DR. FLACK: Because we have contemporary trials that you can go and point to where substantial numbers of people exceed those cut points blood pressure-wise. It would strike me that this is really giving us a message.

DR. HIATT: I think you have raised a lot of really critical points. What I would like to do is really kind of clarify a few of those initially.

The first point which I wasn't clear about, Ray, was the upper end of the duration of these studies, and you said it was three months?

DR. LIPICKY: Roughly. Some were longer. Occasional trials were 6 months.

DR. HIATT: I think it would be really helpful to know because we raised this with the last study. You know, a couple of years on antihypertensive therapy is clearly good, but the question will be what is the duration of exposure to placebo that is truly "safe?"

DR. LIPICKY: Unfortunately, I didn't show that curve. I have it.

DR. TEMPLE: Bill, but given that most of the trials are 4 to 6 weeks, that is where most of the data is going to come from.

DR. HIATT: But can we clarify that point?

DR. TEMPLE: We should but I don't know the answer.

DR. DEMETS: I just did a quick calculation, taking the total patients and the total patient-years that Ray presented, and it is

about 6 weeks on average for all those. Granted, there are some that are 2 years and some that are 2 weeks, but the average of the number of exposures is about 6 weeks.

DR. HIATT: Okay.

DR. TEMPLE: I mean, that is what we would expect. That is what people mostly do. With 12 weeks we are probably discouraging people, at least recently, from even doing that. So, most of the data is going to come from quite short-term studies.

DR. HIATT: I really just want to quantify what that means once again because if we are going to extrapolate and make recommendations "short" has to be defined.

DR. TEMPLE: Yes, my guess is sort of what Dr. Flack was saying, that we may want to conclude that shorter is better even if we didn't see anything. That is sort of what Ray was--

DR. HIATT: That is the next question because, unlike the study we just heard about, you probably have enough information to know if, in

fact, the difference in major cardiovascular events between drug and placebo is constant across your 6-12 weeks of therapy or whether, in fact, the curves are starting to separate at some point or not. And the fist question--

DR. LIPICKY: Our statisticians refused to do the Kaplan-Meier curves. They said look at the point estimate of relative risk here. We are not going to waste our time with that.

DR. HIATT: Well, you probably have enough data to do it.

DR. LIPICKY: They said they wouldn't waste their time.

DR. HIATT: Oh! So, just as a final question, a question that hasn't resolved in my mind is across this window, which is probably somewhere on average around 6-8 weeks. You know, is the risk on placebo--

DR. LIPICKY: Well, there are two elements of data that are pertinent to that. The only one I can recall at the moment is that SHEP has a nice graph that looks at the event rate as a function of

time in trial and it really is linear. I believe that SISTER also has a plot like that and it is linear. These data show the same thing. I didn't show the curves.

DR. TEMPLE: For these data, Ray?

DR. LIPICKY: Pardon?

DR. TEMPLE: These data show for the events that matter, stroke, MI and death, a linear relationship over time but not a difference between treatments over time?

DR. LIPICKY: Right.

DR. TEMPLE: Whereas SISTER and SHEP must be showing a difference over time, but you didn't see that here. Right?

DR. HIATT: That is what I tried to clarify.

DR. LIPICKY: What I was describing was event rates as a function of time, on treatment effect as a function of time.

DR. TEMPLE: So, not surprisingly people with an underlying disease have a sort of fixed rate over time, but you wouldn't expect that to

change particularly, at least not in the untreated group. What you might think is that at some point, as I guess you said, we know what SHEP showed and the separation of curves starts somewhere. We don't know where. I don't remember all these figures. There aren't enough events in those trials to see a clear difference in the first month or two but by 6 months they are starting to spread.

So, we have already been very long-term nervous about doing a trial of any substantial duration. But the question that this is answering is in the very short-term do you see anything? Obviously, you are going to have to have enough events to see something before you can see something and there aren't very many events.

DR. HIATT: Well, there is actually--I wrote it down--about 150 or 160 MI, strokes and deaths.

DR. LIPICKY: Right.

DR. HIATT: Right?

DR. LIPICKY: Yes.

DR. HIATT: Which is actually not an

unreasonable number of events. The question is whether it becomes more unsafe or not to be on placebo at 3 months than 6 weeks.

DR. LIPICKY: Jim, do you remember why you refused?

DR. HUNG: Well, I don't remember, but actually from the beginning, other than dropping for any reason, other questions are sort of--you know, there is a sort of change many, many times and then at some point we think this is purely exploratory type, I mean, other than several primary questions.

DR. LIPICKY: But I guess the basic thing is you have relative risk. The point estimate is 1.03. It is not statistically significant. Now you are going to tell me the way in which the curves look is going to make up your mind about something? Nonsense!

DR. TEMPLE: Well, for it to show the time thing you are worried about it almost has to be going the other way early, which would really be astonishing--I mean, placebo preventing MIs early

and then you get more later. With 1.03 the total number of events is not different. So, it is going to be hard to think that but we should look anyway. I mean, you should look at that.

DR. WARNER-STEVENSON: I guess I think one could postulate that if you are being adjusted on a drug that may make you intermittently hypotensive and other things happen you may have a higher event rate at the beginning, during titration. Whereas, if you are somebody who is not on a drug at all, I would expect to have just sort of a relatively steady, perhaps increasing rate. There is no data here to see that but it is not impossible that you could see it across in those groups.

DR. TEMPLE: Well, it should be looked at whatever one's hypothesis is. It should be easy to do and we should do it.

DR. TEERLINK: I think as we try to find ways that this is worse, we are still actually saying the placebo is probably still okay. You know, in the exact example that you just came up with, it still suggests that short-term--and we

will define what short-term means--placebo-controlled trials will would be okay.

DR. LINCOFF: I would like to ask a question about the hypertensive emergency group. I recognize this was a retrospective different group. You mentioned in the text that it looks like there were about 63 of those patients that you thought probably might have really been something. Now, I realize that is not necessarily an irreversible effect, in fact, they weren't because they would have been classified in those categories if they were. But, nevertheless, I think if you really wanted to be concerned you can say that that is the next threshold.

DR. LIPICKY: I agree and Dr. Mangano is going to support you and say that I should shut up. He is going to say that is a good enough reason to say placebo is not allowed.

DR. LINCOFF: And I am not saying that, but you said the median time course on average is about 28 days for the dropouts but a lot of the

dropouts were nothing to worry about at all. Were they different for event dropouts?

DR. LIPICKY: No, they were not. The median time to dropout was 28 plus/minus 2 days for every category. It was a surprisingly consistent number.

DR. LINCOFF: And did you do any subanalyses of these possibly meaningful hypertensive emergencies versus not, or was that too much of a sub-sub-sub?

DR. LIPICKY: Well, no we did not. I thought about doing it and I think we probably should. It is just that then we ought to account for these 3 strokes I know about. Then we have to call all the case report forms back from the cave somewhere in Kentucky, and then we are in big trouble. So, it is really a problem, unfortunately, to fix things up and my preference would be to not fix them up because it is an enormous problem; really hard and I wouldn't believe it if we found something different.

DR. HARRINGTON: Ray, I want to make sure

I understood you. You said that over time the temporal interaction analyses showed that there was no difference in time of the dropouts. Is that correct? Meaning the years, trials begun in 1973?

DR. LIPICKY: Over that time interval it sort of went up and down and up and down but there was no trend.

DR. HARRINGTON: And did the character of the dropouts change at all?

DR. LIPICKY: No.

DR. HARRINGTON: I mean, it is a little disappointing. It sounds like we didn't learn anything about doing some of these trials over 30 years.

DR. LIPICKY: No, we did not learn anything.

DR. HARRINGTON: Have you done a corresponding analysis by class of drug? Clearly, the classes of drugs that have been studies over the years--

DR. LIPICKY: Yes, sir, we did it by class of drug. There were 6, I believe, and it didn't

matter. They were all the same.

DR. HARRINGTON: So, the dropout ratio was similar by class?

DR. LIPICKY: The numbers changed, obviously.

DR. HARRINGTON: Sure.

DR. LIPICKY: But there was no qualitative thing that happened. You draw the same conclusions about the data.

DR. HARRINGTON: And that includes the more serious events?

DR. LIPICKY: Yes.

DR. TEMPLE: But I bet the reasons for dropout change--you know, we see edema for some for the dihydropyridines and stuff like that.

DR. LIPICKY: Well, the other adverse effects would have changed for sure.

DR. TEMPLE: Right.

DR. HARRINGTON: But the key thing is that the serious events didn't change.

DR. TEMPLE: No, but those are things that, if they occur, are caused by not being

treated. The placebo is the same over time.

DR. HIATT: I wanted to come back to just another point, which is the relative risk at the end of the confidence interval of 1.03. I think I am going to argue that really the thing we should focus on is MI, stroke and death here because the other aspects of potential harm are things that could be picked up and managed during the conduct of a short-term placebo-controlled trial.

But, Ray, I want to point out that when you add up the number of events, which I think is around 150, and then you look at the upper end of the confidence interval you have about a 50 percent increased risk.

DR. LIPICKY: Relative risk.

DR. HIATT: Relative risk, which is what you predict with 150 events. It kind of fits. I would like to also just highlight the absolute event rate. The difference between drug and placebo on major cardiovascular events is 0.13 per 100 patient-years.

DR. LIPICKY: Yes, about 1 per 1000.

DR. HIATT: Right. That event rate is a little less than in the publication, which was 0.36 per 100 patient-years. That included another event which was heart failure.

DR. LIPICKY: Yes.

DR. HIATT: So, I am going to conclude that the upper end of the risk boundary is not that different between the paper using published data, and this study using NDAs and supplemental NDAs.

DR. LIPICKY: Well, I think that is a correct statement. I think the point estimates are probably better here because there are a lot more.

DR. HIATT: Sure.

DR. LIPICKY: But the confidence limits of the upper bound are pretty much the same.

DR. HIATT: Yes. So, I guess I am just saying that because I think we want to talk about not only relative risk to a patient to be exposed to a placebo but the absolute risk.

DR. LIPICKY: That is correct, and I think that really has to be taken into account because if you look at the number of patients who are

adversely affected by being involved in a trial, it really overwhelmingly supports being on placebo if you exclude administrative and blood pressure control.

DR. HIATT: Yes.

DR. TEMPLE: Maybe this is subject to further discussion but suppose there was an unequivocal but very, very small increased risk of having a stroke or dying or having an MI, I would say that would be really a problem to randomize people anymore, even if it was--I don't know--some very small number per 1000 patient-years or per 1000 patients.

So, I think it is fairly critical that we believe that at least in this large database we detected nothing. It doesn't mean the upper bounds are going to be nothing. That can never be. But I would be extremely uncomfortable if there was a low but real risk.

DR. HIATT: We understand the point estimates pretty well, obviously, but I guess if you really want to understand the risk you should

not just look at the point estimates. So, I think that we do have a pretty good estimate here that you might cause MI, stroke and death to about 1 patient per 1000 patient-years.

DR. TEMPLE: Where does that come from? Is that what 1.03 means?

DR. HIATT: No, that is the relative risk increase of 50 percent on an absolute event rate that is very low.

DR. LIPICKY: Yes.

DR. TEMPLE: But 50 percent, that is just the result of not having a million events. That is not the actual risk.

DR. HIATT: That is the worst-case scenario.

DR. LIPICKY: Well, I have a slightly different take on this, Bob, in the sense that I think the PHARM population has the same relative risk that everybody found in the intervention trials. They just had very few additional risk factors; had a very low systolic pressure and, consequently, didn't have much of an effect. It

was a low event trial.

DR. TEMPLE: But you have no way of knowing that. In fact, you don't see a difference between treatments.

DR. LIPICKY: But I have no way of saying that isn't true either.

DR. TEMPLE: Yes, you do. What you have is an estimate of 1.03 which is about as close to 1.0 as--

DR. LIPICKY: But it is a very poor estimate. It could be 1.5.

DR. TEMPLE: That is not the same as saying you don't have--it is not 1.3 like it would be for an outcome study. That is what it would be in all the studies we are talking about.

DR. LIPICKY: That is a true statement--

DR. TEMPLE: It doesn't look like that.

DR. LIPICKY: --but that doesn't say the biology is changed. This is still hypertension.

DR. TEMPLE: Yes, but we don't know what 2 weeks of having an elevated blood pressure is.

DR. LIPICKY: But then it is all

short-term.

DR. TEMPLE: Yes.

DR. LIPICKY: Well, that may be.

DR. TEMPLE: Ray, I have never imagined the idea that if you were to do a 6-month or 1-year study you would find anything except what we always find. Of course, you are going to find that. Now you are looking at what happens if you take people who were known to be hypertensive, were taken off their drug and you do it for a short period of time, is that long enough to do them harm? That is the question. It is the only question.

DR. LIPICKY: And this data says it is not, that that doesn't really hurt you.

DR. TEMPLE: That is what I am alleging also, yes.

DR. LIPICKY: Although that doesn't mean if you were not in the placebo-controlled trial--that being in the trial still increases your risk. It is just very small.

DR. TEMPLE: Well, you can't know that. I mean, if you had 180,000 people or 300,000 people

randomized maybe you would get a different answer. But the answer you get so far is that with short-term with close monitoring--

DR. LIPICKY: Right.

DR. TEMPLE: --there doesn't seem to be any increased risk--

DR. LIPICKY: Right.

DR. TEMPLE: --not that the upper bound isn't above 1.0. I mean, if the point estimate is 1.0 the upper bound is, for sure, going to be above 1.0. I already knew that.

DR. LIPICKY: But the answer you get--

DR. TEMPLE: Anyway, I didn't want to get to that. I guess my main question is I don't think we could tolerate a persuasive finding of increased risk if it looked it real, even if it was very small.

DR. LIPICKY: Well, I don't know that I would go that far but the answer you have now is that it is okay to keep looking because you don't have an answer.

DR. HARRINGTON: But isn't there another

caveat to that, Ray? I mean, what this suffers from is the usual limitations of systematic overviews. Do you have all the data? And do you have all the data that--

DR. LIPICKY: Yes. The answer to that is yes.

DR. HARRINGTON: Through NDAs, but you don't have all the data, for example, of any investigational new drug that never made it to an NDA.

DR. LIPICKY: Yes.

DR. HARRINGTON: We do have that?

DR. LIPICKY: Well, if it made it to an NDA we do.

DR. HARRINGTON: But what would be the number of trials approximately, trials performed and never made it to an NDA?

DR. LIPICKY: We don't know the answer to that.

DR. TEERLINK: But is there any reason to think systematically that the placebo groups in those trials would have been any different than in

the NDAs? In fact, you might argue that it would go the other way. So, I think for relevance of this issue--

DR. HARRINGTON: That is what you would think but it is a clear limitation that you don't actually have the universe of data, that there is some gap.

DR. LIPICKY: That is correct.

DR. TEMPLE: I would like to say I don't think it is correct. Unless you think there is a biased sample, it really doesn't matter whether there is another 30,000 worth of patients that you don't know about. The conclusion is perfectly good for the 86,000 you do have unless there is some reason to think that people were kept out of studies where the placebo did worse. Why would they do that? I mean, that is sort of good for the drug. I think the bias, if there is one, goes the other way.

DR. HARRINGTON: I agree with that but it is not as though you have left out a random number of other studies. You have left out likely a

biased number of other studies that, for whatever reason, people chose not to pursue. You are right, your belief biologically is that it goes in favor of placebo, but you would have to say you don't know that, that that is still a limitation.

DR. TEMPLE: Well, you have left out studies where the drug either didn't work or was too toxic. But, remember, the trials we are talking about are trials of reasonable size so a drug would have to get past the early phase 2 and into phase 3, and we are not aware of a whole lot of drugs that don't make it into an NDA by that point. There must be some.

DR. HARRINGTON: So, that is important then, that qualitatively you don't believe that there are many.

DR. TEMPLE: I don't believe there are many and my view of the bias is that what you are missing goes the other way. Remember, this is about the placebo; it is not about the drug.

DR. WARNER-STEVENSON: I think this data is very reassuring about the magnitude being quite

small, but I would like to emphasize the two ends. As Dr. Flack said, we don't know what happened during the wash-out period that they have to be on to get in. But we actually don't know the other end either. It could be that having the blood pressure uncontrolled for 28 days they got an MI at 35 days, at which point they were no longer in the study.

I feel compelled to point out the irony of the day in which we spent the morning deciding how hard we need to try to convince people how important it is to treat blood pressure but not for 28 days.

DR. TEMPLE: It is not ironic; it is the whole purpose of doing the study. Was it safe to do what we find it useful to do, or were we putting people at risk? Now, you know, we had the Duke data. That was somewhat reassuring a long time ago. But this is a database multiple times larger and it was done solely to see whether it was safe to keep doing what we were doing for a brief period of time.

DR. LIPICKY: Then you are not willing to agree that the zealots this morning were wrong?

[Laughter]

DR. TEERLINK: Lynn brought up one of the points, but to take it actually to another degree, we actually don't know how the placebo group actually performs compared to a free-range human who is not in a trial. So, we are assuming that there is a null effect in terms of just being in a trial so we don't even know that aspect in terms of the baseline rates here as well.

DR. TEMPLE: One more irony I wanted to point out, one of the things we at least think about doing to people who aren't too hypertensive is suggesting that they engage in lifestyle changes and weight loss, not one of which is accomplished in 1 month. That is for sure--or 6 weeks. Yet, that is considered a reasonable thing to do first. So, there must be some intuitive feeling that maybe you have a little time to wait. This sort of tests that question at least a little bit although, personally, I would get them on the drug and then

get them to lose weight.

DR. PICKERING: You wouldn't do that with people with blood pressure of 153/102, or whatever it was in this study.

DR. TEMPLE: I wouldn't do what?

DR. PICKERING: Delay treatment.

DR. TEMPLE: No, I wouldn't. I would just give them the drug and do the lifestyle later but that is not what everybody thinks.

DR. HIATT: I wonder if maybe we should hear the last presentation on interpreting these data. Would you be willing to come back and answer a few questions?

DR. LIPICKY: Sure, any time.

DR. HIATT: Good. Thank you. Dr. Mangano is going to give us another analysis of the data.

Serious Clinical Events in the PHARM Study

DR. MANGANO: Thank you for inviting me. I certainly appreciate it.

[Slide]

I guess the word of the day is orthodoxy, either placebo control orthodoxy, active control

orthodoxy, or dichotomous orthodoxy between those two extremes neither of which I think is a supportable position in the extreme, and orthodoxy in protocol interpretation. My interpretation is simplistic. I have a background in math and physics so I tend to take a physical view toward data. I tend to respect raw data highly. I tend to look at 11 events as 11 events regardless of statistics that are applied and they have to make sense at some integral level.

I am not conflicted. I have never been a consultant or speaker or received stock or owned stock in any medical company. It doesn't mean I am Mother Theresa but it does mean that I am not conflicted.

[Slide]

Here we are. PHARM--you know what it means? Placebo in hypertension and adverse reaction meta-analysis, conceived by Ray, and it had two partners and I represent one of them, which is a non-profit foundation in California. [Slide]

The principal investigators, as we went

into this, were Ray and myself. There is a series of co-investigators, as Ray described. Industry contributed a series of NDAs. This has been a collaborative relationship and the foundation board at least notes that we have given about $875,000 to this project for the employees at the FDA for eight and a half years, and we have almost $100,000 in internal costs. This has cost us about a million dollars. Whoever heard of giving the federal government money? But I constantly argue with my board that it is going to be worthwhile.

[Slide]

This is a minority presentation. It is a literal, per protocol specified interpretation verbatim by word. The protocol is written in cement and we stick to it. Other analyses are mostly hypothesis generating in formal approach. The primary analysis gets nearly 100 percent weight and is the basis for the conclusion. My other bias is that secondary analyses have minimal weight; may provide insight but not basis for conclusion.

The philosophy is that neither placebo

control orthodoxy nor active control orthodoxy is appropriate. Both views discount ethical and methodological complexities of clinical research. Placebo control orthodoxy, for example, discounts reversible events which may portend serious outcome later because they are not heart attacks, stroke or MI at the time. It also discounts others and there are similar criticisms for active control orthodoxy.

I think we should be risk averse, which means that if effective therapies exist there has to be a compelling methodologic reason to conduct a placebo-controlled trial. That is my bias. When effective therapy exists the placebo-controlled trial may be considered if, and only if, placebo-treated patients are not more likely to die, suffer irreversible morbidity which is what most physicians are comfortable with--heart attack, stroke, death that is real but, more than that, and perhaps a substrate for this discussion, suffer reversible but serious harm, which is not reflected in MI diagnosis at the time, stroke diagnosis at

the time, and reported at the time. The last thing that most placebo control advocates eliminate is experience of severe discomfort by the patient.

The working hypothesis for the presentation is when effective therapy exists, placebo-controlled trials are unsafe until proven otherwise, and there has to be a sound scientific reason for their conduct. There are a number of reasons that explain both.

[Slide]

So, let's get to the protocol. The specific aim of the protocol as written was to determine the relative risk of adverse events among patients receiving placebo versus those receiving antihypertensive therapy. The relative risk will be determined for three adverse event spheres, overall morbidity, cardiovascular morbidity and neurologic morbidity.

The protocol defines overall morbidity as cardiovascular or neurologic. Cardiovascular morbidity is defined on the basis of four events, angina, arrhythmia, MI or CHF. Neurologic is

stroke, TIA or hypertensive emergency. None of the adverse events are part of these definitions. None of the adverse events are part of the primary study question, and none of the adverse events are considered primary.

The protocol then states that if the relative risk of placebo to drug is significantly greater than 1.0 in any of the 3 spheres, then reassessment of the placebo-controlled trials for antihypertensive drugs is indicated. Now, it is simplistic to stick to the formal writing but I think it is important to avoid controversy.

[Slide]

Ray did a wonderful job of explaining the methods and has done an enormous amount of work. My job is much simpler here. I am going to focus only on those three outcomes any of which, if occurring, call for reexamination as written in the protocol, and it is going to be a pictorial description. There are plenty of statistics to buttress the findings. Again, I am going to focus on the primary study question to draw a primary

conclusion.

[Slide]

The overall findings, 86,000 patients--

[Slide]

Certainly robust; 93 NDAs and sNDAs, as Ray stated, collected between '73 and 2001; 540 randomized trials; about 20 companies; 86,000 patients enrolled; 9636 patients dropped out, or 11 percent. We base the conclusions on the submission of those dropout reports and their review and on no other information, as discussed.

Over this period of time the patients enrolled in these trials were about 55; 40 percent were women; 30 percent minority; and blood pressures were fairly high.

[Slide]

Significantly high, of course, is the concern that a diastolic of 102--why shouldn't it over a short period of time at least drive an important but potentially reversible finding? The systolic blood pressure mean age, etc., is taken from one of Ray's figures. I won't belabor that.

[Slide]

If you look at the 9600 dropouts and you look for the spheres, that is, cardiovascular, neurologic or cardiovascular or neurologic, then you start to see incidences that are 0.11 percent, 0.05 percent, 0.32 percent for those components of the outcomes. But there is a fair number of events here, as we have noted. Each of these subcategories that we see here--and you can't see all of them I guess--were prospectively defined.

PARTICIPANT: [Not at microphone; inaudible].

DR. MANGANO: Oh, you can't? You probably missed most of my talk. Sorry about that. I couldn't see the slides.

DR. TEERLINK: Can you go back?

DR. MANGANO: Does it go backwards? Let me just go out of there and go back.

[Slide]

For cardiovascular, angina, arrhythmia, MI, CHF all prospectively defined, categorized, blinded. The same thing with TIA, stroke,

hypertensive emergency and death. I know that we could look at these secondarily at this point and question the decision but once driven into cement, we are stuck with interpretation of the data we have, which puts you in a really different position because this is such a large and potentially very important study.

[Slide]

If you multiply the incidence by 100 and plot it you get numbers like this with all the actual numbers and you know what they are. But what is important here is that this outcome here, cardiovascular morbidity, neurologic morbidity and combined cardiovascular and neurologic morbidity are the three spheres which will determine whether or not the primary endpoint has been met.

[Slide]

Now, there are other AEs, as has been talked about, other cardiovascular events--ventricular tachycardia, 8 patients; therapeutic failure; other adverse outcomes and administrative but none of these is part of the

primary definition. Simplistically, I am going to ignore them.

[Slide]

But they do occur, as one would expect rather frequently, more frequently relatively than the others.

[Slide]

What about the difference between groups? The placebo population represented 25 percent of the patients; the drug population or active treatment represented 75 percent of these patients. There was a 14 percent dropout rate in crude numbers among the placebo patients and a 10 percent dropout rate among drug patients, active-treated patients, and these were significant. Nearly everything is significant, as I will indicate.

[Slide]

So, let's examine the three components of the primary endpoint, if you will. If any are satisfied, then we revisit the entire question.

[Slide]

What we see here are the numbers in terms

of primary incidence times 100 but, in effect, they tell a story. The story is fairly clear that with respect to cardiovascular morbidity there really isn't a difference between these two populations crudely. Whereas, with respect to neurologic morbidity there is a difference, and with respect to combined there is a difference. And, all of those are appropriately statistically significant even with comparison taken into account.

Now, these are not unexpected because if you look at some of the short-term effects of lack of blood pressure control, especially going back, you realize that heart failure more than infarction is likely to occur, I believe, by short-term exposure to high blood pressures and then the primary is stroke or papilloedema, etc. with respect to short-term. So, these are not unexpected in terms of what we find.

[Slide]

If you look at the relative risk, the ones in red are significant and again what we find is, of course, that there is no difference between the

groups for cardiovascular but for neurologic and for combined there is a difference between the groups.

[Slide]

That is the conclusion, that two out of three of the categories demonstrated a difference and, therefore, two spheres satisfied the criteria formally and, therefore, placebo-controlled trials must be reassessed, and they are not safe according to the predefined criteria.

[Slide]

There is another argument made and Ray has done a wonderful set of analyses and he has tried to find out the real answer here. Putting aside this approach which is fairly simplistic and easy to make, he is looking at the body of evidence and trying to make sense out of it, and he should be applauded.

Equipoise is justified on the basis of these findings if you consider all 13 adverse events that were coded, the majority of which suggest equipoise--no difference between placebo or

treatment. That supports equipoise. As well, there is a balance between the first two that arithmetically at least or in balance supports equipoise.

When you look at all dropouts you can make the argument that it looks like this doesn't support equipoise but, in effect, what you see is that is driven by treatment failure. So, you could even make an argument that we could exclude this, in some sense, when we look at this picture. Well, when you do that you are left really with only two sets of events that you become concerned about. By putting aside the protocol design considerations which I believe are substantive, you are left with other cardiac events and hypertensive emergencies leading to what I did in terms of trying to understand that balance. Are they arithmetically in balance? If you weigh them up you are going to wind up with equipoise again. But if you just took these as a post hoc secondary look, which was not previously described, are they truly in balance, which forms some of the basis for some conclusions

that might be drawn.

[Slide]

So, are they in balance? The answer is yes. There are 526 hypertensive emergency or other cardiovascular events in the drug group, leading to an incidence of 0.86 percent and, therefore, equipoise is the conclusion if you put aside study design considerations.

[Slide]

So, the conclusion is equipoise. But and I have two but's and then I will be done--the primary endpoint components were not all of these but were only these and they were joined in specific manner in terms of investigating the study question. They were not looked at or designed to be looked at individually. Other cardiac events were excluded from primary definition so the question is should we be even balancing those against hypertensive emergencies formally.

I am going the wrong way again. I am probably going to give you guys a seizure, but it won't be counted because it is not a stroke! I am

still going the wrong way. I hate this. I am almost there. I am Italian, it takes me a long time.

[Slide]

Are they comparable, hypertensive emergency and other cardiac? Even though other cardiac was not prespecified, let's go through that. They are certainly not comparable prospectively because one of them was not included in the prospective definition so we really have no prospective right to analyze that or draw conclusion from that.

[Slide]

Putting that aside, the severities may be different. If you look at hypertensive emergencies and you score these emergencies--and there is a scoring system that is there--you will find out there is a distribution which looks--it is a reasonable scoring system, it was blinded--that looks like this. And, for all other cardiac the scoring system looks less severe. In fact, hypertensive emergencies, in terms of a blinded

severity assessment, look like they are more severe in general than other cardiac and maybe we were not balancing on noise with signal, for one.

[Slide]

So, a scoring system was developed. I won't belabor that, but for hypertensive emergencies we went through a routine. What is important to know is that 6, 7, 8, 9, 10 all employ hypertension plus involvement of one or more organs--brain, heart, eye or kidney. Below that it is sort of a wastebasket with no obviously end-organ involvement.

[Slide]

Similarly, when you get to 6 and above with other cardiac events, you don't have minor symptoms but you have ischemia, stupor, loss of consciousness, 2-organ ischemia, documented MI, stroke and up to death. So, 6 and above in both of these seems like severe events.

[Slide]

So, when you look at hypertensive emergencies and you contrast them, then for all

hypertensive emergencies the placebo risk is about 2.5 to 3 times the drug risk in terms of a hypertensive emergency, and when you look at severe events it is still about 2.5 times and that has been consistent.

When you look at other cardiac overall you find out that it is better to receive placebo. But I maintain that is mostly noise, that there are only a series of events which implicate end organ and in that case placebo carries 2.5 times the risk.

So, I would argue in post hoc secondary analysis that both the cardiac events and hypertensive emergencies when involving another organ, that is, when serious, indicate that the placebo control is dangerous.

[Slide]

So, the arithmetic balance between other cardiac and hypertensive emergencies argues for equipoise. Two arguments discount the inference. One is that the arithmetic balance analysis is a secondary construct and is not prospective. Given

that, severe events likely have short- and long-term physical consequence. The findings for both severe hypertensive emergencies and severe other cardiac support the hypothesis that harm is associated with placebo-controlled trials for hypertension.

Given that the primary hypothesis was satisfied, namely that the relative risk was significantly greater than 1.0 for 2 of the 3 spheres, then I still conclude that reassessment of placebo-controlled trials for antihypertensive drugs is indicated.

[Slide]

Thanks.

Committee Questions on the Presentation

DR. HIATT: We need to clarify a few things. Let me just start with could you or Ray please clarify what the primary endpoint of this study was? Because Dr. Lipicky said it was all-cause dropouts and you are saying there are three spheres, cardiovascular, neurologic and combined. That sounds like different primary

endpoints.

DR. MANGANO: I have the protocol.

DR. HIATT: Well, I just wanted to get some clarity.

DR. LIPICKY: Well, I must admit I haven't read the protocol since 1991. But what you are saying, Dennis, is an absurdity.

DR. MANGANO: Me?

DR. LIPICKY: Yes. That could never have been the primary endpoint but I am willing to look at the protocol if you wish, and I can tell you that I guided the analysis and you don't see combined something or other. This is the slide you showed. Why did I not do that? Why did you not, four years ago, say where is that?

DR. MANGANO: Your primary endpoint and the primary endpoint quoted in the protocol are very similar. I am not arguing. I was asked to present a minority point of view.

DR. LIPICKY: I understand. What you are placing in jeopardy is any interpretation of anything at all by saying the protocol was

ambiguous. I don't think it was. I don't think it ever thought that there was anything to look at in those things that were recorded in the overall primary dropout rate. And, if there is some place where it says two out of three of these things will make a primary endpoint positive, you will have to show me that.

DR. MANGANO: I will. I just quoted from the protocol.

DR. HIATT: Before we go too much further--

DR. MANGANO: But, you know, if I am wrong about the protocol I would be happy to retract everything I said.

DR. HIATT: Can you shed some light, Bob?

DR. TEMPLE: I am sure I can't shed light but I have a crucial question. I think Ray said in presenting it that we thought that hypertensive emergencies would in general be accompanied by something that was physically bad. You know, there would be a description of something that looked like the patient was going to lose it, but that in

a very large number of cases it turned out that there wasn't anything like that. So, the reason it was considered a hypertensive emergency apparently had to do with the blood pressure and nothing much else so that for the hypertensive emergencies, if I understand it, people went through the description of events and decided whether one of these events had happened and, if it did, it would have been called a stroke or a TIA, or whatever it was. But in the absence of that, they concluded there was nothing that was looking irreversible.

What I can't tell, Dr. Mangano, from your analysis, apart from the fact that you just wanted to count hypertensive emergencies because you believe that was part of the protocol and I have no idea what the protocol said, there is still the question of what these events meant to the patients and whether there are, in fact, things that we should be worried about or not. It seems to me that everything turns on that question.

DR. MANGANO: Well, I agree, but once you say that you are going to do it in a blinded

fashion, before the database is unlocked, and you are going to take the coding, good, bad or indifferent of hypertensive emergency and make it a component, if it truly is, of an outcome you are stuck with it.

Now, in the interpretation and the recommendation you can throw all of this out and come up with a conclusion that when you look at these events multiple ways it seems reasonable, with all of the arguments that Ray elegantly listed, that these trials are safe. I am taking the rather trivial point of view--trivial in explanation, that from what I have read in the protocol that I have these were the events and I merely arithmetically tabulated them.

DR. TEMPLE: Okay, but having said that, my understanding--correct me if this is wrong, is that the nature of the event was described before there was any unblinding; that was all done blind. Isn't the most important question what those hypertensive emergency events really were? If they were ominous things then, of course, you should

count them. If you can't figure out why they even thought that is what it was and there was no stroke, nothing irreversible, nothing, then whatever the protocol said, how much should you make of it? It doesn't sound very meaningful. I think that is what the committee has to grapple with.

DR. MANGANO: Well, if you divide the hypertensive emergencies into those involving an organ versus not you still come up with that number. But I don't know how much latitude you have after the fact to go back and start discounting part of an endpoint because it doesn't make sense. But in a discussion of that and the presentation to the community all of those issues, as Ray raised them, can be made. These are two divergent points of view and I didn't mean, Ray, to say anything but--

DR. LIPICKY: No, no, I understand but let me offer three things and see if you agree or not. There are three discussions going on. The first discussion is whether there was a principal

endpoint that is like I declared or as you declared, and that is, would two out of three make it.

DR. MANGANO: Well, any of the three was the way it was written in my version of the protocol, not two out of three.

DR. LIPICKY: Well, what it says is what is the relative risk of adverse clinical events, especially serious cardiovascular events, for subjects receiving either placebo or antihypertensive medications. There is no two out of three or one out of three--

DR. MANGANO: No, no, no, it is any of the three.

DR. LIPICKY: No, it doesn't say that. I just read it.

DR. MANGANO: No, there is another page--

DR. LIPICKY: Hold on, hold on. I can assure you that the primary endpoint in the conception of the people who were gathering the data and who did the primary analysis was are there more dropouts on placebo than other. We never--and

in fact we have a bunch of power calculations before the study--anticipated we would be able to make a decision with respect to death or stroke or something like that individually. And, there may be something in reading the protocol that says maybe combined we might make it but that was never considered to be the principal endpoint. So, I think we are in the multiple comparisons problem. The only real endpoint was did more people drop out. That is point one.

Point two is there is a difference with respect to hypertensive emergency. The analysis that Dennis did says that people who were in the hypertensive emergency category were sicker than people who were in the OC category. I agree with that. I have no problem with accepting that. There were more hospitalizations and more ER visits, and so on and so forth.

But the alternative is looking at the net number of people affected by dropping out and I think dropping out of the study is a big deal. People don't do that lightly. The net with

hypertensive emergencies is still that more people dropped out on drug than on placebo with hypertensive emergencies included. Without hypertensive emergencies included, the net was even much better.

DR. HIATT: Ray, just to clarify that statement, I thought the primary endpoint presented in the material we read was total dropout favors placebo.

DR. LIPICKY: Correct.

DR. HIATT: Not the other way.

DR. LIPICKY: Pardon?

DR. HIATT: Not the other way. Total dropouts were more common on placebo than on drug.

DR. LIPICKY: Yes, correct.

DR. HIATT: Okay.

DR. LIPICKY: Overall, but clearly that comes from the "other" and therapeutic failure.

DR. HIATT: Right. Just before we continue on this too much, your terms and your background I think were pretty clear. There were some subcategories that were shown here that you

presented as well. I would like some clarity on what the cardiovascular morbidity is. Could you give us a definition? Is that on a slide? What the components are? DR. MANGANO: It is arrhythmia or MI or CHF. I can get the protocol.

DR. PICKERING: But it was on one of your slides. You listed all the components.

DR. TEMPLE: Right, but for that category the drugs were similar in any event.

DR. HIATT: But I still want to see a list of what is in the category.

DR. TEMPLE: All the difference arises from, quote, neurologic morbidity but that is because it includes all the hypertensive emergencies.

DR. HIATT: Got it.

DR. TEMPLE: So, that is what leads me to wonder what should we make of hypertensive emergencies as the crucial question.

DR. HIATT: This is converging for us a little bit.

DR. TEMPLE: Yes.

DR. HIATT: Okay. We are seeing two diametrically different conclusions from the same data set.

DR. LIPICKY: That is the problem because I could put this data together any way you would like to have it conclude.

[Laughter]

That is the problem.

DR. MANGANO: You are not allowed to do that.

[Multi-member discussion]

DR. LIPICKY: But I didn't. What I said was I am going to look at what our primary endpoint was and do more people drop out on placebo or not. For the other things I am going to look at from the vantage point--

DR. HIATT: Let's sort of keep a little order here.

DR. LIPICKY: --of what is statistically significant because we had a whole bunch of endpoints and some statistically significant things, and tried to explain how to interpret those

events that were found. Then as a retrospective endpoint that came at the very end, after everything else was done, we looked at a conventional endpoint and that was irreversible harm, CVA, death and MI. That was never an endpoint--ever an endpoint.

DR. TEMPLE: It still seems to me the question is have the people on the placebo group been harmed in some way by being on that group? One set of things to look at is death, stroke and MI but Dr. Mangano is raising the question that there are other things that aren't in those categories that can be found among the people who have hypertensive emergencies that should be taken almost or as seriously. It seems to me that is the fundamental question because there plainly were more of those people in the untreated group. So, we know that. The question is what are those things and do they matter, either because they are harmful on the spot or because they predict something terrible later, or whatever reason? I must say I don't really care in this case what the

primary endpoint was too much because I think that is the question whatever the primary endpoint.

DR. MANGANO: That is your interpretation of evidence. The evidence is written as the protocol, period. Then in interpretation you can evoke all of these other analyses to come to whatever bias you want or however you want to look at it but they are two different questions. One is what does the protocol say; what is the result and what is the physical data and what is everything else.

DR. TEMPLE: But if you are doing your retrospective analysis and you are all still blind and it turns out that there is no description of anything in most of the people with hypertensive emergencies, I think you are entitled to say this doesn't tell me anything.

DR. MANGANO: I don't know if that is true.

DR. TEMPLE: I don't know if it is true either. That is what I am saying is the question. But if that were true, it would be crazy to

redefine an endpoint, especially if you are still--

DR. MANGANO: You mean after the fact redefine it?

DR. TEMPLE: You are still blind actually.

DR. MANGANO: No, you are not. You already know that hypertensive emergency makes a placebo-controlled trial, triggers it to be unsafe. You can't turn that around.

DR. TEMPLE: Sorry, we don't know whether they are in drug or placebo.

DR. MANGANO: Yes, but you can do that with all of the other events.

DR. TEMPLE: All this other stuff was done before it was unblinded. You don't know which patient is on which drug. You might guess I suppose.

DR. LIPICKY: Dr. Hiatt, do you have the protocol in front of you?

DR. HIATT: Yes, we are trying to take a quick look and listen at the same time.

DR. LIPICKY: Is it the same protocol I have?

DR. HIATT: I don't know.

[Laughter]

DR. MANGANO: That is the problem. Most of the hypertensive emergencies had end-organ damage.

DR. TEERLINK: Bill, could I ask you a question?

DR. HIATT: Yes, ask a simple question, please!

DR. TEERLINK: This is very simple. You know, this is actually helpful to see because I actually got the impression that those 251 hypertensive emergency stuff we had no information on but it looks like there was actually information in regards to these patients. So, how was it determined that end-organ damage was there? For example, if someone had diabetic nephropathy starting out with a creatinine of 1.5, if in the case report form it says, you know, blood pressure goes to 200/110 and their creatinine is 1.8--

DR. MANGANO: There is no way. You are looking at one point in time. It is listed as do

you have a symptom referable to one of the other four organs or don't you, regardless of what you brought in and what you didn't, and you are stuck with the endpoint.

DR. TEERLINK: Well, I am just trying to think of how it was constructed.

DR. MANGANO: Oh, a single shot in time.

DR. TEERLINK: Right. So, actually, when you are saying end-organ damage this is not because what we think of as a hypertensive emergency as papilloedema, creatinine going through the roof, the kidneys are shut down and they are having, you know, coma or obtundation--

DR. MANGANO: That is extreme injury.

DR. TEERLINK: Right, but it looks like, from the distribution, that most of it is put in as one organ damage, and if that is just the creatinine having been bumped because that person has hypertension and diabetes or because they have something else, we don't know whether that was an acute change related to the withdrawal or whether that was a preexisting condition. Is that correct?

DR. MANGANO: Correct. There are limitations with that endpoint--

DR. TEERLINK: Of course.

DR. MANGANO: --and there are limitations with all of them and, simplistically, you are stuck with a simple approach.

DR. PICKERING: Could I make a comment while you are searching for the protocol?

DR. HIATT: I have it but go ahead.

DR. PICKERING: I commend you for funding this study and, you know, we respect what the original protocol said but I have a major problem with the classification of morbid events. On the cardiovascular side you have included arrhythmias which is a very nonspecific term and may be perfectly benign but, more importantly, this issue of including so-called hypertensive emergencies as a neurological event and giving it the same weight as stroke I think is entirely inappropriate and potentially quite misleading because, as I understand it from what Ray said, if your diastolic pressure went up by as little as 10 mmHg that could

constitute a hypertensive emergency, and it may be that the protocol has dictated that if that happened you should consult your doctor or go to the emergency room. But the inherent variability of blood pressure means that is going to happen very frequently and it is obviously going to happen more frequently in the placebo group because they tend to have slightly higher blood pressures. So, it has a completely different significance from a TIA and a stroke. So, I basically don't accept the validity of this analysis.

DR. MANGANO: So, if that were a protocol-defined definition would you argue after you have seen the data to remove that component, or aren't you stuck with it?

DR. PICKERING: Well, I didn't design the protocol but I wouldn't have included--

DR. MANGANO: Oh, okay.

DR. PICKERING: If you look at the classification of events in clinical outcomes trials, I think you won't find hypertensive emergencies in there because it is generally

regarded as a soft type of event as opposed to something like a stroke or, to a lesser extent, a TIA.

DR. MANGANO: The argument in favor of the position would be that diastolic blood pressure of 110 is something that may not portend a stroke or a TIA immediately but over some period of time for some patients may portend a serious outcome over weeks. So, we are looking at very hard physical events but the results of a group of people who argue that reversible but serious events that don't portend immediate outcome maybe should be included in the argument for and against placebo control.

DR. HIATT: Let me try to just pause for a second. There are two versions of the protocol--

DR. MANGANO: Oh, no!

DR. HIATT: Let me just try to clarify this. One is '97 and it says that the primary question is what is the relative risk of adverse clinical events, especially serious cardiovascular events for subjects receiving placebo or antihypertensive medicine. So, adverse events,

especially serious cardiovascular.

The protocol you gave me, which is a year later, says that PHARM is to produce a meta-analysis of all deaths and dropouts that occurred during the conduct of randomized, placebo-controlled trials, which I think is consistent with the overall concept that it is overall dropouts with a focus on serious cardiovascular.

In this same version of the protocol the statistical analysis does include the analyses you showed us as primary analyses. So, I think the overall contention of PHARM was, as Ray stated, that there are a number of analyses proposed to evaluate that which includes serious cardiovascular. I think the one thing that we are all sort of wrestling with is whether hypertensive emergencies are serious cardiovascular or not.

DR. MANGANO: But the standard plans in both those protocols say exactly the same thing, which is what I have quoted.

DR. HIATT: The committee I think will

have the opportunity to really kind of wrestle with that information.

DR. LIPICKY: The statistical analysis plans include a lot of things like analysis by age, gender and stuff that wasn't done because it was ridiculous to put in to begin with. So, I think we have to resolve this. Either the protocol was as I said it was or the protocol is as you said it was, and the committee has the protocol.

DR. TEMPLE: I just have one comment on changing endpoints--

DR. MANGANO: It is not you and me, Ray.

DR. HIATT: Let Dr. Temple talk.

DR. TEMPLE: Even in a randomized trial, if you are unblinded you are allowed to change the endpoints because of external information. David can talk on this at length, I am sure. One of the reasons we want steering committees blind to the data while the data monitoring committee looks it over is so if they get smarter they can actually change the endpoints. If these changes, if there indeed were changes, were made without knowledge of

how they would affect the outcome there is nothing illegitimate about that. If one of the things you discovered is that your descriptions of hypertensive emergencies frequently included too little data to interpret so that you were obliged not to just to count them but to read them and conclude something from them, there is nothing inherently inappropriate on that or biasing about that as long as you were blind. If you were not blind anymore, it would raise a different set of questions.

DR. MANGANO: That is a slippery slope, isn't it?

DR. TEMPLE: No. We allow this all the time. We have discussions about it. But you can change a protocol if you are blind if you are persuasively and convincingly--

DR. MANGANO: If you are blind?

DR. TEMPLE: Yes.

DR. MANGANO: Oh, yes, I agree completely.

DR. TEMPLE: Well, these were all analyzed blindly.

DR. MANGANO: I completely agree.

DR. LIPICKY: The second point I want to make, having sat on the events committee, is that if someone had a headache and a change in diastolic of greater than 10, it was a hypertensive emergency. If someone had a nosebleed and a diastolic of 110, it was a hypertensive emergency. We had hypertensive emergencies in the database. The point estimate that is represented is incorrect. If it is an exaggerated point estimate the confidence will be wider. We are, in fact, stuck with hypertensive but we made a mistake. We are stuck with that. It is a statistically significant finding. I think it should be regarded as part of the continuum of therapeutic failure. That is point one.

Then, the last thing is that if you look at the net dropouts, omitting administrative and therapeutic failure, with hypertensive emergencies in it, it still favors being randomized to placebo. So, I don't think the hypertensive emergency thing needs to have a lot of attention paid to it. It

was there. In part it was ignorance. And I don't know what to do about it.

DR. HARRINGTON: Ray, I want to ask both you and Dennis the same question. In the analyses from the events committee on hypertensive emergency, if you had had a change in blood pressure greater than 110 diastolic and you had a stroke or myocardial infarction what would you code it as?

DR. LIPICKY: Stroke or myocardial infarction.

DR. HARRINGTON: So, you did not get counted twice?

DR. MANGANO: No.

DR. LIPICKY: That is correct.

DR. HARRINGTON: In your analysis, Dennis, is that the same?

DR. MANGANO: It is the same definitions. This is nothing new, this analysis. It is exactly the same data.

DR. HARRINGTON: Using the same data, you didn't go back--

DR. MANGANO: No.

DR. HARRINGTON: --and re-look at things?

DR. MANGANO: No.

DR. HIATT: Let's just go around the committee and ask if there are any other points of clarification around what you have seen.

DR. STOCKBRIDGE: I would just like to point out one little thing. Of 279 hypertensive emergency events that were declared in here, in two-thirds of them the end-organ damage that was claimed was a headache.

DR. LINCOFF: Which raises the question of the 63 that are left--maybe it is in here but I don't see the distribution between the two groups.

DR. STOCKBRIDGE: It is in the same paragraph that you have in front of you. It is the first few things that are described there.

DR. LINCOFF: Not divided by treatment.

DR. STOCKBRIDGE: Oh, by treatment? No, I don't know that.

DR. LIPICKY: That is correct. I don't have that data.

DR. HIATT: That is I think a very relevant question though.

DR. LIPICKY: Well, I mean it is a foregone conclusion that it is going to be bigger in placebo. What do you want to know? The point estimate? And you want to know the p value? How the hell am I going to calculate that? It was totally retrospective and everything else will have no inferential meaning. It is going to be higher on placebo. I don't know what the numbers are. I haven't done the analysis but it is safe to say it is going to be higher.

DR. LINCOFF: Well, that may be if you look at the hospitalizations but it is not that much higher. The hospitalizations are 10 fewer. You have 63--

DR. LIPICKY: No, I hear you and I don't mean to be argumentative. It is just that I don't have the number.

Questions to the Committee

DR. HIATT: I am going to ask if we are all comfortable moving to the questions. Yes?

Let's do that then. I guess we need to project the questions.

The committee is being asked to opine on the continued use of placebo in studies of antihypertensive drugs. If antihypertensive drugs, regardless of class, can be expected to reduce death and stroke, and possibly myocardial infarction and other irreversible outcomes as well, how can it be ethical to continue the current practice of including a placebo control in studies of new agents?

1. To address the risk, there are two meta-analyses. The first was conducted by Dr. Al-Khatib and colleagues and based on published reports of placebo-controlled trials. Combining death, stoke, MI and congestive heart failure among 25 trials, they found a net placebo-active difference of 0, ruling out a difference as high as 0.6 per 1000 patients enrolled.

1.1 Assuming these trials were on the order of 8 weeks duration, the upper limit corresponds to about 0.1 per 1000 patient-years,

which is considerably smaller than the benefit of treatment is expected to be. How can you explain that? Any clarification of this question?

[No response]

Who would like to start on this one?

DR. TEMPLE: Yes, I don't understand the question. The benefit is from long-term studies.

DR. HIATT: Right.

DR. TEMPLE: Why would you expect anything like that in an 8-week study.

DR. HIATT: I don't know either.

DR. STOCKBRIDGE: Well, that might be the explanation for it. But, you know, if you thought that the risk, was constant over time this is much smaller than what you think you should have gained.

DR. HIATT: Norman, you are saying there should have been a detectable treatment effect?

DR. STOCKBRIDGE: I am just saying there wasn't one so I am just asking what anybody thinks the implications are.

DR. HIATT: All right. Why don't we start over here?

DR. LINCOFF: I think the implications are really related just to infrequent events in such a short observation period and such an unstable estimate, in addition to perhaps other factors such as publication bias and which trials have enough data. This study had a lot of limitations in terms of which trials had to be eliminated, not as methodologic error but just because there wasn't data. So, I think there are so many reasons why this number would be so unstable you can't draw much from it.

DR. HARRINGTON: I agree, and one other point is if you look at the Science paper and the ratio plots, there are only four of the trials of all of them that actually had a difference in events, meaning that the events actually occurred in only four of the trials. So, most of the trials contributed no information, zero versus zero, or limited information. I agree with Mike. This is an exceedingly low risk population, followed for a very short period of time, and I think that the estimate is probably not reflective of the truth.

DR. TEERLINK: As above people.

DR. HIATT: So, we are all saying it is simply under-powered to detect a difference.

DR. STOCKBRIDGE: Wait a minute. You have an estimate that is on the order of 0.1. That is the upper limit. Are you saying you don't believe that, or that there is something else going on--low risk population or whatever? So, that is not what you would get in practice. That is different from I don't believe the upper limit that was estimated.

DR. HARRINGTON: I think if you take an upper limit of essentially zero you get a very low upper limit. So, I think, Norm, that the very low upper limit is largely driven by the fact that these are exceedingly low risk patients who were followed for an exceedingly short period of time, and the observation is probably not reflective of the truth.

DR. STOCKBRIDGE: Again, truth means it is not--

DR. HARRINGTON: It is not reflective of prior experience.

DR. STOCKBRIDGE: --reflective from practice. But you believe there is an explanation that has to do with duration of trial and the underlying risk factors in the population that was studied?

DR. HARRINGTON: Yes.

DR. HIATT: Bob, just to clarify that, you believe that there is a treatment benefit in that short time, but we just couldn't see it?

DR. HARRINGTON: I think that you can't rule it out, just can't rule it out.

DR. TEMPLE: Well, you can't rule it out but don't you have to consider one possibility, that in that short a time there isn't one?

DR. HIATT: Right.

DR. HARRINGTON: Sure.

DR. TEMPLE: I mean, I do remember what I was taught--this was a very long time ago, that if you see someone with a high blood pressure, bring them back in three weeks and see if it is still elevated. I mean, that expresses total indifference to three weeks or six weeks, or

whatever it was. So, I don't know that anybody really could know whether there is a benefit from a very short period of treatment. I mean, I don't know.

DR. LINCOFF: There is no question that clinical trial populations are not necessarily reflective of populations in practice. So, this is a low risk group. It is the kind of group that helps to determine if a drug has an antihypertensive effect but you wouldn't necessarily want to extrapolate this into clinical practice. Nevertheless, you can extrapolate the results to say that when I do clinical trials with this kind of population of patients would I expect a very low event rate. I think that is realistic.

So, I don't think it necessarily means we don't trust the results or believe the results, but we don't think that they are necessarily extrapolatable to the general population of patients.

DR. STOCKBRIDGE: But that is okay. Right? I mean, the thing I care about is whether

you believe that the 0.6 is, in fact, a reasonable upper limit for participating in a trial. I think I have heard you say you do believe that 0.6 is a reasonable estimate of what the upper limit for the risk is for participating in a trial.

DR. WARNER-STEVENSON: I think one of the flaws here is assuming that you can take a lot of one-month blocks and add them up to make a patient-year. So, I think the issue of the risk per patient-year is not necessarily going to be some multiple of the risk for one month.

DR. HIATT: Let's keep going.

DR. FINDLAY: No comment.

DR. HIATT: No comment? The question is 1.1., assuming these trials were on the order of 8 weeks, the upper limit of 0.1 per 1000 patient-years which is smaller than the benefit of treatment is expected to be, as we just heard discussed. How do you explain that?

DR. PORTMAN: Let me think about it.

DR. HIATT: Okay.

DR. PICKERING: I would say the

implication is that short-term trials in people with mild hypertension, placebo-controlled trials are still justifiable.

DR. DEMETS: My comment is that in the first one that was presented we went from 267 studies published down to 80. I don't know what that does. I mean, there was a terrible winnowing and then among the 80, as you already pointed out, there was a very small number of events. Small numbers are not terribly trustworthy. So.

DR. HIATT: So, you can't interpret those numbers? Is that what you are saying?

DR. DEMETS: You know, given all the potential selection that is going on there, I don't know what that represents.

DR. TEMPLE: Can I ask is there any reason to think there is selection that is related to any of the things we are trying to look at? I mean, it is not clear in whose interest it would have been to do this. This goes to publication bias so it seems unlikely anybody was even thinking about these things when they decided to publish. It

reduces the numbers, for sure, and that is a liability but does it really imply bias?

DR. DEMETS: Neither one of us knows the answer to that, I don't think.

DR. FLACK: Well, after listening to this conflict and stuff, and I will tell you this stuff is not theoretical to me because I see these patients when you take them off their drugs and see them come back in, and all, and I would not dismiss blood pressures going up as being inconsequential. But I think we are really sort of left with a lot of maybe hard endpoints but a lot of things related to sort of patient well being, and all. Those patients many times do not do well when you take them off of a bunch of drugs.

My cutting through all this, I mean there are a lot of arguments and some of them I don't quite understand, but the bottom line to me is that I think the FDA is going to have to issue some guidance about who is suitable, for how long a period of time based on baseline blood pressure control, or something--who is suitable for a

placebo-controlled trial. I think we are making a huge mistake if we don't take some of this data and really try to come to grips with that.

I do not feel comfortable after all these years and after all the trials we have done that we are just going to throw our hands up and say, you know, it is okay to do trials because we looked in aggregate and we didn't see much risk. I will guarantee you there is heterogeneity of risk in this data by baseline risk. It is not constant even within the short time frame. If it is, I would be shocked.

It makes it a little bit more different but it is also a strong signal that we learned something and we are putting patient safety at the appropriate level. I think eventually our IRBs are going to really start balking at placebo-controlled trials, and they should based on some level of baseline risk.

DR. HIATT: Maybe it would be helpful as we go through these questions to think about, first of all from what you have seen, does the evidence

in the populations that were studied suggest risk. If the answer is no, that might lead you to one conclusion. If you think the answer is yes, then it might help to define further what that risk is and maybe we can get to that in a bit.

DR. STOCKBRIDGE: I would like to get John to answer the question that was asked.

DR. HIATT: Right, that is what I was just going to ask him to do.

DR. STOCKBRIDGE: You know, you can at the end of all of this tell us we should still be worried about using placebo. That is fine. But right now you have a set of data that Dr. Al-Khatib presented to you that suggests that the risk is no worse than about 0.6 per 1000 patient-years. I am asking you whether you think that is a reasonable estimate and whether you believe that.

DR. FLACK: I think that it is probably an under-estimate and I will tell you why. I think that in a lot of the trials at the time that this was done people whose pressure shot up, and all, didn't even end up making it onto a randomization

scheme. I think that if there is anything that I would say, it is probably biased toward a lower risk group of people. I think more contemporary trials now randomly allocate them to active therapy immediately and, unfortunately, in some of the trials to inadequate therapy for too long a period of time, and they get these goofy results early on and then they start telling doctors they need to get blood pressure down really, really quick.

I think it really boils down to the fact that you have to have criteria about who you are going to take off drugs, at what level of control and how many, and put them either on a placebo and for how long, or even on monotherapy for a period of time, and all. So, I think it is an underestimate and I don't think it is real. It is an interpretation of data and I just don't take that at face value.

DR. STOCKBRIDGE: But most of your concern then arises because no one here is talking about the risk during the withdrawal phase?

DR. FLACK: I think the risk during the

withdrawal phase in some of the older studies is potentially substantial. I mean, I have seen these people. You take them off drugs and if you don't really put caps on how many these people are miserable and awful. Their pressures are going up and they are hidden because they never make it to the trial because many of them fail on blood pressure.

DR. PORTMAN: Did you want me to comment?

DR. HIATT: Yes, please. Are you ready to?

DR. PORTMAN: I think the study is in a mild population, but answering the question as Norm puts it I am relatively convinced that the placebos are safe. I think you have to have them, particularly in the initial efficacy trials. In pediatrics we have kids who are on therapy. We withdraw. We never know. We take them off therapy, their blood pressure never goes back up. We have the Trofi study that just came out that tells you that a lot of patients are put on therapy for a period of time and when you withdraw them

their blood pressures don't go up. So, I think you have to have placebos.

DR. FLACK: That is not the case though in the adult studies. Adult studies have looked at this over a long period of time and even though everyone's pressure doesn't go back up immediately, the majority of people do become hypertensive again unless they make major lifestyle changes.

DR. PORTMAN: But Trofi is an adult study.

DR. FLACK: I am just telling you that there is plenty data and even if a substantial number of people's pressures don't go up, and it is probably not a huge number, a lot of people's pressure does go up and it goes up rather quick.

DR. HIATT: I think these are fairly general concepts that we need to kind of wrestle with. I guess I am wondering if it wouldn't be helpful if we went through some of these questions and came back to how would you manage--if you thought that it was acceptable to do placebo controls what would your boundaries be? Let's stay with you, John, and ask these next questions around

the publication. Do you think there is publication bias of the component studies? Do you have any questions about effectiveness of the agents used, and other adverse effects not part of the endpoint?

DR. FLACK: Publication bias, I don't know. There is certainly some filtering, whether the filtering is created in a systematic bias I honestly don't know.

The effectiveness of the agents employed, no, I have much more concern not about the agents themselves but the populations that are potentially exposed to them where people probably had no chance of ever being controlled with monotherapy. In clinical practice I would never have taken them off of multiple drugs to enroll them even on a single drug, let alone a placebo-controlled trial.

And, the adverse effects not part of the endpoint, not really. I don't discount the blood pressure rises much. I also think that the problem is we are missing some of the problems that are occurring before the patients ever get to the trials.

DR. HIATT: David?

DR. DEMETS: Well, I have already commented I guess about my concern about publication. Do you want me to answer the rest of 1.2.?

DR. HIATT: Please answer the rest of them.

DR. DEMETS: Well, I have no idea about the agents employed and about other adverse events. I just think that we have a small series of small studies and so I don't put much emphasis or weight on this.

DR. PICKERING: I guess I would say no to all three of those components.

DR. PORTMAN: I agree.

DR. KASKEL: I agree.

DR. FINDLAY: Yes, ditto.

DR. WARNER-STEVENSON: My only concern is with the adverse events before and after the placebo period that we are actually measuring.

DR. HIATT: My concern about publication bias is just the very narrow window of studies

chosen, and I think PHARM says that there may not be a huge difference in people who respond to placebo over time. But this I think is a narrow snapshot.

DR. TEERLINK: Both Bill and Lynn brought up the only two additions I was going to make in terms of the concerns about events before and after, as well as the slice of time. I think these are all issues that need to be considered. Taking them into consideration though, I don't think they would have altered my interpretation of the results.

DR. HARRINGTON: Yes, I think that for me is the key point. I do think there is an issue with all of these, the winnowing or filtering, as it has been called; the low risk nature of the population, which may not have allowed the effectiveness of the agents to come through; and missing both the entry and the departure data. It is reassuring to hear that that is more typically done today but it is a limitation of the study. But I don't think it changes my overall view of the

study.

DR. LINCOFF: I have nothing to add to that. I agree entirely.

DR. TEMPLE: Just one question. I want to understand the concern. If you thought during the withdrawal period the people were about like they were when you didn't give them treatment during the randomization phase you wouldn't be particularly worried. You would see the same thing during the randomization phase. Is the concern that there is a subcategory of people who deteriorate much more rapidly never get randomized because of that and you don't have any data on them? So, one remedy for that in the future perhaps is to find out more about the enrollment period.

DR. FLACK: Yes.

DR. TEMPLE: People would have to tell us but it is not included in this systematic analysis about bad events during that period. If anybody died or stroked we would be obliged to be told but we don't have that as part of the analysis.

DR. FLACK: Speaking from memory, I

think--I may be wrong but I think that we now actually looked at some of this. I may be wrong, but I think there is an analysis out there that talks about this. I know it is one major trial.

DR. TEMPLE: Oh, there may well be but we didn't have it for this analysis.

DR. FLACK: I understand but I see these patients and I know that we are not really capturing a lot of the misery some of these people go through when you withdraw them from multiple medications and their pressures shoot up and they become very symptomatic. I am just saying we don't see that unless you are basically in the trenches with them.

DR. TEMPLE: There is a classic case where the uncontrolled placebo period was the source of important events that were missed, and that is the CAST study. Probably everybody knows this. This is encanide and flicanide. But before you got into the trial you had to show that you were 70 percent suppressed. There were plenty of deaths during that period but there was no control group so they

just went on with the study and figured that, well, they had an MI so they died.

But when CAST-II came along with ethmozine, the first period at which they tested whether the drug could suppress VPBs was done in a controlled way of drug versus placebo and they never did CAST-II because there were 19 deaths on ethmozine and one on placebo in that initial period. So, there is reason to worry about the initial period, or at least there is one good example of when you should.

DR. HIATT: Question 2., the second meta-analysis, PHARM, was based on 93 NDAs, 590 studies and 86,137 randomized patients. Are you concerned about studies in INDs that never led to NDAs, analogous to publication bias? And, trends in safety of active agents since 1973 to 2001?

Let's take both of those. Mike, if you could start?

DR. LINCOFF: I am not concerned about studies in INDs that never led to NDAs. I think it is pretty clear that it is going to be a small

proportion of total patients enrolled and, if anything, the bias should be in the opposite direction because presumably an effective drug would have come to NDA. So, I don't think that is important at all. Nor do I believe that trends in safety of active agents would change the relative differences for what we are looking in the placebo group. There may be different profiles of side effects but we have had drugs to reduce blood pressure since '73 and the issue is still what is happening in the placebos. So, I don't think either of those are relevant.

DR. HARRINGTON: I agree with Mike's interpretation. I thought we had a good discussion about both of these during the open period and I agree with Mike.

DR. TEERLINK: I agree with that.

DR. HIATT: I do also. I think Ray answered pretty effectively that there were no trends over time, nor am I concerned about bias. We are pretty convinced it is a rich database.

DR. WARNER-STEVENSON: It is a very large

database. I am not concerned.

DR. FINDLAY: Agree.

DR. KASKEL: Concur.

DR. PORTMAN: Agree.

DR. PICKERING: I agree.

DR. DEMETS: I agree. I just want to comment that large numbers doesn't get rid of bias. It reduces variability but does not get rid of bias but, nevertheless, I am okay.

DR. FLACK: I agree.

DR. HIATT: Let's move on to the next question. This table is based on the PHARM report. It is sorted by the absolute value of the "excess" column, which shows the placebo minus active treatment difference in events per 1000 patient-years. You can see the table before you.

Question 2.2., the primary analysis was the relative risk for simply any reason for withdrawal--and we did talk about that and I think I will stick with that as the primary analysis--analysis that counted treatment failure and MI equally. Was this reasonable? Let's just

take that one. John?

DR. FLACK: No.

DR. HIATT: David?

DR. DEMETS: I don't think I would have done it that way.

DR. PICKERING: Well, I guess it is how it is interpreted. I mean, I think it is a reasonable thing to do but on its own it doesn't mean much. I am not quite sure whether that is a yes or a no.

DR. PORTMAN: I can't equate treatment and failure where you just don't control the blood pressure to an MI.

DR. KASKEL: I agree.

DR. FINDLAY: Agree on that.

DR. WARNER-STEVENSON: Agree.

DR. HIATT: I agree too, and I think that the reason that we treat hypertension is to do what you said this morning, prevent MI, stroke and death. I think that should have been the primary endpoint. I think that we are allowed as a committee to still look at major cardiovascular events as things of most concern. So, I don't

think it was a reasonable primary endpoint.

DR. TEERLINK: I agree.

DR. HARRINGTON: I don't agree. I think that we frequently do clinical studies that have composites of components that are of varying severity, and I think the important thing that investigators did is that they then showed us all the data so that we could make our own decisions about the contribution of the various components. It may not have been what I would do but I do think what they did was reasonable and I commend them for showing all the data.

DR. LINCOFF: I actually take that approach as well. I think philosophically this is not a prospective trial being brought to a committee, saying these are the ground rules we set, we did or did not meet our ground rules now approve our drug. This is a mining, a retrospective mining of prospectively collected data and we, as a committee asking any question, have the right to look at which parts of the data we feel are relevant. That doesn't mean that their

choice of endpoint was or was not appropriate as long as they provide all the data. So, for our considerations I don't think it is appropriate but I think it was appropriate to use as an endpoint of their study.

DR. HIATT: Any other comments?

DR. STOCKBRIDGE: I am horrified that we have two committee members who didn't care what the primary endpoint was.

DR. HARRINGTON: I didn't say I didn't care. I said that I gave credit to the investigators because this was their choice and we frequently have composite endpoints that have components of much, much different severity. I mean, we have things that include readmission for worsening shortness of breath in the same endpoint as we do death. So, you know, we do it all the time and, for whatever reason, they decided to do this. I suspect it was largely driven by their power considerations. They showed us all the data on the individual components and I agree with Mike that we can delve into the individual components

and see what is important to us. Again, it might not have been what I would do but I don't fault them for having done it.

DR. LINCOFF: If you chose to be horrified, it is because you are picking the semantics. The reality is, again, this is a data set that is retrospective. You can look at whatever you want. In the part of making decisions here, I choose to look at things I think are clinically important, which I believe are the irreversible endpoints, and I am glad that they provided the data for that, and if they hadn't they could go back and do it but they did. But I don't think it matters what you collected. This is a retrospective collection.

DR. TEMPLE: That sounds right but you have heard one point of view from Dr. Mangano that says what you call your primary endpoint really matters because you mustn't really look at anything else. So, if you really believe that a lot and include treatment failure, you can guarantee it is going to dwarf everything else and obliterate

anything else. But I think what you are saying is, fine, call it whatever you want; we are going to look at the data. And, I think that is probably what everybody thinks.

DR. LIPICKY: This was a retrospective study. It was a data mining study. There was no hypothesis being tested. It is probably inappropriate for me to even say there was a primary endpoint. It is a matter of what happened in these trials and what happens to people who are randomized to placebo. There are lots of things to analyze and I fell into a trap. Everybody wants a primary endpoint; I gave you one. That was stupid--ignorant, not stupid.

DR. TEMPLE: Let me make one other thing clear. This was started because we have long been worried about not giving people a therapy known to save strokes, lives and death. We hadn't seen any evidence that people in trials were disadvantaged. They were short term and bad events were infrequent. We became aware of the Al-Khatib study and that was at least somewhat reassuring but it

was still not very large.

So, it was very clear what we wanted to find out. We wanted to find out whether people were disadvantaged in some meaningful way. I don't think anybody would have thought that finding your blood pressure is not controlled was a disadvantage in a meaningful way. That was an inevitability if these drugs work. But the other things that have consequences, that is what we want to find out, if they were there. That is what the whole point is but, of course, you don't know exactly what to look for until you start looking in these retrospective studies.

So, I would say we would have been content to find anything that looked persuasively adverse and be troubled by it, and we are hoping that, since we like the idea of doing placebo-controlled trials, that those didn't show up.

DR. HIATT: In a way you are behaving like a DSMB without stopping rules.

DR. TEMPLE: Something like that.

[Laughter]

DR. HIATT: Comment?

DR. MANGANO: Yes, it is perfectly reasonable for you to look at this body of data and make decisions. We are not talking about you publishing something from this. But the argument that data that had been collected and, therefore, is retrospective I think is simplistic, to put it bluntly. Even if you have a database and it is unblinded you can prospectively ask the question and you can commit to that question, otherwise you are on the slippery slope of finding anything you want.

So, though data are collected for another purpose, put in a database, blinded, I think scientific rigor demands that you identify the study question otherwise you shouldn't even be publishing the study. It should just be a substrate for a future trial and design. I think you have to, in terms of publishing, stick to a protocol whatever the protocol is--Ray could be right and I could be wrong, but you must stick to that protocol, that primary hypothesis and, if

after the fact, everybody is prejudiced toward this question and your prejudice is going to dictate what analyses you do--so, I perfectly understand multiple questions and choosing other guidelines, other than what was asked.

DR. TEMPLE: You know, by that reasoning you would say if your first worry was stroke and you make that your primary hypothesis and you find a highly persuasive adverse effect on heart attacks, you are obliged to ignore it.

DR. MANGANO: No, I never said that.

DR. TEMPLE: Why not?

DR. MANGANO: Your primary endpoint is your primary endpoint. You report secondary analyses and post hoc analyses if they are important to put into the public domain. I am not saying throw out those analyses. I am saying that you must label them as primary or post hoc.

DR. LIPICKY: I think that this is really to the crux of the matter here, that is, I have never seen a meta-analysis that is hypothesis testing or acceptable as having proven that a

hypothesis is affirmed. PHARM was not a hypothesis testing study. It was a descriptive study of what happens when people are randomized to placebo or active drug. Please ignore the fact that I declared a primary endpoint.

DR. HIATT: Thank you for all those clarifications. I have just been reminded that protocol kind of dictates that we try to stick within if the committee has any questions for any of the presenters, please let them know.

Next question, the overwhelming majority of events in the PHARM analysis were discontinuations for treatment failure, not surprisingly much more common on placebo than drug. Is this alone reason for concern about the use of placebo, or is it just a reflection that trial procedures appropriately caught most cases of need for treatment?

John, you get the last word on this one because I think this is one of the things you mentioned. So, Mike, let's start over here.

DR. STOCKBRIDGE: While he is gathering

his thoughts, let me point out that the premise here isn't quite true. What the introduction to that probably ought to say is something like the overwhelming majority of the excess events, it is not the largest category of events which is, in fact, the administrative ones. The reason why it is first on here is that it is 246 of the net 251.

DR. LINCOFF: It is expected and it is good that they stopped it and dropped the patients out, and I don't know what else more to say about it. It is not something that in and of itself means that it is unsafe to use placebo. If a patient is being watched carefully in a trial and has a treatment failure and is taken off the trial, that is certainly preferable to not being dropped out having treatment failures. So, I think that this is an event but it is not an event that influences the decision of safety of placebo.

DR. HARRINGTON: I think that is a reasonable argument and the answer to this question that I would agree with. I feel more strongly, as John has well described today, about perhaps the

treatment withdrawals. As you come into these clinical trials there is probably going to be more discussion as we go on through the afternoon.

DR. TEERLINK: I agree with both of those points. In addition, I think this is the one area where selection bias actually does have quite a bit of impact in terms of the INDs because the only things that are submitted for NDAs are going to be the drugs that are effective. So, if we actually had the full database including inactive drugs we might actually see more of a balance in terms of treatment failures. Anyway, it does not, to me, argue for a concern in terms of the placebo trials.

DR. HIATT: I think that the things that we are most concerned about are the irreversible harm events, and that this doesn't change my perception on that. But what it does say is that if you do consent to go into a short-term placebo-controlled trial there is a risk of increasing your blood pressure to a higher level that might require some urgent emergent therapy. So, I think that gets to the boundaries of who

should get into these things and how we define that. So, in that case I think this is an important issue around informed consent but it doesn't change how I view the overall data.

DR. WARNER-STEVENSON: I agree. It is intrinsic to this comparison and it does highlight how important it is to define reasons for treatment failure, and what you do about it and how often you look for it.

DR. FINDLAY: I agree with the last two comments, but that said, it seems primarily to be a reflection of dropout for the need for treatment. But I agree with the comments.

DR. KASKEL: I do as well.

DR. PORTMAN: And I agree. I think that it is not a concern to stop the use of placebo but I think you have to monitor them very carefully and be sure that if they become hypertensive you other have rescue therapy or you end it at that point and then put them on therapy.

DR. PICKERING: I agree, not a major concern.

DR. DEMETS: I don't have any clinical comment, other than that I think it really matters what happens later.

DR. FLACK: In and of itself, having more treatment failures in the placebo groups is predictable and I don't think that this means you can't do placebo-controlled trials. I think you can. But I think there are groups of people where the risk is going to be higher and they are going to have characteristics that are going to allow you to identify them, even from the analyses we have seen today, whom you don't want to put on placebo-controlled trials; you won't want to put through a placebo wash-out period and/or enroll them into monotherapies.

DR. HIATT: Next on the list, the second most important class of events contributing to differences in overall event rates was other cardiovascular events, which included such things as angioedema, dependent edema, hypotension, syncope, and nonspecific chest pain or ECG changes. These events were more common on active drug. Yes.

The third biggest contributor to placebo-active treatment was hypertension emergent events. The clear intent was to capture a class of withdrawal more ominous than the treatment failures. Did it do that? John?

DR. STOCKBRIDGE: You might want to keep on reading before having people answering, to 2.4.1 or so. I think that is really just the general introduction to this.

DR. HIATT: Okay. Hypertensive emergencies were defined by the combination of clinical signs or symptoms in blood pressure criteria.

The clinical presentation was supposed to include new end-organ damage or symptoms plausibly related to blood pressure. Were these criteria sufficient to establish that the hypertensive emergency events were clearly worse than the treatment failures? So, across that whole context of questions, John?

DR. FLACK: The answer to the first is that I don't think so. The hypertensive

emergencies really are probably a mixture mostly of what we call hypertensive emergencies where the pressure is high but there is no end-organ damage and probably that wasn't the most of them.

Were the criteria sufficient to establish that the events were clearly worse than the treatment failures? Not consistently, no.

DR. HIATT: David?

DR. DEMETS: Well, given my limited knowledge of blood pressure variability and the definitions that were set forth, it seems like we have potential for a lot of noise in that definition. So, I don't think it obtained what it really was trying to get at.

DR. PICKERING: I agree. I think they are largely uninterpretable though there are probably some patients in there who genuinely did have what all of us would call hypertensive emergencies but it is very hard, if not impossible, to really separate it out from the data that is available so I would place very little weight on those data.

DR. PORTMAN: I agree. I think it didn't

do that. The answer is no. Secondly, I recently got asked to do a talk on hypertension emergencies in pediatrics so, since there is absolutely no data in kids, I went to the adult literature and reviewed it and I have never seen a bigger mess of definitions as to, you know, what one calls emergency and emergency end-organ damage. Today I cannot tell you what a hypertensive emergency is.

DR. KASKEL: I agree with that.

DR. FINDLAY: I don't think I understand this issue or this question well enough to pass judgment.

DR. HIATT: Well, the hypertensive emergency category included just blood pressure changes and end-organ changes. Do you think it captured a more serious event than just overall dropouts?

DR. FINDLAY: Well, hypertensive emergency is clearly serious. If forced to answer, I would say no.

DR. WARNER-STEVENSON: I think clearly there were 279 events and only 52 ER visits or

hospitalizations so how much of an emergency could it have been?

DR. HIATT: I agree with that too. I think it is kind of a dirty endpoint. One thing that I think Dr. Mangano showed us is that the distribution of severity in this category was worse on placebo. So, if you believe the categorization of end-organ, that might have suggested some concern.

DR. TEERLINK: I certainly think it is an important endpoint to look at and would be something for future trials to actually define very specifically and very prospectively and it is a useful thing to try to interpret. I commend the investigators for trying to do it. I think, given the limitations of the CRFs and how they slice in time but don't give what the patient's state was before or after, it is an impossible task and I think we are asking an unreasonable question of the data. I think that most of these hypertensive emergencies actually represent really just treatment failures and don't necessarily represent

what we would call clinically hypertensive emergencies and I think, actually, Dr. Mangano's subgroup analysis of that suggests that as well. So, I don't know what that means in terms of the yes or no answer, but that is my answer.

DR. HARRINGTON: I agree with Ray that in retrospect the original definition was a very weak one and created some of the problems that we are facing today. Having said that, I think that the attempt to scale this on secondary analysis, as done by Dr. Mangano, was a reasonable attempt. The problem is, as John has laid out, that I don't think the investigators had that level of data to make an accurate assessment and, therefore, leave us still in the dark. I think Lynn's comment about the hospitalization being very low in relative proportion to the number of total events speaks to that.

DR. LINCOFF: I agree with that. I don't think this is a valid endpoint. I think that the grading of severity is also not valid, not because of the attempt but it went by the number of

end-organs involved and that equates erectile dysfunction with an eye hemorrhage. I mean, there is not enough data to really identify hypertensive-related organ dysfunction here. So, I don't think that helps. I think the most compelling issue is the 52 patients who went to the ER.

DR. HIATT: So, the only end-organ data we got was this list from the CRFs. We don't have any reason to believe that there is bias in how those end organs were ascertained.

DR. LINCOFF: No, but the majority were headache. That may or may not have been related to the hypertension but we don't think we consider a headache necessarily to be severe or irreversible.

DR. HIATT: So, we will get to that. So, they weren't really end-organ events. Why don't we go on to that then?

Next question, which of the following cited evidence of end-organ involvement should have been the basis for declaring hypertensive emergency? You can see the list there. So, Mike,

what do you think?

DR. LINCOFF: I have to work my way down the list here, but I think retinopathy, eye hemorrhage. Visual disturbance is very soft if you had a really good collection of data, but I don't think retrospectively. CNS alteration is pretty soft but I guess you would probably want to include that. I wouldn't include headache. Chest pain--we already have separate criteria for angina so if it is chest pain that didn't meet angina, I am not sure what that means. I don't think palpitations. Dizziness is very vague. Edema, shortness of breath I think is real. Erectile dysfunction, I don't know how you could relate that directly to emergency. Flu-like syndrome, rash and vomiting, not particularly.

So, I guess the ones I would be concerned about would be retinopathy, eye hemorrhage, CNS alteration and shortness of breath in a retrospective collection of this sort of data. Others might be more relevant if you had very strict criteria.

PARTICIPANT: [Not at microphone; inaudible].

DR. LINCOFF: The question was any particular retinopathy, but I don't know in a retrospective study.

DR. HIATT: Right, there are grades of retinopathy.

DR. LINCOFF: you would have had to have had a paired analysis pre and post to say anything. So, you would want to be cautious.

DR. HIATT: Would you say there might be some things on this list that weren't included as hypertensive emergent end-organ definitions?

DR. LINCOFF: Things that should have been included?

DR. HIATT: Yes.

DR. LINCOFF: Yes, there are some. Renal dysfunction--I mean, there are a lot of issues and I don't know--

DR. STOCKBRIDGE: This is just what was observed. You know, what the panel would have done or the data entry people would have done if they

had seen a renal event and high blood pressure, presumably they would have called that an event. This is just all of what was associated with hypertensive emergencies in the observed data.

DR. TEERLINK: So, are you saying that they did not see any renal events in these?

DR. STOCKBRIDGE: None of them were renal events.

DR. HIATT: All right, let's carry on.

DR. HARRINGTON: Mike's summary is a good one. I had the same concern about retinopathy. Is it chronic changes or is it something acute? Eye hemorrhage, visual disturbances, again, depending upon how one might define it. CNS alteration, which would include stupor and coma, would raise to the level of concern for me. Shortness of breath with worsening heart failure I guess may be a challenging one to figure out in this context, but perhaps is demonstrative of end-organ damage. I think the critical element is that you need strict definitions around these and how you capture them.

DR. TEERLINK: I agree with most of the

above. I would also add that I think you are looking for something that is more permanent rather than kind of transient findings that can occur as a result of this transient elevation in blood pressure. So, I would even, you know, kind of look more at saying, as I think Bob was referring to, it would require a hospitalization, an emergency room visit, some therapy directed specifically. So, we end up kind of more towards the endpoint definitions.

That being said, the list that I would be interested in from this list includes the eye hemorrhage, the CNS alteration. Chest pain should be captured under angina if it is angina. If it is not angina, then I am not so sure it is important. Edema and shortness of breath, once again, should be captured by CHF. I guess whatever is not captured by heart failure you can capture here. Then, the others I am not particularly concerned about.

DR. HIATT: I really don't think I have much more to add to that. I think the absence of

what we normally consider to be severe is really not here.

DR. WARNER-STEVENSON: I agree.

DR. KASKEL: Again, it is hard to imagine that there were no renal symptoms somewhere along the line.

DR. PORTMAN: Just to clarify, I assume all of these are sudden events over and above baseline. I mean, that is really the key. I mean, if a patient got retinopathy already the presence of retinopathy at a visit is not anything related to acute hypertensive emergency. So, I mean, I think that is part of the issue.

DR. TEMPLE: That is what it should be but we don't really know if they took a really careful look at that or not.

DR. HIATT: Ray, hold on just a minute. Does anyone want to ask a point of clarification?

DR. LIPICKY: [Not at microphone; inaudible].

DR. HIATT: What was that?

DR. PORTMAN: He said it was true for

blood pressure.

DR. HIATT: I think we are just fundamentally limited by CRF kind of definitions and things. Tom?

DR. PICKERING: I basically agree with what has been said, but would just add that many of these symptoms and acute increase in blood pressure are characteristic of panic attacks, which are very common in hypertension patients.

DR. DEMETS: I have really noting to add, I don't think.

DR. FLACK: I counted that 8 of the 14 are kind of bogus for calling hypertensive emergencies. I think if you see fresh hemorrhages in someone's eye and their blood pressure is really elevated, the likelihood is that that is probably not anything that is chronic. It may be but most of the time it is not--papilloedema, ring hyperemia, early papilloedema. But a lot of retinopathy, like hemorrhages and exudates or even severe arterial or narrowing stuff is chronic, segment spasm. Headache, a lot of patients have headache. Chest

pain I agree with. It is a problem. Palpitations, dizziness, edema, erectile dysfunction, rash and vomiting--that is all wastebasket. It may occur in people who have hypertensive emergencies, and all, but in and of itself you just can't lay any stock in that. So, that was way too broad of a definition for target organ dysfunction.

DR. HIATT: Okay. Then related is the next question, the blood pressure criteria were either a diastolic pressure greater than 120 mmHg or a rise by 10 mmHg to greater than 110. Were these criteria sufficient to establish that the hypertensive emergency events were clearly worse than the treatment failures? John?

DR. FLACK: I think yes. The question is by how much. They are at the upper range of treatment failures. That includes some of the really more nasty events. So, I think to some degree yes, they do but it is more being just at the upper part of the continuum and I don't necessarily think that a lot of these crossed a threshold that needed immediate intervention, like

you would do in a true hypertensive emergency.

DR. PICKERING: I don't think the events, as defined, are worse than treatment failures.

DR. PORTMAN: I would vote no.

DR. KASKEL: I agree with no.

DR. WARNER-STEVENSON: No.

DR. HIATT: I agree with that too. I think it is a number so I would vote no.

DR. TEERLINK: No.

DR. HARRINGTON: Same.

DR. LINCOFF: I agree with John and others.

DR. HIATT: Yes, please?

DR. FLACK: One thing, you know, I don't see this as like the end of the world or Rome is burning, but when you are doing a clinical trial and you have them showing up with pressures of 120 or higher, or you get them with a diastolic over 110 and it has risen by 10 mmHg, I think it is cavalier for you to basically say that that is not worse than other treatment failure. I mean, think about it. Do you want your family experiencing

this stuff? To me, that is the litmus test, and the answer is no. I think it is not that they need to be hospitalized and immediately treated but this is a problem and it is more than just a treatment failure.

DR. HIATT: Certainly I wasn't saying it cavalierly. I think that it may represent the upper extreme of a treatment failure but I don't think it constitutes hypertensive emergency.

DR. FLACK: I didn't say that either, and I said very clearly that I think that this is an upper continuum but is this more than just a treatment failure? I don't see how it is not.

DR. HIATT: I will agree with that, but I interpreted the question of is this hypertension emergency which was different than treatment failure. That is how I interpreted it.

DR. FLACK: Yes, I don't think these are hypertensive emergencies. I think that they are elevated blood pressures maybe with a few emergencies. Even if you threw out the emergencies, these would still be worse than just a

treatment failure.

DR. HIATT: And I think the context here is we are going to try to interpret whether overall the data are compelling that it is safe or not. Clearly, if this happens you would need criteria for discontinuing from this short-term study and you would be enrolled into some form of therapy, and the consent form would say you would be at risk of your blood pressure going up and we would do something about that. Paradoxically, you might even do yourself a favor by enrolling in a placebo-controlled trial because someone would actually pick up something like that. So, we just want to understand whether these kinds of events are going to affect your overall decision about whether it is safe or not.

DR. TEMPLE: That is partly because they were cited as evidence for possible end-organ involvement, and I think what people have said is that it doesn't do that. That doesn't mean you are not worried about how they got that hypertensive and maybe they should have been seen more often.

That is a different question.

DR. HIATT: There is a series of questions on the Mangano analysis of hypertensive emergency and other cardiovascular events. We also saw that ahead of time. I think maybe we will run through these if we can as a group.

DR. STOCKBRIDGE: The questions here go into more detail than Dr. Mangano's oral presentation did. You guys should feel comfortable making general comments if you want. I, personally, don't need for you to go through the sequence of whatever it is--six specific questions here.

DR. HIATT: Good! Thank you. Do you need me to read them all? No. Mike, do you feel comfortable reading these and then answering or not?

DR. LINCOFF: Do you want me to read them out loud?

DR. HIATT: No, you don't have to.

DR. LINCOFF: You know, basically there are two groups. There is the hypertensive

emergency criteria then there is the criteria for other cardiovascular events. Is that what we are discussing?

DR. HIATT: Yes.

DR. LINCOFF: So, the hypertensive criteria, I think I have already mentioned. The blood pressure criteria is always the same, 200/100, and it is just the number of end-organs and we have just said that most of those end-organs we were not convinced were relevant.

So, I don't think there is a graded effect that we could say much about for the hypertensive. Now, the other cardiovascular event grading was--I mean, grade 10 was death and there was stroke. These include those irreversible events that we are interested in anyhow, and we almost equate them. I mean I would think MI, stroke and death are all events that we would consider severe enough to make this a decision, any of them equally severe enough to make a decision that it wouldn't be safe to continue placebo. So, I think it is relevant but I don't think we necessarily need to have a graded

effect. If a patient had those irreversible events, then they are there. It is binary from my point of view.

DR. HARRINGTON: I am going to take Norm's prerogative to comment generally on this. I do think that it is rational and appropriate to look at certain categories of events and try to provide some more insight into the severity of the scale of that event. So, I actually commend Dr. Mangano for attempting to do that. I think that that is a rational thing to try to gain some insight into what these data actually mean. That is philosophically. For the logistics or the more specific comments on these data I would very much follow Mike's outline.

DR. TEERLINK: I agree with both of those, and then I would add that I think what would have been and will be very useful is if you include a frequency table of what those specific--you know, how many of each of these there really were per group, as there is in the general discussion, with regards to the definitions, rather than the ranking

per se, but actually what were the related events. So, it was hypertension with retinopathy; hypertension with eye hemorrhage. How many of these were there actually may be more informative than the kind of ranking system that was established.

DR. HIATT: Yes, I think the scaling of this was post hoc. Right? This wasn't a prespecified analysis.

DR. MANGANO: It was post hoc.

DR. HIATT: Yes.

DR. MANGANO: [Not at microphone; inaudible].

DR. HIATT: So, just to clarify that, I think the challenging part, we all agree, is that scaling these was critical. I don't think the database allows us to do a lot of that because, as we all know, you have event committees if you really care about these things and people get other kinds of sources of information to make those determinations. To try to do that off of CRFs, where the reporting may be quite variable, I think

is a limitation as to how far you can take the scaling.

So, I think it is a great idea. I think the way you did it was nice. I am not sure how much decision-making I can weigh based on that evidence.

DR. MANGANO: I wouldn't make any decision on that evidence. It is a nice way to color the picture but it is very limited in terms of any formal analysis.

DR. WARNER-STEVENSON: I don't have anything to add.

DR. FINDLAY: I appreciated the differing perspectives and differing interpretations, to some extent competing interpretations of the data. I thought they added insight and richness to this database that is informative for what we are doing here.

DR. KASKEL: I agree.

DR. PORTMAN: Nothing further to add.

DR. PICKERING: I agree.

DR. DEMETS: I don't think I have anything

new to add, other than just to say that it was interesting to try and develop an overall score but it has all the limitations we know about.

DR. FLACK: The only thing I would say is that the grading helped a little bit with that very broad category of hypertensive emergencies and was not unreasonable even though it was post hoc.

DR. HIATT: Okay. The next question, the fourth biggest contributor to placebo-active treatment differences was administrative events. This was the category with the largest number of total events. Why do you think these events were somewhat more common on placebo? John?

DR. FLACK: I am going to say something wild here. I honestly don't know but one of the things I know about hypertension is that, contrary to the myth that it is asymptomatic, it is not. As people's pressure is going up or down they become symptomatic. People on placebo don't experience that rapid fall in blood pressure that people do when they are on treatment. If you take care of these patients you know they don't feel good

oftentimes when their pressure falls immediately.

So, if I had one thing I might say, and I don't know how accurate this is, it may have been that their blood pressure simply may have gone up and gone down and they felt the yin-yang.

DR. DEMETS: I don't know, of course, the answer but one guess is that it is hard to distinguish between administrative events and other things like kidney failure. Whatever the investigator puts down, it is hard to know what is in his mind when they do that.

DR. PICKERING: I don't have anything to add to John's suggestion.

DR. PORTMAN: I don't know that there is a way to know.

DR. KASKEL: I agree.

DR. FINDLAY: No clue.

DR. WARNER-STEVENSON: I don't know but I think investigators may have been a little bit nervous, thinking that they patient may not have been on active drug and it would have taken very little to push them over to want to put them on

active drug.

DR. HIATT: Yes, I have a hard time interpreting this any way.

DR. TEERLINK: My sense is that it is confounded by treatment failures and that people are much more willing to withdraw consent and to withdraw from studies when they think they are not getting the active treatment.

DR. HARRINGTON: I think those are reasonable explanations. I would also throw out Ray's explanation earlier on which I still find reasonable, the relative risk was 1.09 with a p value of 0.03. With multiple comparisons this may mean nothing.

DR. LINCOFF: But aside from potentially meaning nothing, I think it is pretty striking that every trial I have been involved in, whenever there is any type of withdrawal, roll-off or whatever, the most common category is always "other" and I think that it is just very hard to get investigators to accurately classify what they are really thinking at times.

DR. HIATT: Let's move on. The fifth biggest contributor to placebo-active treatment differences was other adverse events, which included headache, lab abnormalities, rash and fatigue. These were more common on active treatment than placebo.

The next largest contributor to placebo-active treatment differences is 10-fold less common, but generally the remaining event classes--arrhythmia, heart failure, angina, myocardial infarction, stroke, death and TIA--represent serious, often fixed, outcomes, mostly those that one would expect to be better on drug than on placebo. That kind of harkens back to where we started.

The next, excess on placebo is about 2 events per 1000 patient-years. Is this what one would expect for the benefits of active treatment?

Together, death, stroke, and myocardial infarction--not quite the Al-Khatib endpoint--give a relative risk of 1.03, p 0.9. Is that what one would expect for the benefits of active treatment?

Mike, these are some big ones.

DR. LINCOFF: I think that harks back to the discussion we had on one of the first questions regarding this on the same thing for the Al-Khatib analysis and I agree. I also think that Lynn's point that you can't multiply a month by 12 and get the year event is also a very good point. So, I think that this is just short exposure, low events over that short exposure of serious things and very difficult to extrapolate out to get a reliable endpoint per 1000 patient-years.

DR. HIATT: The question though I think this begs still is should antihypertensive therapy have worked over this short interval and you would have seen it or not?

DR. LINCOFF: I think it works--I mean, it is an effective drug and it prevents events, but if it prevents in that short period of time such a vanishingly small number of events that in nearly 90,000 patients you couldn't see it, then I think that says that the risk is so small for that period of time as to not necessarily be considered. I

mean, you can get into risk/benefit like benefit to society, but I don't think you even have to do that. I think you can say that, you know, we have looked in a huge database that should be fairly exhaustive and you can't perceive a risk over that short period of time. Theoretically, there is no reason why somebody should be protected for four to six weeks. There is no magical period there, but it is true that often guidelines are--or were--that you tried other therapies, conservative therapies, etc. so it fits in with practice as well. It may also be that in a clinical trial people are carefully watched, probably more carefully watched than they are in practice. So, the real risk may be essentially negligible. I don't think there is ever any way to say it is zero because the drugs work. But I think it is so small as to be negligible.

DR. HIATT: I think those are very reasonable comments. Ray also showed I thought some interesting analyses that tried to tease out are there levels of risk beyond which this

risk/benefit ratio begins to shift. Not surprisingly, as you get older, as you have higher blood pressure at entry, perhaps the difference between placebo and active treatment is a bit greater and, hence, the comment in his conclusion that perhaps we should consider cut-offs for enrollment into placebo-controlled trials even of a short term. And, I think these data are consistent with that.

DR. HARRINGTON: I think these data support the concept that for the patients who were enrolled in the trials that were analyzed by the PHARM database there is negligible risk. How that extends and whether we can extend that to, say, refractory hypertension patients or the kinds of patients that I think we will increasingly have to study now that we have effective general therapies may be a little more problematic. But for the purposes of this specific group, I think it shows that there is negligible risk.

DR. HIATT: I am going to agree with that too. I think the two databases, the two components

of this question, are actually remarkably consistent, and I think the slightly higher upper limit of the confidence interval for Al-Khatib is just because there is another component to the bundled endpoint. So, I think it is very hard to detect an absolute level of risk here that is meaningful in this period of time with lots of brackets around that. The population has to be defined as a relatively low risk.

I think the other comment is that these point estimates and their boundaries ought to inform patients during the informed consent process, if they are enrolling in a placebo-controlled trial, here are the data and I think they should understand what these data are showing in addition to the other less concerning but still potentially harmful hypertensive emergency kinds of things. These are informative data. They don't exclude you from a placebo-controlled trial but I think they need to be part of what the patients and physicians should understand if they choose to enroll a patient in a

placebo-controlled trial. So, my answer is that I think the absolute risks are really negligible.

DR. WARNER-STEVENSON: I am comfortable that the risks demonstrated are the risks that were found. I have a broader philosophical concern. One is with the concept of equipoise. I don't think there is anyone in this room who feels that it probably doesn't matter whether you treat someone with a blood pressure of 150/100, other things being equal. I have to deal with that.

I also think we have to deal with not only our message to the public, which is a different issue as we said this morning, but our message to the individual patients who go into this trial with a placebo comes as, well, I really think it won't matter for a month or so whether I treat you or not, but after that it becomes really important and I want you to take every medicine that I give you.

I have considerable discomfort with both of these, and I would suggest that we may need to define a placebo population in which can get close to equipoise, which might be that group of

patients, as you discussed this morning, in whom we are willing to give lifestyle modifications a chance for a couple of months; patients in whom I could say comfortably that I have some equipoise in whether I should treat this patient or not, not just that the risks don't seem to be very large.

DR. HIATT: Lynn, along that, I think you are keying off a point that started this whole conversation. All the risk is borne by the patients. The benefit of placebo controls are societal. Right? So, we shouldn't forget that concept.

DR. LINCOFF: I maybe dissent a little bit from that. It is not entirely true because if you have to do a non-inferiority equivalence trial you have to expose a lot more patients, so not just society but a lot more patients to what may be an ineffective therapy. So, there are scenarios, and I have seen several published, you know, realistic scenarios where you end up with more patients who suffer harm because of the much larger sample size of an equivalence trial or a non-inferiority trial

than you would if they had just had a small superiority trial that is placebo controlled. So, for an individual patient maybe, but you will expose more patients potentially to risk by mandating that non-inferiority be done.

DR. HIATT: I agree that the societal is a broader definition. Any other comments on that before we move on?

DR. TEMPLE: Well, just a couple of things. Equipoise is a term that is used in a lot of different ways, but you would not be in equipoise if you were randomizing people to a long-term placebo-controlled trial. You would know they were going to be harmed by being in it. With respect to this, you are not in equipoise on whether the blood pressure is likely to be lower on the treatment. It surely is.

But this study I think is supposed to provide equipoise on whether people would come to any material harm. With this study we are so far ahead of where we were on that question that it is really a sea change and you actually could give

people appropriate information on what the risk was. We never thought it was very large or we wouldn't have allowed the studies. We had no idea quantitatively what it is. But this sort of puts an upper bound on worrisome things that puts us way ahead. So, I would contend that with respect to the important question of harm for people you are in equipoise. Of course, that is not even what you are studying here. You are just studying whether the drug lowers the blood pressure.

You know, when and how equipoise applies to things that don't harm people, like a pain study, you are not in equipoise on a pain study. You already know that you are overwhelmingly more likely to do better with the pain medication but you don't care that much because no harm comes to people from it. So, equipoise is a term that is used generally. I think it only applies to outcome studies where you are worried about doing harm to people, not that that doesn't need more discussion.

DR. WARNER-STEVENSON: I would agree with you. I think we are rarely in equipoise on things

where we supposedly are at equipoise. But, you know, I do think the concept is that my patient is at a higher risk of a hypertensive emergency for a month not on drug than on drug. I think that is highly suggested by this even though it may be very small. I think that is something that has to be faced squarely.

DR. TEMPLE: Yes, so you would say your blood pressure is more likely to go up. You need to know that. We are going to watch you closely and sometimes it will go up a lot and we will be worried but nothing seems to come of it.

DR. WARNER-STEVENSON: I would feel more comfortable demonstrating the effect of a new drug on a patient who, in fact, I felt was really at amazingly low risk for hypertensive emergency, which is somebody who has a blood pressure range in which one might consider lifestyle modifications--sort of a relatively borderline range where it is exceedingly unlikely that they would develop a hypertensive emergency or anything else.

DR. TEMPLE: One of the things we are clearly going to have to come to you with is guidance on antihypertensive drugs. There was a time, believe it or not, when we thought that if you didn't have data on severely hypertensive, moderately hypertensive and mildly hypertensive people you hadn't done your job. We have long since got away from that. You lower the blood pressure in any population and we are content that your drug lowers blood pressure. But I think we will have to come back with thoughts on that very thing, who should be in trials, how long.

Actually, I have one other question. I did not understand Ray to be saying that there were data that suggested an increased risk with older people from which therapy you were on.

DR. HIATT: You are right.

DR. TEMPLE: Fine. Well, that was your overall risk of having a problem given the blood pressure, but not that these data were allowing you to tease out a greater risk people.

DR. HARRINGTON: I agree, and I was

extrapolating that it is likely that people at higher risk--right.

DR. FINDLAY: As the consumer representative on the panel, I would just underscore the informed consent point that I think has already been made eloquently by several.

DR. KASKEL: There was a study in this week's in a journal about placebo-controlled trial of an A-2 receptor blocker in patients who are pre-hypertensive, who have had one or two mild elevations, outpatient. It was very finely controlled and I think we can learn from that in terms of how to set up and how to monitor the placebo group, looking for any changes that might be a clue that something is going wrong.

DR. PORTLAND: Well, I agree with what has been said. I think it is perfectly acceptable, you know, as it is shown here in a relatively low risk population that is extremely well controlled, and I would have no trouble doing that.

DR. PICKERING: I agree with Ron.

DR. DEMETS: I think I came in today

thinking that the place to test this would be the mild hypertensives, not this extreme where you feel like you have to do something. All you really want to do is move blood pressure and that population should do it just fine and they are not at risk. So, that is where I started out and that is where I am now.

DR. FLACK: Lynn took the words right out of my mouth. I would also refrain from taking two meds from pre-hypertensives because hypertension begets hypertension and once you start the pressure starts going up, be it more vascular damage and a whole host of things, it just perpetuates itself and you are talking about a different animal than a pre-hypertensive person.

I am not surprised at all at this net excess in risk not being that great because in most studies when you look at even very pressure sensitive events it takes several months for even the stroke curves to start to diverge. It make take three, four, five, six months. I think ALLHAT was a really unique study where the heart failure

just diverged almost immediately, but typically you don't see that. So, I am not surprised by that. I think it is going to be basically who is appropriate for these trials to go on placebo control and for how long.

DR. HIATT: Okay. Two more questions, if placebo-controlled studies continue, what do you advise to minimize risk? Just answer all these, if you wouldn't mind, just quickly.

DR. FLACK: I think certainly duration of exposure to placebo, and we need some more information about how risk changes over time. I think that the high risk patients defined by blood pressure from their intensity of treatment is going to make sense. Also, perhaps minimizing the time on monotherapies and having stepped up kinds of interventions you can do, and people get into a study and their pressures are elevated, would be important like escape therapy. I mean, those are the major things I would do. I just wouldn't withdraw too many people from too many meds or too higher a pressure, and all.

DR. DEMETS: Well, I think the first two resonate with me. I would keep the exposure to a period where you needed to follow patients to make sure you had something in terms of reduction. And I would pick the mild hypertensive not the severe hypertensive.

DR. PICKERING: I guess I would support all of these suggestions.

DR. PORTMAN: I certainly agree with the first two. I think the third one can sometimes be monitored with blood pressure monitoring, particularly since that can be objective and, certainly having good, strict criteria for that particular part of the study, and when the patient would have to leave that and go on to active therapy.

DR. KASKEL: Nothing to add.

DR. FINDLAY: Yes, yes, yes, yes. Then, for others I think I am not wrong in saying that some short-term trials are pretty large and involve a lot of patients and it can be multi-center. In that case, it might be worth considering having

independent groups that would oversee the informed consent process and the monitoring process of patients on placebo.

DR. WARNER-STEVENSON: I agree, and I would emphasize that we need to specify a very mild intensity of any previous therapy that needs to be withdrawn, and that we need quite a careful definition of the criteria for treatment failures so that when they get to a certain level they clearly will leave the study.

DR. HIATT: Yes, you would think that you could develop a new drug class and understand its effects on blood pressure in maybe a month or six weeks, and the data with the data we are shown maybe go out two to three months. So, I am guessing that the window of no risk that we are declaring--I don't know what the upper boundaries of that window is but I am assuming it wouldn't be that hard to fall well within that boundary.

DR. TEMPLE: We think they are getting smaller. They have been four to six weeks lately and they used to be 12. We now get a lot of

long-term data from comparative trials, preferably with a randomized withdrawal thing at the end to see if they are really still hypertensive because you do want to know that it keeps working.

DR. HIATT: Right.

DR. TEMPLE: Then, studies are almost always dose-response studies in hypertension so you get that from duration of the study, whatever it is. If it is one of those cases where you have to titrate, that is a bit of a problem because those tend to be a little longer. So, we will have to think about all that.

DR. HIATT: But I think you have some data and that it is possible to look at whether there is any separation in curves in the PHARM study over time. Maybe that is impossible. But my note of caution would be to try to define an upper window.

I think the second point is sort of defining risk by the blood pressure and I would just like to harken back to who I would not include would be total risk assessment of the patient, not just blood pressure itself. So, I would consider

low risk for these events ought to be the cholesterol level, smoking status and other things besides their blood pressure. Certainly, rigorous oversight. We talked about informed consent. I want to emphasize that again. These data are informative. Then, DSMBs ought to use these data as well. It ought to be incorporated in these kinds of studies.

DR. TEERLINK: I agree with all the above. I think actually the point I was going to make was what to do about titration studies. I think there is an issue but that may be addressed by minimizing the time between visits or that may be challenged by longer half-life drugs. So, there is going to have to be some given and take along those lines.

The other suggestion is to have patients who are only on monotherapy be included in these trials or de novo hypertension patients so you don't have, or I don't believe you would have as big a risk of withdrawal aspects. Then, I would second Bill's point about other risk factors being taken into account.

DR. TEMPLE: You don't object inherently to doing a trial on, say, a diuretic background. You wouldn't withdraw the diuretic, you would just withdraw the other drug?

DR. TEERLINK: Right.

DR. TEMPLE: The other thing is that I just want to remind everybody that one of the concerns we all have all the time is having too healthy a population that doesn't show any of the risks of the drug. So, one of the things we are going to have to grapple with is how you get data of that kind. Plainly, we haven't been getting six-month placebo-controlled data anyway. It has to be active control. But in most studies, presumably, you would put people in with lipid problems and diabetes and other stuff but you are comparing it to another effective therapy.

DR. TEERLINK: The other thing, and maybe it is a little tangential, but there has to be a reason why everybody chooses atenolol to compare against.

DR. TEMPLE: There is very good reason.

DR. TEERLINK: Yes.

DR. FLACK: About nine out of ten of the people who come into these trials, when you do them now, are previously treated. So, getting the de novo hypertensive for most of these trials, that is a pipe dream.

DR. TEERLINK: I don't think it is a pipe dream for the initial--if we are just proving that you can show a decrease in blood pressure, I am not sure that it is a pipe dream to require de novo or monotherapy patients.

DR. FLACK: I don't disagree at all with some severity but I am just saying that unless you do something really, really special, about 85 or 90 out of 100 people that you are going to get in these trials are going to tend to be people who have already been treated to some degree. I mean, that is our experience and that is published experience. I have seen a lot of the other trials.

DR. TEMPLE: You certainly may want to limit the period of drug withdrawal. When reserpine was around that was a problem. But with

most of the current drugs they are pretty much gone in two weeks, should be.

DR. HARRINGTON: I agree with the comments about moving towards a lower risk population and trying to limit the exposure to the drug, but I was glad that Bob brought up this final point, which I had also written down. At some point we also have to grapple with the issue that this can't be the only evidence; that we need some evidence in the population that is actually going to take the drug ultimately to look at safety, to look at drug-drug interactions, to look at the effect with other co-morbidities. So, while I certainly support the discussion this afternoon of limiting the risk in a patient population who would be withdrawn from medicines and randomized to placebo, I don't want to get away from the basic tenet that we need to study drugs in the population that ultimately is going to take them. Now, how to do that is probably not something to answer at five o'clock.

DR. FINDLAY: And I agree with those as well, and also the idea to try to systematically

collect data after withdrawal to develop a database to be sure that we are really not contributing to later events, although that is obviously more of a future issue.

DR. HIATT: We are up to the last voting question. Under which, if any, of the following circumstances should placebo controls be discouraged? Dose-ranging studies for a new drug; withdrawal studies intended to show long-term effectiveness; factorial studies for approved drugs. I think what you mean there is maybe combination so you have two components and you want dose response around each one of those. And others. Mike?

DR. TEMPLE: The first one, dose-ranging studies, it is written that way because almost all the studies we see are dose-response studies. But that just means placebo-controlled trials with new drugs, usually with four doses or whatever. So, that is the major thing we have been talking about really.

DR. LINCOFF: Yes, I would assume the

first is where you really needed but, by definition, withdrawal studies are on drug and you are randomizing to come off. Right?

DR. TEMPLE: Right. I mean, the longer-term studies we have are frequently active-control trials. We have not insisted that there always be a randomized withdrawal phase at the end to verify that the drugs were really doing something, but it is possible that we really should because otherwise you don't really know. You might have a really non-hypertensive population. So, the way to establish continued effectiveness is to have a short randomized withdrawal phase and as soon as the blood pressure goes up they are out of the study so there is no long period on treatment if you follow them closely. Then you use the comparison to the other drugs as best you can to get an idea of long-term toxicity, and so on.

DR. LINCOFF: I think that should be subject to the same safety as a brief period beforehand, assuming you didn't start with a patient that you knew was very hypertensive or very

high risk. So, subject to the same criteria of risk, I think that that certainly is a safe issue.

In factorial studies, if you are talking on top of another drug, you still have some treatment so I am not sure really how to answer that. I think it is somewhere between. It may not be as well controlled but that is what you are testing but most of those would be on some background therapy. Correct?

DR. TEMPLE: Well, a typical one to develop a hypertensive combination would be placebo, two doses of a diuretic, three doses of the drug. It could run four weeks and you would have every combination of those things going for four weeks. You would still throw people out if their blood pressure goes too high.

DR. LINCOFF: I am not sure why it would be any different from any of the others as long as you meet the criteria of low risk patients, a short period of time, watching them carefully. I am not sure it would matter.

DR. HIATT: Forgive me, I think there are

a few members of the committee who actually have to leave so maybe if we could turn to whoever has to go vote on this, that would be very helpful. Tom, do you want to start?

DR. PICKERING: I would just like to say that I would not want to shut the door on placebo studies for any of these. I think the studies should be judged on their individual merits and risks.

I would just point out that in terms of assessing the effect on blood pressure, as has been mentioned, with use of home and ambulatory monitoring you could avoid much of the placebo direct effects on blood pressure. But there are a whole lot of other things, of course, that you want to know.

DR. HIATT: So, just so we get your vote on that, what is your vote?

DR. PICKERING: Well, I wouldn't in principle discourage any of them. As I say, I want to judge each study on its merits.

DR. HIATT: So, none of these would cause

you to discourage going forward with any of these?

DR. PICKERING: Not in principle.

DR. PORTMAN: I agree. I wouldn't discourage placebo with any of these studies. Obviously, as has been said, we have long-term studies, say, looking at effect on renal failure, or whatever. That should be an active control but these would be fine.

DR. HIATT: Okay. Is there anyone else who needs to leave?

DR. KASKEL: I think I agree with what has been said, and I would mention that there are clinical trials where the agents are withdrawn. I am currently involved in one of those, and some very fine mechanisms have been set up to monitor for any potential side effects in those patients. I would encourage that for future studies if you withdraw treatment.

DR. HIATT: Let's to back. Mike, are you done?

DR. LINCOFF: I voted no for all three. No, I would not discourage.

DR. HIATT: No, you would not discourage--a double negative. Okay.

DR. FLACK: No, I would not discourage all three.

DR. HARRINGTON: No, I wouldn't discourage all three.

DR. TEERLINK: No, I wouldn't discourage all three, nor most of others.

DR. HIATT: I agree with those votes. I wouldn't discourage any of these. I would also say I think Dr. Hung has a method that you don't need a placebo to test dose-ranging in a factorial design. So, there is a method where you don't have to worry about that. Maybe that doesn't apply here.

DR. STOCKBRIDGE: To be clear, there is a methodology that lets you decide that there is or is not some interaction there. But in order to ascertain what the absolute magnitude of a blood pressure effect is, there is no way to do that without a placebo--

DR. HIATT: Right. In the same context, I don't think that is prohibited either.

DR. WARNER-STEVENSON: I would agree with all of them, with some caveats about the withdrawal studies. It would have to be shown convincingly why we would have to use a placebo. To demonstrate that there was long-term efficacy if you had an active control but your new drug, in fact, had a declining efficacy, I think that would be apparent compared to the other drug. So, I would have to see convincing mechanistic reasons why we would have to use placebo in a withdrawal trial.

DR. TEMPLE: One reason is that sometimes people enter patients into trials, especially active-control trials, who aren't really hypertensive in which case by the end of it they are all still under control but none of them get their blood pressure up when you stop the drug.

DR. WARNER-STEVENSON: But then the blood pressure would be higher in the group if you felt that this drug were losing its effectiveness than it would be in the active control of something we know.

DR. TEMPLE: No, I am hypothesizing that

people who aren't really hypertensive--

DR. FLACK: He is suggesting that you use an active control.

DR. TEMPLE: If they are not hypertensive then an effective drug and an ineffective drug might look the same, or almost the same.

DR. HIATT: Where are we in the voting process? David?

DR. DEMETS: I don't think that I would discourage any, although if I have reservations it would be on the withdrawal studies. That would be the part I would think about the hardest.

DR. HIATT: John, the last word?

DR. FLACK: You need placebo for the new molecular entity or you are always going to overestimate the treatment effect. The placebo effect in some of these studies can be really small or really large, at least the trials that I am familiar with.

I have trouble with number two. I think it is going to be very hard to convince people to go into a long-term placebo-controlled studies in

the future, and over the long term you can argue, even with really mild hypertension, that you get benefit from treatment. So, I think there I would tend to really favor discouraging--I don't say ban but discouraging placebo-controlled studies. If you want to withdraw people from therapy beforehand you can set a level where their pressure has to go before they get entered, and all, maybe a little bit low than a virgin hypertensive. But you really shouldn't get a lot of people who truly don't have some blood pressure elevation, I would think.

I would be less enthusiastic about the number one, but sort of intermediate between one and three about factorial studies for approved drugs. I mean, you can do it. You can have a placebo-placebo as one of the arms. I think what you have to do though is just make sure that all of the other criteria fit about who is appropriate to be in there, and at least you are going to be potentially on two drugs.

One final thing I would say is that for modern and severe hypertension, I don't think that

you have to not study those individuals but I think that we have to get smarter about how we design these trials for participant safety in regards to switching them over from the therapies they are on to other therapies and entering them in a trial. Maybe for some of those you don't do placebo wash-outs and you have just better designed trials about getting more intense therapy early on.

I don't know what the answer to some of these things is we are talking about, but I would rather err on the side of particular safety than err on the side of making it easier for me or other investigators to recruit people into studies.

DR. TEMPLE: Just one thing about the randomized controlled study, if you look at the effect sizes in active controlled studies, there are four times the size of the placebo effect. Whatever goes on in those trials, it completely distorts the effect of the drug. The only way you can actually find out the effect of the drug is to randomly take it away. In those trials the period of exposure to placebo is extremely short. It

could be a matter of days, depending on the drug. So, the risk to people is virtually nil. But it really validates the performance of the whole study. We really don't know much from an active control trial. Maybe with automated blood pressure cuffs.

DR. FLACK: Are you talking about withdrawing therapy from people and then randomly allocating them to the active treatment or placebo?

DR. TEMPLE: No, no, no. I am talking about a randomized withdrawal study. That is, you start everybody on therapy, randomized to drug A versus drug B, drug A being a drug you believe works--

DR. FLACK: I don't have a problem with that, no.

DR. TEMPLE: No, I wouldn't think you would.

DR. FLACK: I understood it very differently.

DR. TEMPLE: This is just a way of validating the long-term effectiveness by showing

that when you take the drug away they respond.

DR. FLACK: That is fine. I misunderstood the question there.

DR. HIATT: So, John, we need to get your vote on these different items. Would you discourage--

DR. FLACK: No for one; no for two; and less enthusiastic for tree but wouldn't ban it.

DR. HIATT: That is a no? You would not discourage or you would?

DR. FLACK: Well, I would qualify it and say that I would be less enthusiastic. I wouldn't ban it, no.

DR. HIATT: So, it is a no.

DR. FLACK: A qualified no.

DR. HIATT: Qualified no.

DR. FINDLAY: My vote is no on one; yes on two with the long-term studies; and no on three.

DR. HIATT: I think we have all the votes. Are there any other closing comments? If not, I think we are adjourned. Thank you very much.

[Whereupon, at 5:12 p.m., the proceedings

were adjourned.]

- - -