DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

98th MEETING

Tuesday, January 7, 2003

8:00 a.m.

Kennedy Ballroom, Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Jeffrey Borer, M.D., Chairman
Jayne E. Peterson, R.Ph., J.D., Acting Executive Secretary

Members:

Michael F. Artman, M.D.
Thomas Fleming, Ph.D.
JoAnn Lindenfeld, M.D.
Paul Armstrong, M.D.
Alan T. Hirsch, M.D.
Steven D. Nissen, F.A.C.C.
Beverly H. Lorell, M.D.
Susanna L. Cunningham, Ph.D, Consumer Representative

Consultants (Voting):

Thomas G. Pickering, M.D., DPhil
Marc Pfeffer, M.D., Ph.D.

Acting Industry Representative (Non-voting):

John F. Neylan, M.D.

FDA:

Douglas Throckmorton, M.D.
Robert Temple, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. BORER: Okay. Everybody has had his or her three minutes grace period. We are going to try and get this show on the road.

Today, we are going to be reviewing NDA 20-297 from GlaxoSmithKline, which is based on a supplement that was submitted requesting an indication for the use of carvedilol in patients with left ventricular dysfunction after myocardial infarction.

We will introduce the committee again. As I noted yesterday, we have for the first time an Acting Industry Representative who is non-voting, that is John Neylan, and today, two SGE consultants who are voting, Tom Pickering and Marc Pfeffer, and they will all introduce themselves as we go around.

Why don't we start from your side today, John.

Introduction of Committee

DR. NEYLAN: John Neylan, Wyeth Research.

DR. PFEFFER: Marc Pfeffer, Brigham & Women's Hospital.

DR. PICKERING: Tom Pickering, Mount Sinai, New York.

DR. NISSEN: Steve Nissen, Cleveland Clinic Lerner School of Medicine.
DR. HIRSCH: Alan Hirsch, University of Minnesota Medical School.
DR. FLEMING: Thomas Fleming, University of Washington.
DR. LORELL: Beverly Lorell, Beth Israel Deaconess Medical Center, Boston.
DR. BORER: Jeff Borer, Weill Medical College of Cornell University.
MS. PETERSON: I am Jayne Peterson, the Acting Exec. Sec. of the committee.
DR. LINDENFELD: JoAnn Lindenfeld, University of Colorado.
DR. ARMSTRONG: Paul Armstrong, University of Alberta.
DR. CUNNINGHAM: Susanna Cunningham, University of Washington.
DR. ARTMAN: Mike Artman, New York University.
DR. THROCKMORTON: Doug Throckmorton. I am the Director of the Cardio-Renal Division.
DR. BORER: Jayne, can we have the conflict of interest statement, please.

Conflict of Interest Statement

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Dr. Michael Artman has been granted a waiver under 18 U.S.C., 208(b)(3) for his employer's contract with the sponsor on an unrelated matter. Funding received is less than $100,000 a year.

Dr. Jeffrey Borer has been granted a waiver under 18 U.S.C., 208(b)(3) for consulting for the sponsor on an unrelated matter. He receives between $10,001 to $50,000 a year.

Dr. Tom Fleming has been granted a waiver under 18 U.S.C., 208(b)(3) for his consulting for the sponsor on unrelated matters. He receives between $10,001 to $50,000 a year.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. John Neylan, a full-time employee of Wyeth Research Labs, is participating in this meeting as an Acting Industry Representative, acting on behalf of regulated industry.

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 participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

Thank you.

Dr. Borer.

DR. BORER: Thank you, Jayne.

Again, the supplemental NDA from

GlaxoSmithKline for carvedilol proposes an indication to reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of myocardial infarction--I am sorry--the supplemental NDA was based on a proposal to reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction less than or equal to 40 percent.

The sponsor's presentation will be introduced by Dr. Kahn.

sNDA 20-297/S-009, Coreg (carvedilol),
GlaxoSmithKline Sponsor Presentation
Introduction
Clare Kahn, Ph.D.

DR. KAHN: Good morning, ladies and gentlemen, Dr. Borer, members of the Advisory Committee and FDA. My name is Clare Kahn and I am the Vice President for U.S. Regulatory Affairs responsible for cardiovascular, urogenital, and metabolic products at GlaxoSmithKline.

The meeting today is focused on carvedilol. It is a beta-blocker which nonselectively inhibits both beta-1 and beta-2

receptors and, in addition, blocks alpha-1 receptors. The drug's action on beta receptors is far more potent than on the alpha receptor and it has no intrinsic sympathomimetic activity at any of these receptors.

Carvedilol was first approved for the treatment of hypertension in 1995 and in 1997, the drug was approved in patients with mild to moderate chronic heart failure. In 2001, the indications for carvedilol were expanded towards the end of the heart failure continuum to include the treatment of patients with severe chronic heart failure and to include prolongation of survival.

Today, we are proposing that the current labeling for carvedilol be modified to include experience towards the beginning of the heart failure continuum, specifically the treatment of patients who have recently survived a myocardial infarction and who have left ventricular dysfunction.

GSK met with the FDA, Cardio-Renal Division, and Dr. Temple in May of 2002 to review the data that the panel will see today. FDA advised GSK to submit the file and was subsequently granted priority review.

Just to give you an overview, the scope of today's presentation, we will review the use of beta-blockers in patients who have recently experienced an acute myocardial infarction and the favorable effect on reducing subsequent risk of death and recurrent MI.

Then, there will be two trials discussed - CHAPS, which was actually conducted by Boehringer Mannheim, and CAPRICORN, conducted by Roche, but the data submitted by GSK for the supplement.

CHAPS is a pilot trial of about 150 patients which supported our decision to proceed with the large pivotal trial CAPRICORN, which is the focus of today's presentation.

Now, at the outset, the primary endpoint for CAPRICORN was all-cause mortality. However, following a recommendation of the DSMB, the primary endpoint was changed to include a co-primary of death or cardiovascular hospitalization in addition to the all-cause mortality. You will hear about that later, the reason for that.

Now, although this co-primary was not met, there was a 23 percent reduction in mortality, and we are here today to discuss the merits of these findings and their inclusion into labeling.

The proposed indication statement that Dr. Borer already alluded to is as follows. Coreg is indicated to reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of less than or equal to 40 percent.

Now, the language includes the indication of a reduction in mortality since this was a primary endpoint of the trial, however, we believe there is also support for an indication of reduction in the combined risk of death and reinfarction, and you will see data to support this during the course of the presentation.

To adhere to the agenda, we will begin with a background presentation by Dr. Mary Ann Lukas of GlaxoSmithKline, and this is followed by a tandem presentation. Dr. Henry Dargie will present the primary endpoints of CAPRICORN and Dr. Milton Packer will describe the implications of these results.

Now, this will be followed by a presentation of the effects on non-fatal events by Dr. Dargie, then concluding with safety data and concluding remarks from Dr. Packer.

We are being assisted today by four consultants, all of whom played an important role in the CAPRICORN trial. Two are from the University of Glasgow. These are Dr. Henry Dargie, the principal investigator for CAPRICORN, Dr. Ian Ford, the principal biostatistician, and two other consultants from Columbia University, Dr. Milton Packer, who was an original member of the CAPRICORN Steering Committee before leaving to become the primary investigator for the sister study, COPERNICUS. Dr. Jonathan Sackner-Bernstein was on the Endpoint Committee for the CAPRICORN trial.

Now, I would like to introduce Dr. Mary Ann Lukas to provide some background presentation to today's topic.

Background to the CAPRICORN Trial

Mary Ann Lukas, M.D.

DR. LUKAS: Good morning, Dr. Borer, members of the Advisory Panel and FDA, ladies and gentlemen. My name is Mary Ann Lukas and I am Senior Clinical Director for carvedilol for GlaxoSmithKline.

Currently, there are three other beta-blockers approved for the long-term use in the post-infarction patient: timolol, propranolol, and

the immediate release formulation of metoprolol. While atenolol also carries an indication for use in post-MI patients, that indication is primarily based on the seven-day follow-up data from ISIS-II.

The major large-scale, long-term trials that were conducted with these drugs are listed on this slide. All were landmark studies when they were carried out 20 years ago, and despite some limitations as to their conduct and analysis, the totality of the data from these studies clearly established the efficacy of beta-blockers in reducing mortality in survivors of an acute myocardial infarction.

However, specific cohorts of patients were not well represented in these early studies and, in particular, high-risk patients were generally not enrolled. Patients with heart failure were either excluded or were enrolled in small numbers and only if they had no or minimal evidence of pulmonary congestion.

Many currently available treatments for the immediate management of the post-infarction patient were either not available or not used including ACE inhibitors, I.V. nitroglycerin, heparin, and thrombolytics.

In addition, many currently available treatments for the long-term management of the post-infarction patient were not allowed because of the effect that they might have had on showing a benefit of beta blockade.

For these reasons, physicians now are uncertain about the role of beta-blockers in the management of the post-infarction patient in the modern era. Many wonder whether beta-blockers are still needed if a patient is already receiving drugs that reduce infarct size, reduce the process of cardiac remodeling, decrease the risk of infarction, and minimize the adverse effects of neurohormonal activation.

Others are concerned about the safety of beta-blockers in high-risk patients, particularly the risk of worsening heart failure in patients with a low ejection fraction and the risk of hypotension in patients who would be receiving ACE inhibitors or vasodilators.

Complicating matters further is the fact that beta-blockers that are approved for use in post-infarction patients are not approved for patients who have overt heart failure and, in fact, they currently carry a contraindication for use in

these patients.

Conversely, the beta-blockers that are approved for use in chronic heart failure are not approved for use following a recent myocardial infarction.

Specifically, timolol, propranolol, and the immediate release formulation of metoprolol are indicated for use in the post-infarction patient, but their use is currently primarily focused on patients at low risk, whereas carvedilol and the sustained release formulation of metoprolol are indicated for use in patients with chronic heart failure. However, no beta-blocker is currently indicated for the patients in the middle, specifically, those with left ventricular dysfunction that is recognized early in the post-infarction period.

Therefore, these patients are least likely to receive such treatment even though, given their high risk, they are most likely among post-infarction patients to benefit from such treatment. They are also the most likely to develop an approved indication for beta blockade in the following months and years when symptoms of heart failure develop.

Now, carvedilol has been formally evaluated in controlled clinical trials across the entire continuum of patients from those within 24 hours of an acute infarction to those with post-infarction left ventricular dysfunction to those with mild, moderate, or severe chronic heart failure.

The U.S. Carvedilol program and the COPERNICUS trial focused on patients with advanced left ventricular dysfunction, all of whom had heart failure, but only about half of whom had a history of a myocardial infarction, and that generally occurred years before enrollment in the trial.

In these two studies, carvedilol significantly reduced the risk of death, as well as the combined risk of death and cardiovascular hospitalization, and the direction and the magnitude of these benefits were similar and remained significant if the analyses focused only on the patients in those trials with a history of myocardial infarction, which as I said represented about half of the patients in these trials.

Now, the Australia-New Zealand or ANZ study was a moderately sized study of patients with mild chronic heart failure who had moderate left

ventricular systolic dysfunction. All of these patients had an ischemic cardiomyopathy and nearly all had a history of a prior myocardial infarction.

Carvedilol significantly reduced the combined risk of death and cardiovascular hospitalization in the ANZ study during a follow-up of 18 to 24 months both when all patients were analyzed, as well as when the analysis was confined to those patients who had a previous MI.

It should be noted that the ANZ trial was not a survival study and that only about 50 mortality events were recorded in the trial.

So, the two trials that are the focus of today's discussion were conducted with the intention of evaluating the effects of carvedilol in post-infarction patients even earlier in the disease process.

The CAPRICORN trial evaluated patients who had survived an acute MI an average of 10 days earlier, all of whom had left ventricular dysfunction, but about half of whom had heart failure. The mean ejection fraction in this trial was higher than those in the trials that were conducted in patients with chronic heart failure.

The CHAPS study evaluated patients who

were within 24 hours of their acute myocardial infarction, most of whom had preserved left ventricular function and no heart failure. Therefore, the CHAPS and the CAPRICORN trials were carried out with the intention of determining if carvedilol would be beneficial if initiated far closer to the time of myocardial injury than had earlier trials evaluating post-infarction patients.

The main focus of today's discussion will be on the CAPRICORN trial, but before turning our focus to that study, I will briefly review for you the results of the CHAPS trial.

Now, CHAPS, which stands for the Carvedilol Heart Attack Pilot Study, was a single-center trial which was designed to evaluate in a preliminary manner the effects of carvedilol in the immediate peri-infarction setting.

The purpose of the study was to gain comfort about the use of carvedilol in this setting since the drug had not been used early post-MI before. Patients were enrolled if they had an acute myocardial infarction within the preceding 24 hours, but they were excluded if they had an indication for, or a contraindication to, treatment with a beta-blocker.

Patients who fulfilled these entry criteria were randomly assigned in a 1-to-1 ratio to placebo or carvedilol. Treatment with the study drug was initiated with an intravenous bolus of 2.5 mg of carvedilol or placebo, after which patients received 6.25 mg/twice daily of the study drug orally beginning four hours later.

This was increased to 12.5 mg/twice daily after 2 days. The dose of the study drug was not further increased in most patients although if after 12 days, patients taking 12.5 mg/twice daily met the blood pressure criteria and heart rate criteria that you see on the bottom of this slide, their study drug could be increased to 25 mg/twice daily.

Treatment with either carvedilol or placebo was maintained for a total of 24 weeks following randomization.

Now, the primary endpoint of CHAPS, as defined in the original protocol, was timed to a prespecified cardiovascular event, which included death, heart failure, recurrent MI or unstable angina, stroke, ventricular arrhythmia requiring medical therapy, emergency revascularization, or the use of a new cardiovascular drug with the

exception of nitrates or diuretics administered within 72 hours of the onset of their chest pain.

A total of 151 patients were randomized, 74 to placebo and 77 to carvedilol. Of these, a total of 5 patients, 3 in the placebo group and 2 in the carvedilol group, were found to have violated one of the exclusion criteria. These patients either never received study drug or had their study drug withdrawn within 4 days.

So, the remaining 146 patients entered long-term treatment and most received 12.5 mg/twice daily. Only 87 of these patients continued to receive study drug for 24 weeks and by far the most common reason for withdrawal from study drug was the occurrence of the primary endpoint.

The baseline characteristics of CHAPS are shown on this slide for the 146 patients who were randomized, had a confirmed myocardial infarction, and received at least 1 dose of study medication.

As you can see, this is largely a study of patients who were experiencing their first myocardial infarction, who had received appropriate therapy for their infarction including thrombolytics, aspirin, and intravenous heparin, and who had a normal left ventricular ejection

fraction.

Overall, the two groups were similar with respect to the majority of the baseline characteristics.

This slide tabulates the events that contributed to the occurrence of a primary endpoint in the two groups. A primary endpoint event was achieved in 31 patients in the placebo group and 18 patients in the carvedilol group.

All categories of the events were less common in the carvedilol group especially those related to the occurrence of myocardial ischemia.

This slide shows the Kaplan-Meier plots for the primary endpoint. The difference between the two groups was apparently early and was maintained for the duration of follow-up. The difference between the curves was statistically significant at a p value of 0.01.

On this slide, we show you that if the 5 patients who were randomized into the trial, but who did not receive long-term treatment with the study drug because of their failure to meet the key entry criteria, if those patients are included in the analysis according to the intention-to-treat principle, the effect of carvedilol remains

significant.

The mortality results from CHAPS are shown on this slide. Mortality was a secondary endpoint, and there were a total of 6 deaths that occurred during the 24-week planned duration of the trial. Four deaths occurred in the placebo group, 2 deaths occurred in the carvedilol group, and this slide shows the reason for deaths and the time that the deaths occurred following randomization.

Overall, the drug was well tolerated in the study, as described in the briefing document that was distributed to the committee.

I would like to say in summary that the data from this pilot study support the ability of carvedilol to reduce the risk of death, reinfarction, and arrhythmias in the post-infarction patient, and, in addition, demonstrate the tolerability of carvedilol in the immediate post-infarction period.

However, CHAPS was a small trial which observed few cardiovascular events and in which a large proportion of the patients did not continue double-blind treatment for 24 weeks due to the protocol requirement that patients achieving a primary endpoint stop study drug.

For this reason, at this point, we would like to turn our attention away from the CHAPS trial to a much larger and more definitive trial known as CAPRICORN. I would call Dr. Henry Dargie to the podium to describe the primary results of CAPRICORN to you, but would be happy to take any questions that you might have.

DR. BORER: Does anyone have any questions about study design at this point?

I have one. It is just a question for information only, there is no suggestion that there is anything wrong with having done it. The starting dose and up-titration schedule in CAPRICORN and also in CHAPS where the ejection fraction was a little bit higher, of course, starts at a higher dose and moves up faster than what is labeled for the use of carvedilol chronically.

I have no problem with doing that, I just want to understand how you came to the rapid up-titration and the higher starting dose for this trial of patients with heart failure.

DR. LUKAS: I can answer that specifically for CAPRICORN primarily, because GSK was not involved in the design of the CHAPS study back in 1992, but the feeling at the time was that it was

important to achieve beta-blocking levels in these patients as rapidly as could be within the bounds of safety, which was why the up-titration period itself was shorter than what was used in the heart failure trials.

For the same reason, the initial starting dose was higher, and the safety of that was assessed as will be described later by the Data Safety Monitoring Board looking at the data from the first 100 patients or so to make certain that was not--

DR. BORER: Was there some retrospective review of data from the prior trials that suggested you could do this safely? You know, it wasn't just picked out the air. I assume that there was some experience that suggested it was okay to do this, and it turned out to be okay.

DR. LUKAS: Yes. I don't want to say that I can remember exactly a retrospective analysis to support this point, but I do remember that the U.S. carvedilol trial data were looked at and that particularly the dose-related information from MOCHA and from the overall program to make certain that we--all of those trials, by the way, started at 6.25 in the U.S. carvedilol program, so we got

a lot of our sense that the starting dose would be safe from those trials.

DR. BORER: Paul.

DR. ARMSTRONG: Could you clarify two points for me? In Table 3, reporting on CHAPS, the death is 3 placebo, 2 carvedilol, and you said 4 placebo in your presentation. Did I misunderstand?

DR. LUKAS: No, there were 5 deaths that were counted as a primary endpoint, and there were 6 deaths that occurred during the follow-up period, so 1 patient who died had a primary endpoint event prior to their death, so that by the time to first event analysis, 5 deaths are included in the primary analysis, but the 6 deaths are reported for occurring in the entire follow-up period.

DR. ARMSTRONG: The issue of the concurrent use or lack of use of ACE inhibitors in this population and the instructions, there were at least 10 episodes of heart failure, but very low usage of ACE inhibitors here by design.

Could you help me understand that issue?

DR. LUKAS: Again, with apologies for not knowing all of the details of the design when it was first put together back in 1992, the use of ACE inhibitors, as you said, was excluded from the

beginning although there were 5 patients I believe in total who actually entered the trial and were receiving an ACE inhibitor, but the feeling was that, in fact, the establishment of the use of beta-blockers in the protocol and in the report was still felt to be deserving of further confirmation by the investigator. That is how they put it in the rationale, and they did not address the desirability or need to use an ACE inhibitor.

DR. ARMSTRONG: So, we should interpret the safety and efficacy of this study in the absence of ACE inhibitors which would now be, of course, background therapy.

DR. LUKAS: Absolutely true, and, of course, the CAPRICORN trial, as you will see, the majority of patients did receive an ACE. The only other thing I would remind you is, although I can bring up an exclusion criteria slide for you, but the exclusion criteria for CHAPS were Killip IV heart failure, and Killip II and III heart failure were allowed, but as you said, those patients were not receiving anything.

DR. BORER: Okay. Why don't we move ahead.

DR. LUKAS: Thank you.

CAPRICORN Trial - Primary Endpoints

Henry Dargie, M.D.

DR. DARGIE: Good morning, Dr. Borer, members of the advisory committee and the FDA, ladies and gentlemen.

My name is Henry Dargie. I am from the University of Glasgow. I was the principal investigator for the CAPRICORN study.

The primary objective of the CAPRICORN trial was to evaluate the effects of carvedilol on all-cause mortality in patients with left ventricular dysfunction who had recently suffered an acute myocardial infarction.

CAPRICORN was a multi-center, randomized, placebo-controlled parallel group study in patients with left ventricular ejection fraction equal to or less than 40 percent, with or without heart failure, and the trial was conducted worldwide in 163 centers in 17 countries.

The trial was conducted under the auspices of the Steering Committee, of which I was the chairman, an Endpoint Committee chaired by John McMurray, and a Data and Safety Monitoring Board chaired by Desmond Julian.

Now, all patients in the CAPRICORN trial

had had an acute myocardial infarction during the previous 3 to 21 days. The use of all modern evidence-based treatments for myocardial infarction are including thrombolytics, aspirin, heparin, lipid-lowering drugs, et cetera, was encouraged.

Patients were required to have an ejection fraction of equal to or less than 20 percent, and importantly, to be receiving an ACE inhibitor for at least 48 hours and to have been stable for 24 hours. In all, about 80 percent of patients were hospitalized at the time of study entry.

Patients were excluded if they had unstable angina or various other unstable features, but it is important to emphasize that patients may have had primary edema or even cardiogenic shock during their index MI, but they were required to be clinically stable at the time of entry into the study.

Patients were not enrolled, however, if they had an indication for, or a contraindication to, treatment with a beta-blocker.

Now, patients who fulfilled all the entry criteria were randomly assigned in a double-blind manner to carvedilol or placebo, carvedilol beginning at a dose of 6.25 mg/twice a day,

increasing every 3 to 10 days to a target dose of 25 mg/bid.

Should the initial dose of 6.25 not be tolerated, the patients could then be challenged with a dose of 3.125 mg/bid. Patients were then maintained on their maximum dose of treatment study drug until 630 patients had died.

If the patient's condition deteriorated during the study, the investigator could, of course, utilize any interventions that were clinically indicated, however, investigators were instructed not to institute open-label treatment with a beta-blocker unless there was a compelling and unequivocal reason for doing so.

The original primary endpoint of the study was all-cause mortality. The protocol originally also specified three secondary endpoints: (1) the combined risk of all-cause mortality or cardiovascular hospitalization; (2) sudden death; (3) progression of heart failure.

The original protocol anticipated that the study would enroll 2,600 patients based on the assumption that the 21-month mortality in the placebo group would be 29 percent, the risk of death would be altered by 20 percent as a result of

treatment with carvedilol, and the study would have 90 percent power to detect a significant difference between the treatment groups with an alpha of 0.05.

The protocol specified the trial would continue until 630 deaths had occurred with a minimum follow-up of 12 months to allow the effects of carvedilol to become apparent.

This number of events did not allow for any dilutional effect created by patients who discontinued the study medication or who were treated with open-label beta-blocker, however, fatal or non-fatal events were recorded and included in all analyses whether or not they occurred while the patient was on study medication.

Enrollment in the CAPRICORN trial began in June of 1997. Nearly two years later, in March of 1999, the DSMB notified the Steering Committee that it was recommending a change in the protocol.

As you recall, the original protocol for the CAPRICORN trial had strongly discouraged the use of open-label treatment with a beta-blocker, however, public announcements in late 1998 and early 1999 that beta-blockers had been found to prolong life in trials of chronic heart failure, namely, CIBIS II and MERIT-Heart Failure had raised

ethical concerns within the DSMB about our policy of withholding treatment with a beta-blocker until the completion of the study.

The DSMB believed that patients who developed heart failure during the course of the CAPRICORN trial should now be actively considered for treatment with a beta-blocker even though it fully recognized that a high frequency of open-label beta-blocker use would impair the ability of the study to detect a difference between the two groups.

As a result, and in view of the fact that the mortality rate in the trial at that time was lower than anticipated, the DSMB felt that the best approach would be to expedite completion of the trial by changing the primary endpoint to one that would allow a critical number of events to be achieved as soon as possible.

I must stress that this recommendation was made prior to having conducted any analysis of unblinded data by treatment group.

This slide summarizes the changes made in the protocol by the Steering Committee in response to the DSMB's recommendation. All-cause mortality or hospitalization for a cardiovascular reason was

added as a new co-primary endpoint. Of the studywise alpha of 0.05, 0.045 was allocated to this new endpoint and 0.005 to the original and retained primary endpoint of all-cause mortality.

All-cause mortality or cardiovascular hospital was added as a co-primary endpoint because it had been the first prespecified, the first listed prespecified secondary endpoint in the original protocol, and because the critical number of 630 events would be reached rapidly if either death or any cardiovascular hospitalization were to count as events.

Now, a total of 1,959 patients were randomized into the CAPRICORN trial, 984 to the placebo group and 975 to the carvedilol group.

As you can see, the two groups were rather similar with respect to their baseline characteristics. It is interesting, however, to note that even though about 30 percent of the patients had a history of a previous myocardial infarction, most of these patients were receiving neither a beta-blocker or an ACE inhibitor prior to their index MI, and the index MI was complicated by the development of primary edema in nearly 20 percent of patients.

The next slide tabulates other baseline characteristics, many of which distinguish these patients and those enrolled in the previous beta-blocker trials, beta-blocker post-infarction trials.

About half the patients received thrombolytics or a primary coronary intervention during their index MI. A large majority received aspirin, heparin, intravenous nitrates, and about a quarter received a lipid-lowering drug.

Furthermore, about half of the patients had heart failure, many of whom had recently received an I.V. diuretic and, of course, all of the patients or virtually all of the patients were receiving an ACE inhibitor or, in a very small number of cases, an angiotensin receptor blocker.

The mean ejection fraction, as you can see, was 33 percent in both groups. The mean systolic blood pressure was about 120 millimeters of mercury, but in nearly 25 percent of cases, the systolic blood pressure was, in fact, less than 110 millimeters of mercury.

Now, it should also be noted that patients generally were initiated on treatment with placebo or carvedilol more than 1 week after the qualifying

event, so that this trial was not an evaluation of carvedilol for the immediate treatment of an evolving myocardial infarction, rather, it was an evaluation of carvedilol in the early management of post-infarction survivors who had heart failure or were at high risk of developing it.

Now, of the 1,959 patients randomized into the CAPRICORN study, 10 were randomized, but didn't receive any study medication. They were, of course, included in all analyses.

The target doses were achieved in 84 percent of placebo and 17 percent of the carvedilol patients within 12 weeks. Generally, this level of medication was maintained for the duration of the study, and the duration of follow-up ranged from 3 to 33 months with a mean of 15 months.

This slide illustrates compliance with study medication. During the course of follow-up, 24 percent of the patients permanently discontinued study medication, very similar in both the placebo arm and carvedilol groups, but importantly to notice in this study is that 12 percent of the patients received open-label therapy with beta-blocker. This occurred more often, earlier, and for a longer time in the patients in the

placebo group than in the carvedilol group.
I would like now to review the results of the CAPRICORN trial on the two co-primary endpoints.
DR. BORER: Henry, before you get to that, let me ask if anyone has questions about design issues at this point.
I have one. The beta-blocker used before randomization, how was withdrawal from beta-blockers handled in the patients who were already receiving beta-blocker post-MI?
DR. DARGIE: The patients admitted to coronary care units who were already on beta-blockers, these are sometimes withdrawn by the discretion of the physician, but it is the case that some patients who were on beta-blockers and appeared to be stable, on being counseled or discussed, the trial being discussed with them, could have had that beta-blocker withdrawn then to be subsequently randomized.
This occurred in a relatively small percentage of patients because as you can see, not that many patients were receiving beta-blocker prior to admission.
DR. BORER: It said 35 percent.

DR. DARGIE: Yes.
DR. BORER: So, there would have been some formal withdrawal period and then you would have randomized.
DR. DARGIE: Yes.
DR. BORER: Okay. Tom?
DR. PICKERING: It was basically the same question. You said 3 percent had beta-blockers before their MI, and then it went up to 35 percent, so there were some who were put on it just temporarily, is that correct?
DR. DARGIE: That is absolutely right.
DR. TEMPLE: Tom can tell me if this is a silly question, but did you consider different allocations of the alpha--
DR. DARGIE: Sorry?
DR. TEMPLE: What was done, would be appropriate if the two endpoints had no relationship, weren't correlated at all? Sort of equivalent to a Bonferroni, but oddly distributed, but, in fact, one of the endpoints is included in the other, so those numbers seem a little more conservative than necessary, right? I just wondered if you had thought about other ways of arranging that.

DR. DARGIE: Other ways of expressing the alpha?
DR. TEMPLE: Yes.
DR. DARGIE: Well, we did certainly consider that. We could have split the alpha evenly.
DR. TEMPLE: My point is that, for example, if there were two endpoints and you did a Bonferroni, you test each at 0.025, but what I have learned is that that is over-conservative if the two endpoints are correlated.
You didn't divide it equally, so the numbers aren't that way, but maybe they didn't have to be as conservative as you chose. It is a little late to fix that, but I was just curious.
DR. DARGIE: I wonder if, with your permission, since I am not a statistician, I could perhaps get some statistical advice from my advisor, Dr. Ford, Professor Ford.
DR. FORD: Hello. My name is Ian Ford from the University of Glasgow. I think that is an interesting statistical point, as you said, but whatever the answer to that question would have been, we would still be having the same discussion today.

We did consider it, but we thought it would be better to take a conservative approach to the problem.

DR. TEMPLE: We plan for future meetings and events at the same time, so I was just curious.

DR. BORER: JoAnn?

DR. LINDENFELD: An amendment was made I noticed to decrease the follow-up from 12 months to 3 months to complete the study more rapidly. Can you tell me how many patients had a follow-up of less than 6 months?

DR. DARGIE: Not off the top of my head.

DR. LINDENFELD: Or just approximately?

DR. DARGIE: Would it be possible to answer that question a little later on in the presentation when we have established that figure?

DR. LINDENFELD: Yes.

DR. BORER: Steve.

DR. NISSEN: I have a couple of questions. The ejection fraction had to be less than 40 percent.

DR. DARGIE: Equal to or less than.

DR. NISSEN: Yes. How was that measured and when was it measured in the time course of the infarction?

DR. DARGIE: Ejection fraction could be measured by any of the established techniques for ejection fraction, so it could conceivably be measured also by invasive technique, so that was very uncommon.

The most common method of measuring ejection fraction was echocardiography. This was generally measured at a time when the patient was stable following their admission for their index MI. So, it was very close obviously to randomization.

DR. NISSEN: Right, not necessarily in the very acute phase of their infarction.

DR. DARGIE: That's right. The ejection fraction was measured generally at the time when people were stable, not in the hyperacute phase.

DR. NISSEN: And they had to have ST elevation MI, is that correct?

DR. DARGIE: No, they didn't. They had to have a definite diagnosis of myocardial infarction. They could have non-ST segment elevation myocardial infarction.

DR. NISSEN: Do you have any sense of what the distribution was between ST elevation and non-ST elevation MI?

DR. DARGIE: Yes, about 25 percent were non-ST segmental elevation, the majority were ST elevation.

DR. NISSEN: Does it surprise you that there was such a--I mean usually, non-ST elevation MI's don't result in ejection fractions of less than 40 percent. I presume most of those were people with a second infarction, is that right?

DR. DARGIE: Well, it is very interesting question. Of course, patients could have had a previous MI and therefore have a depressed ejection fraction prior to coming in, but that is probably the most common reason.

DR. BORER: John.

DR. NEYLAN: I was curious about some of the deliberations that went into the calculation of the sample size since this is relevant to an important element of the submission, I believe, with regard to the strength of the signal.

You describe a roughly 25 percent dropout rate, roughly equally distributed between the two treatment groups and I was wondering if you could share with us some of the thoughts in the original design as to why a dropout rate was not taken into account when considering the original sample size.

DR. DARGIE: What wasn't taken into account was the dilutional effect of open-label beta-blocker. That was the thing that wasn't taken into account. I think that we probably anticipated the dropouts would occur probably early in either group, but the sample size was simply an arithmetic calculation from the power and the reduction in mortality and the alpha and power that we wanted for the study.

DR. BORER: Ian, did you want to comment about that?

DR. FORD: Yes, I think it would be useful to say something. There are two ways you can do power calculations. You can either start with a theoretical benefit assuming everyone will continue on study medication and then adjust that down on the basis of an assumed withdrawal rate, or you can start with an effective treatment effect after taking into account the patients will inevitably withdraw from medication.

We took the latter approach assuming there had been no untrivial withdrawal rate in the study and we adjusted the effect size down to 20 percent to adjust for that.

DR. BORER: Marc.

DR. PFEFFER: While we are on this topic, so there must be some table of your projections at the time you made the change, and we are talking about drop-ins, so that would influence the process. Somehow you must have had some estimate of what the events would be and what your drop-ins would be.

Is there a table that one could look at to say this is what we thought in 1997?

DR. DARGIE: I don't think we have one.

DR. BORER: Henry, I would like to ask one question, and I will ask it again later because you may not have the information now.

A number of people were censored at the point where they received beta-blockers, and that is perfectly understandable and that is fine. I saw nowhere in the briefing document--all right, then, they weren't censored, that is just as well, even better, even better.

The point is that people received beta-blockers and they received beta-blockers for some reason, and I didn't see in the briefing document or the FDA review any discussion of specifically why the beta-blockers were given.

Now, you may not know, you may not have

collected documentation sufficient to answer this question, which I think would be unfortunate in a way because there is such a clear skewed distribution of administration of beta-blockers.

If, for example, people received beta-blockers because they were developing heart failure, and that was happening more in one group than another, that might well strengthen the case for the efficacy of the drug.

So, I am wondering, number one, do we know why they got the beta-blocker and was an analysis done, even though it wasn't given to us to account for that, and, if not, why there was no effort to do that.

DR. DARGIE: Dr. Lukas perhaps might be the best person to answer that.

DR. LUKAS: Yes, thank you, Dr. Borer. The answer I am going to give you may not be satisfying on all levels. The information on the patients who received an open-label beta-blocker was taken from the concomitant medication records and did include an indication for why the drug was given.

However, when the amendment was made in August 1999, suggesting that people should consider

putting patients on a beta-blocker if they had developed heart failure, the investigators did not really receive specific instructions as to indicate that that was the reason why they were being put on a beta-blocker.

So, when we looked in detail at the records for these 400 and some-odd patients who received a beta-blocker across the two groups, we really have a mixture that is difficult to interpret in a very clear way.

Most of the people who received long-term open-label beta-blocker, the indications that the investigator gave were post-myocardial infarction or ischemia, but there was no effort made--because this was not given, I will just tell you, it was not given a lot of importance at the time the analysis was being done. In retrospect, likely it should have been.

But we cannot give you based upon the information that we have in hand an answer that says 30 percent of the people were for heart failure, 40 percent were for other reason, and so on. I can only tell you from looking at the data in general that most of the information from the investigators said post-MI use.

DR. BORER: Thank you.
Tom.
DR. FLEMING: A few questions. The study's enrollment began in June of '97 and by our notes here, was completed, the follow-up was completed on February 3rd of 2000, is that correct?
DR. LUKAS: On March the 1st, 2000, the investigators received a fax saying that the 633 endpoints had been accrued and that they should contact their patients, bring them in, begin down-titration, do the end of study assessments, and so on.
The actual last dose of study medication including the down-titration was given on May 30th, 2000, so that was the actual end of the medication being administered. The last follow-up of patients actually went out to about July, August of 2000 to get the vital status on all of the patients for whom the vital status was not known at the time of the end.
DR. FLEMING: So, the last survival data that exists is through June of 2000?
DR. LUKAS: Actually, the last death recorded was July 18th, 2000.
DR. FLEMING: So, there haven't been any

survival updates beyond that.

DR. LUKAS: No.

DR. FLEMING: A design question. Just as you look at this philosophically, you have given us the history of development of evaluations of carvedilol. Among those trials were the Australia-New Zealand, the U.S. Carvedilol trial, and COPERNICUS, where you referred to the time frame there being two to five years post-MI.

From a scientific perspective, the question that CAPRICORN would be addressing would be whether it would be useful to use carvedilol earlier in the process, initiating it earlier. So, the logical question then is really not one of carvedilol, yes versus no, but immediate versus delay.

In essence, you are randomizing people that are now within 21 days of MI to immediate use of carvedilol versus a strategy that would delay initiation of beta-blockers to a time period where clinical conditions would indicate proper initiation.

That, I assume is, in fact, your perspective here, you are looking at, by design, an immediate versus delay design here, intending to

find out whether or not there is a 20, 23 percent reduction in death rate over time from such a design. Is that correct?

DR. DARGIE: Relatively immediate in the sense that it wasn't given within the first 24 hours as the first medication.

DR. FLEMING: Right.

DR. DARGIE: And given in the context of the use of beta-blockers in other LVD and heart failure circumstances when its limit has already been on-board, so it was within that time frame.

DR. FLEMING: And that makes sense to me. Why then is it not possible in that framework to have a mortality endpoint? Why was the Steering Committee and the sponsor of the perspective that the endpoint needed to be changed from something other than mortality?

DR. DARGIE: I could go through the history of that, if you like. I mean basically, it was considered that because of the use of beta-blockers further out in the trial, after three months or so, and that that would have a drop-in effect, and obviously lead to difficulty in detecting a difference between the two groups. That was the reason for that.

DR. FLEMING: Because it was thought that it would be implausible that you could have a mortality difference that would be meaningful if you had an immediate versus delay?

DR. FLEMING: You know, the power calculations, of course, are on the 630 deaths originally, and that obviously wouldn't have occurred within that time frame.

DR. FLEMING: Since you haven't had a chance to present the data, et cetera, I would like to return to that theme a little bit later. Let me move to another question.

You referred to the Data Monitoring Committee, and there are a number of issues that are perplexing to me in this. First, the membership of the committee, if I understand one of the earlier slides, Dr. Ford was a member of the committee.

Normally, we would anticipate that the Data Monitoring Committee would be an independent committee that would have no representation from the sponsor or investigators.

Dr. Ford, were you independent of this process?

DR. FORD: My group was the independent

statistical center for the study, was responsible for constructing the report for the Data Safety Monitoring Committee. I was the person who delivered the report to the committee, and I was a non-voting representative on the committee.

DR. FLEMING: So, you are what I would call the liaison statistician between the database and the Monitoring Committee, but not a member of the committee.

DR. FORD: That's correct.

DR. FLEMING: Was there a statistician on the committee?

DR. FORD: Yes, Simon Thompson, who is the Director of the MRC Biostatistics Unit in Cambridge University, was the statistician.

DR. FLEMING: The second question. In the materials we had received, there was indication the committee was blinded. Can you tell us more about that?

DR. FORD: The reports that the committee received were on an A/B basis or a treatment 1/treatment 2 basis. They received the report on the subjects who were in what we call the "warm-up" phase of the first 200 subjects where we got very detailed information. They got that data on an A/B

basis. The more detailed information for the rest of the study, they got in a treatment 1/treatment 2 basis.

For all-cause mortality, where the data came directly from the sponsor because there was a significant delay in the adverse event data passing through the CRO, which was processing the data and then coming to my group for analysis, the data was all treatment 1 and treatment 2. For the data from the sponsor on all-cause mortality, the committee decided that with the exception of interim analysis, they only wanted to see completely blinded data as they saw the data as a single group for all-cause mortality with the exception of the single meeting where they carried out an interim analysis.

DR. FLEMING: As an aside, since the primary responsibility of the Data Monitoring Committee is to safeguard interests of study participants, and have serious ethical concerns about a monitoring committee that is not fully unblinded to information evolving in the trial.

Moving ahead, though the recommendation now came down from the Monitoring Committee based on having seen results of CIBIS II and MERIT, and

this seems very appropriate that looking at emerging external information, the Monitoring Committee, in their judgment, believed that it would be important for patients who, in fact, progressed to heart failure, to be provided beta-blockers.

That was the recommendation. I have no concerns with that, that seems reasonable, but the sponsor has indicated that it was then the Data Monitoring Committee's recommendation to change the endpoint, which is a separate issue.

One issue is, is there a need to alter the way patients are managed, and I understand the role of the Monitoring Committee in that process. I don't understand the role of the Monitoring Committee in the process of changing the endpoint. That is the Steering Committee and sponsor's responsibility.

But seemingly from what you are telling us, you viewed it as the Data Monitoring Committee's responsibility to change the endpoint in the trial?

DR. DARGIE: No. As you say, the responsibility of the DSMB is to oversee the safety in the trial. I received a letter from the DSMB in

which they advised that we should consider, I think was the word used, a change in the primary endpoint, but the decision to implement that, of course, was entirely the Steering Committee.

DR. FLEMING: In the document, it was worded, and I can find the wording in a bit, something to the effect that it would have been extremely difficult for the--yes, the study failed to achieve its primary endpoint at the prespecified alpha because of a strong recommendation by the Data Safety Monitoring Committee to change the primary endpoint, a recommendation that would have been difficult for the Steering Committee and the sponsor to ignore.

This really is perplexing to me because the Data Monitoring Committee, first of all, should be unblinded, in which case they are the last group that I want to be intervening in changing my endpoint, but in this case, you are saying they were blinded.

But even with that being the case, it is not the Data Monitoring Committee's responsibility to alter endpoints in trials, so it is perplexing to me that you have indicated that it would have been difficult for the Steering Committee and

sponsor to ignore a recommendation from the Monitoring Committee to change an endpoint.

That is entirely your purview to decide what the endpoint is, and it is still not clear to me why, if you believed that immediate versus delay could influence survival, why you felt it compelling to change the endpoint whether or not you believed it was the Data Monitoring Committee's recommendation.

DR. DARGIE: It is, of course, interesting for me as the chairman of the Steering Committee to look back on those events and consider what we thought at the time.

We had appointed what I considered to be an extremely knowledgeable and very experienced DSMB. Desmond Julian had experience of previous MI trials, being on many more DSMBs than probably anyone in the room. We had experience on the DSMB in the areas of heart failure and also myocardial infarction.

So, it would be fair to say that, as the Steering Committee chairman, I was taking very, very seriously any information that would come from the DSMB. They didn't tell us that we should do anything. They didn't tell us that we should

change the primary endpoint. They didn't insist it be any given change, any given endpoint that would be the new co-primary.

They simply advised us to consider the possibility of a change in endpoint in order to expedite the completion of the study. At the time, I considered that was within the role of the DSMB in their role for the safety of the patients in the study.

I agree with you that it is not their role to actually decide on those things, but I would say that it would certainly be within their role to ask the Steering Committee to consider that in the interest of the safety of the patients in the trial.

It was in that spirit that I received the message and we discussed it among the group. It wouldn't be any surprise to you to know that this was greeted with a mixture of warmth and otherwise by the members, many wanting to maintain all-cause mortality.

It was only after quite a lot of discussion, and not just at one meeting, that we decided that we would adopt the strategy of accelerating the completion of the study,

maintaining its viability, of course, that was our primary concern, and also to maintain the identity of the study as a mortality trial.

So, within that framework, I felt not uncomfortable, if not comfortable, with what the DSMB had advised, and I didn't think, and still don't think, that they had overstepped the mark.

But insofar as the workings of DSMB are not the subject of written-down textbooks and instructions as yet, I think there will definitely be a spectrum of opinion on that.

DR. BORER: Steve.

DR. NISSEN: I guess what we were trying to get at here is there appears to have been, at least as I read the documents, two things going on. One was the recognition that in the interests of safety, that allowing patients to drop in was appropriate, and I personally find that highly commendable and the correct decision, and I just can't find any fault at all with that decision, period.

Obviously, it was a terrible challenge for you, but I think what some of us have been trying to understand better as we move forward toward this decision was there was also the problem of a trial

that was enrolling very slowly, so, you know, changing the primary endpoint, was the primary endpoint changed because enrollment was slow and this was a way to get the trial done more quickly, or were these issues of the drop-in the predominant issues.

It is confusing to us as we read these documents to understand the thinking. I would have loved to have seen the actual letter that was communicated to the Steering Committee. It would be very helpful to see exactly how this was communicated.

I don't know if that would ever be appropriate for us to actually see that, but it is one thing to change a trial for safety, it is another to change the endpoint because things are not going well or you are going slowly and you want to try to move things along, so you use a looser endpoint.

I don't know if I am speaking for anybody else, but I would like to get a sense of that as we move forward.

DR. DARGIE: I have a series of backup slides that describes the way in which this process took place. Would you be interested in seeing

those? In a nutshell, one can say that this process was the result of three things.

One was the slow recruitment. One was the fact that the overall mortality rate was considerably lower than I expected, but I think, if you like, the straw that broke the camel's back or the thing that activated the process at the time was the announcement of the results of CIBIS II, which by the way, I was the chairman, and also MERIT-Heart Failure, and that set the process going.

But there was, of course, concern about the slow recruitment even at the beginning, but I think it was that plus the low mortality rate plus the drop-in of the beta-blockers.

DR. NISSEN: What Tom I think was hinting at or maybe he was really saying it is that you could have said we will allow the drop-in, but we are not going to change anything else about the trial, and that was the alternative decision that might have been made, so to understand the process about why the endpoint was changed is really an independent decision of the decision to allow drop-in.

We are all trying to understand how those

things weighed upon the group that was responsible for conduct of the trial, because it does have an impact on how much leeway we give on this whole discovery process.

DR. DARGIE: I think it is very difficult to answer that particular issue about letting the trial continue with drop-in beta-blockers because we really didn't know exactly how common that would be. I mean it could have been very common.

It could have been along the lines we had, we really didn't know, but casting your mind back to 1998 and 1999 and the publication and presentation of these data, I think did engender a sense of urgency at least within the DSMB, which I suppose it communicates to the Steering Committee.

Since many of us have been associated with those trials and their clear results, we felt and I think you agreed that that was the appropriate thing to do.

DR. FORD: Maybe it is appropriate for me, since I was party to the discussions at the DSMB, to comment on what actually happened. I should say, first of all, that the DSMB had a charter and it was very clear to all members of the DSMB that they were an advisory committee to the Steering

Committee, and I think they were acting in good faith in giving advice when they wrote to the Steering Committee.

The issues that they considered were, as has been indicated, that at that time it appeared that the mortality rate was about 50 percent of what had been predicted. The study was experiencing difficulties in recruiting in addition to that, but we had the early stopping of the CIBIS II trial and then the MERIT trial.

At the beginning of this critical meeting that took place, there was an open discussion with the chairman of the Steering Committee on the impact of CIBIS II and MERIT. After that open discussion, the committee then decided that this was a very significant finding and that the investigators and essentially the patients would have to be informed of the results of those studies.

Because of the poor recruitment rate, the very low mortality rate, which was particularly important, it was considered that the impact of a significant number of patients going on to open-label beta-blocker treatment would make it, particularly after subsequent non-fatal events

would have occurred during the trial, would make it extremely difficult to hit the mortality outcome.

It was for that reason that they felt obliged to comment to the Steering Committee that they thought there was a difficulty that they should consider, but the decision always was actually in the hands of the Steering Committee to make a decision.

DR. BORER: JoAnn.

DR. LINDENFELD: I have a slightly different question, so I just want to be sure that nobody has any more on this one.

DR. FLEMING: Maybe if you are going to change, just to summarize and maybe reinforce a bit, too, what Steve just said, the role of the Monitoring Committee here is in looking at emerging evidence, external evidence, and making a recommendation about what they viewed to be important for ethical management of patients, is entirely appropriate.

Ultimately, the recommendation to the Steering Committee to make such a change is advisory, and the Steering Committee would act on that recommendation.

A change in the endpoint is entirely in

the hands of the Steering Committee and the sponsor. If the DSMB has no access to emerging data, then they, in fact, can be in a position to provide advice on that. Once they have access, it is very inappropriate for them to be in that position.

Ultimately, one of my objections or concerns is a statement in the Executive Summary that seems to suggest that the Data Monitoring Committee was ultimately limiting the options the sponsor and Steering Committee had on the endpoint.

I don't see that whatsoever, and I am perplexed in a sense because we are saying here there are conditions that can emerge post-randomization that would lead the patient to be in a position to need beta-blockers, and as a result--if we call that drop-ins, I don't call that drop-ins, I call that delayed administration--as a result, it is not plausible that you could see a 20 percent reduction for immediate versus delay when we are now being asked today to look at these data to determine whether or not immediate is better than delay.

So, if you believed that it wasn't plausible to see a difference, and yet you are

coming before us today with data to ask us to judge whether or not there is evidence that immediate is better than delay, so it seems rather odd that the Steering Committee, whether it was a recommendation from the DSMB or not, reached the conclusion that mortality wasn't a viable endpoint if we are being asked today to determine whether immediate would improve survival.

DR. BORER: Marc.

DR. PFEFFER: The same topic. I think the internal knowledge and external knowledge, so that the external information available is not only the two studies you mentioned. You had the U.S. carvedilol trials, which was done even before that, known to the leaders of the trial.

The recruitment rate was known to the leaders of the trial. Often, the leaders of the trial know global overall without dividing by treatment assignment the mortality rate, so did the Steering Committee know those three ingredients without the DSMB?

In essence, you knew recruitment, you knew the U.S. carvedilol, you knew CIBIS as the leader of CIBIS. You didn't need the DSMB to tell you that. What did you need from them that you didn't

have?

DR. DARGIE: We didn't need that from them. Basically, the DSMB exercised their role as far as the safety of the patients to draw that to our attention, not insofar as we weren't aware of it. We discussed it at the open session of the meeting in March of 1999.

Insofar as the U.S. carvedilol trials are concerned, I mean the CIBIS II, of course, was the first single randomized, controlled trial to demonstrate an impact on mortality of beta blockade, and so the question was still in discussion, but you are quite right.

When CIBIS II and MERIT-Heart Failure came along, there was no longer any doubt, but you are right, we were in possession of those facts. It is just that the DSMB I guess were exercising their role in drawing that to our attention, and invited me--we have an open session, that was the plan before each meeting to discuss matters of concern and of interest, and it was at that meeting that we jointly discussed it.

DR. LINDENFELD: Could you clarify for me how the beta-blocker drop-ins were handled? Just administratively, if an investigator decided to add

a beta-blocker, the study was unblinded, or exactly how was that handled?

DR. DARGIE: No, the study was not unblinded, but the patients then had to be down-titrated and then up-titrated on the beta-blocker.

DR. PACKER: There are minutes of the DSMB meeting. I just want to share with the committee an excerpt of that, just so that there is clarity as to what the DSMB recommended and what it did not recommend, just one paragraph.

DR. BORER: For the record, that is Dr. Packer who is speaking. When you are speaking, you have got to introduce yourself.

DR. PACKER: I am sorry. D36?

DR. DARGIE: Right.

DR. PACKER: This comes from the minutes. This is a verbatim quote from the minutes of the Data Safety Monitoring Board that was held on March 10, 1999. This comes from the closed--it was called "closed section"--this is the section where the principal investigator was not present.

You can read this for yourself. "The best option was thought to be a change in the primary endpoint to death or cardiovascular

hospitalization, keeping the target number of events for the primary endpoint unchanged."

I will let you read the rest of it. Professor Julian was going to write to the Steering Committee with this proposal, and I do not want to say this was the right thing or the wrong thing. I just want to be able to say that that, in fact, did take place in precisely the manner, and I wanted to show you the documentation from the minutes that, in fact, the process by which this took place.

It could be that the Steering Committee could have figured this out all on their own, and didn't need the DSMB, but the DSMB did make the deliberation. They did, in fact, go as far as they did, and did, in fact, make this particular recommendation to the Steering Committee.

So, I just wanted to make clear exactly what took place.

DR. BORER: Okay.

DR. PACKER: For right or wrong.

DR. BORER: Why don't you go ahead with the results.

DR. DARGIE: Oh, yes. You stopped me in the middle. Here we are. Results on the primary endpoints.

This slide shows the effects on the co-primary endpoints of all-cause mortality or cardiovascular hospitalization. You can see there were 367 such events in placebo arm and 340 on carvedilol. This reflected an 8 percent reduction, which was not lower than the amendment prespecified alpha of 0.045.

The next slide is the Kaplan-Meier curve for that combined endpoint. You can see the curves are virtually superimposable here, but do separate towards the later phase of the trial, but this was not statistically significant.

This shows all-cause mortality. There were 151 deaths for all causes in placebo and 116 in the carvedilol group. This was a 23 percent reduction in the risk of death and at a p value of 0.031, which also was higher than the amendment prespecified alpha of 0.004.

This is the Kaplan-Meier curve which shows that the curves do separate early, continue to diverge throughout the course of the study.

Now, the annual placebo mortality rate was 12.1 percent in the placebo group and 9.8 percent in the carvedilol group. For information, that placebo mortality was nearly twice that observed in

the earlier post-infarction beta-blocker trials.

At this point, Dr. Borer, I was going to pause and ask Dr. Packer, because he is going to elaborate on those primary endpoint data.

Why Are We Here?

Milton Packer, M.D.

DR. PACKER: Dr. Borer, members of the Advisory Committee, and FDA, ladies and gentlemen. Today, the Advisory Committee is being asked two important and interesting questions that have been discussed I think at various regulatory meetings for many years, but never have been I think specifically answered.

First, can the findings from a trial that did not meet its primary endpoint be used as the primary basis for labeling, and, if so, what criteria should the data supporting such a finding fulfill to justify incorporation to labeling?

I think it would be fair to say that these questions are what today's meeting is all about.

Let's look at the first question. Can the findings from a trial that did not meet its primary endpoint be used as the primary basis for labeling? I guess if the answer to that is no, I guess we could simply stop here and end the meeting early

and go home, but I think that, in fact, there would be no reason for me.

But the questions from the FDA indicate that there is a reason for meeting, and that is because in the past, the FDA has granted an indication based on trials that did not meet its primary endpoint because it found the data from such trials to be credible and persuasive.

I want to cite two specific examples. The first example is digoxin. Digoxin is currently indicated for the treatment of mild to moderate heart failure to reduce heart failure related hospitalizations. This is true even though the trial that observed this benefit, the DIG trial, did not achieve its primary endpoint of all-cause mortality.

Current labeling for digoxin contains a detailed description of the trial including mention of the fact that the drug did not have an effect on the primary endpoint.

The second example is enalapril. Enalapril is currently indicated for the treatment of clinically stable, asymptomatic patients with left ventricular systolic dysfunction to decrease the rate of development of overt heart failure and

decrease the incidence of hospitalization for heart failure.

This is true even though the trial that observed this benefit, the SOLVD prevention trial, did not achieve its primary endpoint of all-cause mortality. Current labeling for enalapril contains a detailed description of the trial including mention of the fact the drug did not have an effect on the primary endpoint.

I should mention that the decision to approve enalapril for asymptomatic left ventricular dysfunction was almost certainly favorably influenced by the FDA's knowledge that enalapril reduced all-cause mortality in the SOLVD treatment trial which enrolled patients later in the disease process. I want to get back to that in just a few minutes.

Therefore, in the past, the FDA has concluded that data supporting the existence of a drug effect can form the basis for labeling even when the measure of benefit that had been identified a priori to be of primary importance in the trial, was not significantly influenced by therapy.

Given these examples, I think that the

real question today is not whether one can base labeling on trials that did not meet their primary endpoint, instead I think the real question before the committee is what criteria should the data supporting such a finding fulfill to justify incorporation into labeling, or as the FDA has phrased it in its questions to the committee, what rules should guide the decision to allow inclusion of a discovery into labeling.

To my knowledge, there are no formal rules, in fact, I don't think that this issue has ever been fully discussed before at an advisory committee meeting, but it is a terribly interesting and important question.

Let me propose one answer to the question. Specifically, I would propose to the committee that the criteria that will allow inclusion of a discovery into labeling should have the strength of evidence comparable to that which would allow labeling based on a trial or trials that achieve their primary endpoint.

In fact, I would say on a personal level that the committee needs to set an extremely high standard here, a standard that would be met only by the most persuasive of circumstances. So, first,

we need to define these criteria and then we need to determine if these criteria are fulfilled by the current circumstances with carvedilol.

The first step is to define the criteria and I would begin by proposing that any benefit being considered for inclusion into labeling should be an outcome measure of major importance. Ideally, it should be a reduction in mortality. I say this because I think everyone would recognize that death is a very special and unique endpoint. The finding of a treatment-related reduction in the risk of death is always compelling since death is an unbiased endpoint of paramount clinical importance.

Indeed, the FDA reviewer has written that the FDA has acted as if all clinical trials implicitly have an alpha of 0.05 assigned to the analysis of mortality independent of the primary endpoint.

Well, I think we can begin there, but I think we need to go further because there are several important examples of how the wrong decision would have been made if our only criteria were that all trials implicitly have an alpha of 0.05 assigned to mortality.

Here are two examples. In an initial study of vesnarinone in heart failure, which enrolled about 450 patients, observed a 62 percent reduction in mortality, which was highly significant, but was based only on 46 deaths, observed in a trial designed primarily to evaluate exercise tolerance.

Subsequently, a larger study, which was specifically designed to evaluate the effects of vesnarinone on mortality and which recorded 10 times as many events, concluded that the drug significantly increased the risk of death.

Similarly, an initial study comparing losarten and captopril, which enrolled about 700 patients, observed a 46 percent reduction in the risk of death, which was significant, but it was only based on 49 events, and a trial primarily designed to evaluate renal function.

Subsequently, a larger study, which was designed specifically to evaluate the effects and compare the effects of losarten and captopril mortality, recorded 10 times as many events, demonstrated that losarten appeared to be somewhat inferior to captopril.

So, I think we need to be very careful

before reaching conclusions about mortality effects of drugs based on data from trials that were not designed to find them. Such trials generally observe very few events, and thus, any mortality risk reduction can only reach statistical significance if it is probably large and has very wide confidence intervals.

That is why the current example with carvedilol is so interesting. Mortality was not an incidental observation or discovery in the CAPRICORN trial. The CAPRICORN study was designed and carried out as a survival trial, and it observed a substantial number of deaths.

Furthermore, given an annual mortality rate that was nearly twice that in earlier post-infarction trials, the trial could provide a reasonably precise estimate of the effects of carvedilol on mortality with relatively narrow confidence intervals.

In fact, the final results of the study demonstrating the effect on the original primary endpoint of all-cause mortality, had a p value less than that specified in the original protocol with a magnitude of effects similar to that anticipated in the original protocol.

Now, I don't want to ignore the fact that there was a protocol amendment, but I think it would be unfair to use the existence of the amendment to claim that mortality reduction noted at the end of the CAPRICORN study was an accidental discovery.

There is no doubt that CAPRICORN was first and foremost a survival study, and it continued as a survival study even after the protocol amendment.

So, there are many characteristics of the CAPRICORN trial that distinguish its mortality findings from the experiences with vesnarinone and losarten, however, the most important distinction between the results of CAPRICORN and earlier experiences with vesnarinone and losarten is reproducibility where the mortality observations with vesnarinone and losarten were not reproduced, the mortality effects in the CAPRICORN trial have been replicated in other post-infarction trials with other beta-blockers.

Now, this last point is really important because even if one were to agree that all trials implicitly have an alpha assigned to mortality, some may argue it isn't 0.05, it is far smaller than that. That is because if we are to believe in

the existence of a therapeutic effect, it must not only be credible, it must be persuasive.

Some may argue that a p of 0.031 for the mortality finding in CAPRICORN isn't persuasive, the p value needs to be far smaller than that, say, 0.00125.

Now, I want to make note of the fact that the FDA perhaps has generally not required mortality effects to have extremely small p values in order to be persuasive, but I think we need to set a higher standard here because the alpha assigned to the mortality analysis in the CAPRICORN trial was not 0.05, it was 0.005.

That means for better or for worse, the CAPRICORN investigator set an extremely high standard for reproducibility, one which can be met by one trial with a very small p value or by two or more trials with the same finding, each with a p less than 0.05.

Prior to CAPRICORN, there were five trials with five different beta-blockers that reported a mortality reduction during long-term treatment with these drugs in post-infarction patients.

These studies were considered sufficiently persuasive individually and collectively to lead to

the approval by the FDA of three of these beta-blockers - timolol, metoprolol, propranolol, specifically for the management of post-infarction patients.

Now, this slide summarizes the key features of the four large-scale randomized trials that had been carried out with these three beta-blockers in patients with a recent MI.

The first two trials carried out with the nonselective beta-blockers timolol and propranolol were large-scale studies that observed about 2- to 300 deaths, and each reported highly significant effects on mortality. The results of the next two trials carried out with metoprolol are also favorable although less impressive.

Now, if one combines the data from all placebo-controlled trials carried out with beta-blockers in the long-term management of post-infarction patients--and this analysis is the most recent analysis that has been done, it is based on more than 2,400 deaths observed in nearly 25,000 patients enrolled in 31 trials--the evidence supporting the existence of mortality effect with beta-blockers in this setting is extremely persuasive.

The magnitude of the effect is a 23 percent reduction in risk of death with fairly narrow confidence intervals.

Now, the results of the CAPRICORN trial are extremely concordant with those of earlier trials with beta-blockers approved for the management of post-infarction patients. The trial observed a large number of deaths and the magnitude of the mortality effect with carvedilol observed in the CAPRICORN trial was identical to that seen in the meta-analysis of all placebo-controlled, post-MI beta-blocker trials with relatively similar confidence intervals.

Now, this was true even when the meta-analysis was restricted to patients who had clinical evidence of left ventricular dysfunction or heart failure following their acute myocardial infarction.

So, I think if we look at the concordance between the mortality data with CAPRICORN and the results of other post-infarction beta-blocker trials, it would be fair to say that the strength of evidence is quite substantial, equivalent to a very, very small p value.

Now, this argument holds only if it is

appropriate to consider the results of other post-infarction beta-blocker trials in gaining reassurance about the reproducibility of the results with carvedilol in the CAPRICORN trial.

Now, the committee has recently dealt with this specific issue in another therapeutic area. Earlier this year, the advisory committee looked favorably at the results of a controlled trial with losarten in diabetic nephropathy, but it expressed skepticism about recommending approval based on the findings in a single trial, whose primary endpoint, which included a component of questionable clinical importance, was achieved at a significant, but unimpressive p value.

However, the committee recommended approval of losarten when the findings in the losarten trial were considered together with the highly concordant findings of a similar trial with irbesarten in the same disease, a trial which when considered alone, did not lead the committee to recommend the approval of irbesarten.

So, I think the committee felt comfortable with this recommendation because they believed that neither irbesarten nor losarten had effects that might detract from their ability as angiotensin

antagonists to prevent the progression of renal disease, so we should apply the same criteria to the current situation with carvedilol.

Specifically, does carvedilol have effects that might detract from its ability as a beta-blocker to reduce mortality in the post-infarction setting. Well, not all drugs that block beta-1 receptors have similar effects in reducing mortality in post-infarction patients.

This trial summarizes the findings of a recent meta-analysis by Freemantle and colleagues that explored possible relations between the pharmacological properties of specific beta-blockers and their effects on mortality in long term, post-infarction trials.

Overall, long-term treatment with a beta-blocker reduced the risk of death by about 23 percent, however, the magnitude of the effect appeared to be attenuated in trials with beta-blockers that had intrinsic sympathomimetic activity, and therefore it is possible for beta-blockers to have ancillary effects that detract from their mortality benefits, and it is possible using this kind of analysis to detect such effects.

It is therefore noteworthy that carvedilol is a nonselective beta-blocker that has no intrinsic sympathomimetic activity. In fact, if one adds the data from CHAPS and CAPRICORN to the data with other beta-blockers, the magnitude of the effect of carvedilol are precisely what might be anticipated from its known pharmacological similarity to timolol and propranolol.

However, one could look at this and argue that it is still possible for carvedilol to exert an unknown pharmacological effect that might detract from its survival benefit in a manner that might not be picked up by this kind of analysis.

To address this possibility, we need to examine the effects of beta-blockers in a disorder closely related to left ventricular dysfunction following a recent myocardial infarction, and that is left ventricular dysfunction following a remote myocardial infarction.

Now, the two disorders are part of a single disease continuum with patients moving from one phase of the disease to the next over a period of weeks, months, or years. In fact, similar neurohormonal factors are believed to be important both early and late in the disease process,

explaining why both ACE inhibitors and beta-blockers are effective in improving outcomes at both time points in the disease continuum.

Please remember it is exactly the same thinking process that was used by the FDA when it relied on the mortality reduction seen in the SOLVD treatment trial to gain reassurance about their decision to approve enalapril for patients in the SOLVD prevention trial.

Now, three different beta-blockers - bisoprolol, carvedilol, and metoprolol, have been shown to reduce mortality in patients with left ventricular dysfunction and chronic heart failure, and the magnitude of this benefit for each drug is similar in patients with or without a remote history of a myocardial infarction.

Carvedilol has been shown to reduce mortality in patients with left ventricular dysfunction and chronic heart failure, and the magnitude of this benefit is extremely similar to that produced by other beta-blockers in this disorder both in patients with and without a remote history of an MI.

If carvedilol had a pharmacological property that detracted from its ability to reduce

mortality, for example, alpha blockade or an antioxidant effect, such an action should have been apparent in trials with the drug in chronic heart failure and should have negated or diminished its effect relative to other beta-blockers, and this was not the case.

In fact, just as in the post-infarction setting, intrinsic sympathomimetic activity has also been associated with reduced survival efficacy in chronic heart failure.

So, I think we can conclude that long-term blockade of beta receptors can be expected to reduce mortality in the post-infarction setting, that drugs classified as beta-blockers can exert effects that may detract from their ability as beta-blockers to reduce mortality, and current approaches are able to detect such effects; that the pharmacological properties of beta-blockers that may diminish their survival effects appear to be similar in the post-infarction setting and in chronic heart failure, and that the observed effects, the observed effects of carvedilol in both post-MI patients and in chronic heart failure indicate the drug does not exert effects that might detract from its action as a beta-blocker to

prolong life.

Thus, the current situation with carvedilol, I think fulfills all the requirements that might reasonably be proposed to allow the committee to consider the results of other post-infarction beta-blocker trials in making judgments about the credibility and persuasiveness of the mortality findings in the CAPRICORN study.

So, let's return to the original question - is the totality of available data sufficiently credible and persuasive to conclude the carvedilol reduces mortality in the post-infarction patient with left ventricular dysfunction even though the CAPRICORN trial did not achieve its primary endpoints at prespecified levels of significance?

I think it would be fair to say that the circumstances surrounding the current application are fairly unique. First, the benefit of treatment with carvedilol we are talking about today is not a surrogate endpoint or a minor clinical effect, but a meaningful reduction in the risk of death.

The mortality benefit of carvedilol seen in the CAPRICORN trials was not an incidental or unexpected finding, but seen in a trial that was specifically designed and carried out to evaluate

the effects of the drug on survival and was of a magnitude anticipated in the original study protocol.

Second, the nature and magnitude of the mortality effects of carvedilol in this trial are almost identical to those seen in other post-infarction trials. This provides external confirmation within the same class of drugs, an example very analogous to the situation with losarten and irbesarten in diabetic nephropathy.

Third, experience with carvedilol in trials of chronic heart failure shows that the same drug prolongs life when added to an ACE inhibitor in post-MI patients who are later in their disease process.

This provides yet another type of external confirmation with exactly the same drug, but in patients who are treated several years later. This example is very analogous to the situation with enalapril, which was evaluated in the SOLVD prevention and SOLVD treatment trials.

So, I think we really do have a fairly unique situation. We have an endpoint of unquestioned clinical importance observed in a trial designed to find it, and in addition, we have

two types of external confirmation, confirmation in the same disease, within the same class of drugs, confirmation with the same drug later in the same disease state.

This means we not only have persuasive evidence of a class effect, but we also have persuasive evidence that this class effect applies to carvedilol.

So, when the committee considers the questions posed to it this afternoon and discusses the criteria that need to be fulfilled to allow the inclusion of a discovery into labeling, let me suggest one possible set of criteria, in fact, let me suggest the most stringent criteria that I can think of.

Here they are. The findings should be a reduction in mortality. The trial should have been designed to detect the finding, and the magnitude should have been anticipated in the original study protocol.

The observed magnitude of the benefit should be both clinically relevant and realistic, and conclusions about benefit should be based on a meaningful number of events.

There should be substantial evidence of a

similar benefit both in nature and magnitude in the same disease state with other members of the same class of drug. There should be substantial evidence the drug produces the same benefit later in the disease process, and the magnitude of such benefit should be comparable to that with other members of the same class.

Finally, the findings should be supported within the trial by additional evidence of clinical benefits without overriding safety concerns, something which you will hear about in the final two presentations.

Now, I realize that these criteria fit precisely the current situation with carvedilol, but can anyone think of more stringent criteria than these?

In my own view, the only way someone could reject these criteria would be to insist that a trial must meet its primary endpoint to be incorporated into labeling. That would mean the concept of discovery as defined in the FDA questions would be impossible.

Now, later today the committee will be asked how much it is willing to inflate the false positive rate by accepting data in a clinical trial

that failed to meet its primary endpoint. I do not know how the committee will answer this question, but my own personal response would be zero.

I do not think the committee should accept any inflation in the false positive rate in making clinical or regulatory decisions. So, in my view, today's discussion should not be about how much the committee should be willing to inflate the false positive rate.

The real question is, in making regulatory decisions based on trials that missed their primary endpoint can one reduce the false positive rate to acceptable levels given the opportunity considering, not just the results of one trial, but the totality of available data.

If one rejects the concept of discovery entirely, it would mean one would be giving great weight to concerns about an increase in the false positive rate in the single trial while at the same time giving little weight to the totality of available data which in the case of carvedilol should lead to a marked decrease in the false positive rate.

It is up to the committee to determine whether the balance of concern and reassurance that

I think are unique to today's discussion is in favor of approval.

I would be happy to take any questions the committee might have.

DR. BORER: Not at this point. What we will do since this actually is a philosophical regulatory discussion that is handled in the questions, is to table that discussion until we get to that point and maybe we can hear the remainder of the results now and proceed with the sponsor's presentation.

CAPRICORN Trial
Effect on Non-Fatal Events
Henry Dargie, M.D.

DR. DARGIE: Thank you.

I am now going to talk on the effect of carvedilol on non-fatal events in the CAPRICORN trial. We have focused so far on concordance of the mortality results in the CAPRICORN trial with the mortality results of other studies.

But looking for concordance, it is important to look not only at mortality, but at non-fatal endpoints across the studies. For example, there were two co-primary endpoints in the CAPRICORN trial, the effect on all-cause mortality

and the effect on all-cause mortality or cardiovascular hospitalizations.

The effect on mortality was very similar to that seen in the earlier post-myocardial infarction trials, as Dr. Packer has said, but was the observed effect of carvedilol on the combined risk of death or cardiovascular hospitalizations similar to the earlier post-infarction beta-blocker trials.

Well, of course, this question is difficult to answer because this endpoint was never assessed in early beta-blocker trials, which did not record the recurrence of hospitalizations as endpoints.

We can attempt to answer this question, however, by looking at the specific events that were responsible for a cardiovascular hospitalization. Now, in the CAPRICORN trial, a cardiovascular hospitalization was defined as an admission for any cardiovascular reason except for an elective procedure.

As you can see from this slide, which is the time to first event analysis of the combined endpoint, you can see many of these admissions were for the occurrence of a major cardiovascular event,

such as death, myocardial infarction, worsening heart failure, cardiac arrhythmia, or stroke.

The frequency of these admissions was generally lower in the patients randomized to carvedilol, however, about 30 percent of the admissions were not related to a major cardiovascular event, and the frequency of these admissions did not seem to be affected by carvedilol.

I think this is important because in comparing the CAPRICORN trial and interpreting the results, we have to realize that previous large-scale trials have focused only on admissions for major cardiovascular events.

For example, the primary and secondary endpoints prespecified in earlier post-infarction beta-blocker trials were the occurrence of a non-fatal infarction or arrhythmia, and no analysis was ever carried out of the effect of treatment on all cardiovascular admissions.

In fact, if such an analysis had been performed, it is unlikely that effect of beta-blocker would have been found because in the beta-blocker group, there were consistent reports of increased frequency of heart failure,

hypotension, bradycardia, et cetera, in most of the trials as you can see. Such events were included in the cardiovascular hospitalization endpoint in CAPRICORN, but not in these previous trials.

Probably the most detailed information we have about the occurrence of non-fatal cardiovascular events comes from the beta-blocker heart attack trial. In that study, the proportion of patients reporting cardiovascular events other than reinfarction were similar in the placebo and propranolol groups with respect to heart failure, angina, and so on.

Now, in all recent large-scale post-infarction trials of patients with left ventricular dysfunction, which were carried out with ACE inhibitors and more recently with aldesterone antagonist eplerenone, the prespecified endpoints that reflected the effect of treatment on fatal and non-fatal cardiovascular events always focused on major cardiovascular events, specifically, the occurrence of myocardial infarction, heart failure, arrhythmia, stroke, or varying combinations of these events.

So, it is important to note, and this slide is important in that respect, that if the

effects of carvedilol in the CAPRICORN trial were to be reanalyzed using any of the definitions of a cardiovascular endpoint used in any of these earlier trials, treatment with carvedilol would have been associated with a clinically and statistically significant result.

This slide lists the various definitions of a cardiovascular event used in earlier trials from the most selective at the top with diffuse events to the most comprehensive with the largest number of events at the bottom.

Regardless of which definition is used, carvedilol would have reduced the risk of a cardiovascular event by 17 to 30 percent, all with nominally significant p values.

There is an important point to make here, is that we are not showing you these data to conclude that carvedilol does reduce the risk of these non-fatal cardiovascular events.

We are showing you these data to provide a credible explanation as to why the expected effect on the combined risk of death or cardiovascular hospitalization was not met, so the committee need not necessarily give great weight to such failure in its deliberation of the persuasiveness of the

mortality finding in CAPRICORN, which is the preeminent event.

I would like now to show some additional data showing the concordance of the results of the CAPRICORN trial with the results of other post-infarction beta-blocker trials specifically with respect to subgroup analyses, mode of death, recurrent myocardial infarction, and cardiac arrhythmias.

First of all the mode of death. This slide shows the prespecified subgroup analyses for the effect of carvedilol on all-cause mortality. The magnitude of the treatment effect across all subgroups was similar to that seen in the analysis of all randomized patients.

Any trend towards a different response in a specific subgroup for all-cause mortality was not, in fact, confirmed when that same subgroup was analyzed for the combined endpoint of all-cause mortality or cardiovascular hospitalization.

Now, of the prespecified subgroup analyses of which this is a list, only one of them suggested the possibility of heterogeneous effect. Specifically, for both of the primary endpoints, carvedilol appeared to have an adverse effect in

patients who were in Killip class III at baseline.

These were the patients, I stress, who had pulmonary rales more than halfway up on physical examination, however, there were only 65 patients and 21 deaths in this subgroup, so one needs to interpret this fairly cautiously.

Nevertheless, even the possibility of a finding here raised our interest since these patients had been systematically excluded from earlier post-infarction beta-blocker trials. So, we went back and carried out two post-hoc analyses looking for patients who were similarly under-represented or were shown to respond less well to beta-blockers in earlier post-infarction trials.

This slide, in green, shows two post-hoc analyses based on the presence or absence of elevated cardiac enzymes and based on the pretreatment systolic blood pressure.

For both primary endpoints, carvedilol exerted its most marked effects in patients who had enzymatic confirmation of their index myocardial infarction, and for both endpoints, the higher the baseline blood pressure, the better the response to carvedilol or vice versa.

Again, this is interesting because patients without enzymatic confirmation of their index infarction and patients with lower systolic blood pressures were either excluded from or were shown to respond less well to beta-blockers in earlier post-infarction beta-blocker trials.

So, we submit that these analyses provide additional evidence that the results of CAPRICORN are, in fact, similar to the results of these earlier beta-blocker trials.

Now, let's move on to analysis of the mode of death. In all earlier post-infarction beta-blocker trials that showed a reduction in mortality, there was also reduction in cardiovascular death and in sudden death.

This was also true in the COPERNICUS study, a trial of carvedilol in patients with left ventricular dysfunction and chronic heart failure.

This slide shows the hazard ratios and corresponding 95 percent confidence intervals for the risk of cardiovascular death, sudden death, and death due to worsening heart failure in the CAPRICORN trial.

Patients in the carvedilol group had a 25 percent lower risk of a cardiovascular death, a

lower risk of sudden death, 26 percent lower risk of sudden death, and a 40 percent lower risk of a pump failure death. Now, each of these effects was normally significant or nearly so.

This slide shows Kaplan-Meier curves for the analysis of time to sudden death. Although this was prespecified as a secondary endpoint, the CAPRICORN study, however, I must note, was not powered to detect a significant effect on any particular mode of death.

Nevertheless, this effect on sudden death is also concordant with that seen in earlier post-infarction beta-blocker trials.

The earlier post-infarction trials of beta-blockers not only showed a reduction in cardiovascular death and in sudden death, but they also showed a reduction in the risk of a non-fatal reinfarction.

Indeed, in several meta-analysis of these early studies, low-term beta blockade reduced the risk of a non-fatal myocardial infarction by 26 percent.

This slide shows the effect of carvedilol on the risk of non-fatal recurrent myocardial infarction and combined with fatal events in order

to address the issue of competing risks.

Carvedilol reduced the risk of a non-fatal myocardial infarction by 41 percent, the combined risk of a fatal or a non-fatal myocardial infarction by 40 percent, the combined risk of a cardiovascular death or a non-fatal myocardial infarction by 30 percent, and the combined risk of all-cause mortality or non-fatal myocardial infarction by 29 percent.

All of these effects, as you can see, were nominally significant and concordant with those seen in earlier post-infarction beta-blocker trials.

I should note here that there is a question to the committee concerning the effect of carvedilol on the risk of recurrent non-fatal infarction. The question suggested there were only 45 recurrent MI's in the placebo group and 27 in the carvedilol group.

This appears to be the result of some confusion because these are the correct numbers of recurrent infarctions only if one were to look at the fraction of first cardiovascular hospitalizations that were due to recurrent infarction, but there are many patients who had

recurrent infarction after first being hospitalized for some other reason.

So, all together there were 60 recurrent infarctions in the placebo group and 37 in the carvedilol group. However, none of these analyses account for the fact that patients who die cannot experience a recurrent infarction, and so the most appropriate analysis is one that combines mortality and recurrent infarction.

This slide shows a Kaplan-Meier plot for the combined risk of death or recurrent myocardial infarction in the CAPRICORN trial, which I should note is the least biased. We are looking at the risk of recurrent infarction.

There are 331 events represented in this analysis. The curves separated almost immediately following randomization and continued to separate for the duration of follow-up.

Finally, in all earlier post-infarction beta-blocker trials, long-term beta blockade reduced the frequency of cardiac arrhythmias.

This slide shows the effect of carvedilol in the CAPRICORN trial on the risk of supraventricular arrhythmias or ventricular arrhythmias reported as an adverse event.

Carvedilol reduced the risk of any supraventricular arrhythmia, atrial flutter, or atrial fibrillation, any ventricular arrhythmia, and ventricular tachycardia or ventricular fibrillation, all with very small p values.

This slide shows a Kaplan-Meier plot for the analysis of time to the first occurrence of atrial flutter or atrial fibrillation on the left, and the time to first occurrence of ventricular tachycardia or ventricular fibrillation on the right, and in both cases you can see the difference between placebo and carvedilol. Again, these effects are concordant with those seen in earlier post-infarction beta-blocker trials.

Therefore, the effects of carvedilol in the CAPRICORN trial are not only very similar to the effects of other beta-blockers in other post-infarction trials with respect to all-cause mortality, but also with respect to all other reported benefits of beta-blockers in the clinical setting.

Specifically, like other beta-blockers, carvedilol reduced the risk of cardiovascular death and sudden death, reduced the risk of fatal and non-fatal reinfarction, and reduced the risk of a

clinically significant atrial or ventricular arrhythmias.

In summary, it is also important to observe that all of these benefits were observed in patients already taking an ACE inhibitor and receiving all the other appropriate treatments for the immediate and long-term management of post-infarction patients.

I would like now to pause there and ask if the committee has any questions on anything that I have presented in this section.

DR. BORER: Beverly.

DR. LORELL: Thank you very much. That was a very thorough summary. I do have one question relating to the Killip class III patients and the original all-cause mortality curve, slide 58, that was presented.

One of the things that is very interesting to me about the survival curve admitting the risk of teasing apart time points in survival curves, which I recognize, is that to my knowledge, previous trials in chronic heart failure with both carvedilol and Toprol XL have not shown this early dip, if you will, in mortality that was seen here, which raises the question that there might be a

little problem.

Was early mortality confined to the patients who were Killip class III?

DR. DARGIE: No.

DR. LORELL: No, okay.

DR. DARGIE: That wasn't the reason. This slide certainly has been the subject of some debate. We know that the curves do separate early. There appears to be a little blip here, as you have said, and then they continue to separate, but the number of deaths during this period, during the first 30 days, was significantly less on carvedilol than on placebo just at that particular point that the curves do appear to come together.

DR. LORELL: My second question related to your Killip class III data. Admittedly, that was a fairly small fraction of the overall experience.

Has that led you to think about any specific recommendations or thoughts as to whether, at this point in time, early post-infarction carvedilol should be started in patients who are Killip class III at least using this protocol of dosing?

I would like your thoughts and maybe Dr. Packer has some thoughts on that.

DR. DARGIE: I think it is a very important point. As you have observed and as I stated, the numbers in this classification were very small, but reminding ourselves that these are patients who have rales more or less all over their chest.

The question is how does that reconcile with the requirement in the protocol that the patients were to be clinically stable. I suppose that one could also address that issue to anyone other than in Killip class I, because in Killip class II, there were 600 patients or so who, in fact, experienced the benefit.

I think one would have to regard that event, that adverse trend as a safety signal and that in the management of the patient with heart failure either post-infarction or chronic heart failure, one would want those patients to be clinically stable, would include absence of evidence of fluid retention, so I interpret that as a signal for a greater emphasis on that approach, but I don't think it negates the use of carvedilol in the post-infarction period provided the patients correspond to those requirements.

DR. PACKER: Bev, I just wanted to clarify

a point that you made about the similarity or no similarity between this curve and COPERNICUS. We truly looked at these curves, as you might imagine, very carefully, and to non-statisticians, I am not certain what the curves separating and coming together and separating mean.

We have been told by statisticians that there is a certain amount of wobble that occurs in curves and that we shouldn't make too much out of these things. Having said that, in the first month in CAPRICORN, there were 33 deaths in the placebo group and 19 deaths in the carvedilol group. That is the first month after randomization.

The other thing that is worthwhile looking at, I do this only for entertainment purposes. If you look at this curve in CAPRICORN, and can we have the corresponding survival curve for COPERNICUS. It's the survival curve for COPERNICUS.

Look at the early separation. It comes together at about, oh, three four months, and then it separates again. C3. We haven't blown up COPERNICUS in a similar way, but I think you will get the impression.

DR. BORER: While we are waiting for the

slide, Bob, did you have a comment to make about this particular issue?

DR. TEMPLE: Yes. I am sorry I missed the first few minutes of this, but these patients were randomized on an average of 10 days after their infarct. That is quite different from most of the other post-infarction trials, which were later, BHAT and timolol, I think you had to be 25 days or something like that.

It reminds me that in acute studies like ISIS I, there was some early damage in patients especially those who got low blood pressure, so I wonder if you want to comment on whether the earlier nature of it might have been disadvantageous to some of the patients.

DR. DARGIE: That really--

DR. LORELL: Before you answer Dr. Temple's question, I actually think, Dr. Packer, your comment about the very early mortality is quite helpful, at least to me, because I think one of the really different important points of this trial is can you give a beta-blocker early post-infarction in people with very depressed ejection fraction, many of whom have clinical heart failure.

So, I think knowing what that signal is in the first month, the first 30 days after starting it, mortality is very important.

DR. PACKER: I only put up this slide because the committee has asked the question to try to compare mentally the curves with COPERNICUS and the curves with CAPRICORN, so I just want to show you that although the scale here is different, and I need to emphasize that, there is an early separation in COPERNICUS that comes together at three months and then separates again.

We have done extensive analyses in the first month and two months of therapy in COPERNICUS, and the difference in mortality seen in CAPRICORN is exactly superimposable in what is seen in COPERNICUS in the first month, and I don't know why the curves come together at three months and separate. I just wanted to show you the parallelism.

DR. TEMPLE: If I could just add to my question. With ISIS I, we analyzed the response in relation to initial blood pressure, and although there was considerable debate about noodling with subsets, people whose blood pressure was initially low clearly did fairly badly in that trial.

It makes you wonder whether there are some people who are more vulnerable to early beta blockade than others, and perhaps that is what you are picking up in this relatively sick population.

DR. DARGIE: I am sure that must be correct. We did show in the subsequent analysis that the lower the blood pressure, the effect of carvedilol was less, but just to stress that since we consider the most important outcome here to be mortality, the mortality during that early period was not in any way increased on carvedilol, indeed, quite the opposite.

In fact, if we combine that with important other events arguably, recurrent myocardial infarction in that period, there is still also that very clear, even clearer separation of the curves at an early stage.

So, I don't think insofar as these major events are concerned, that this early administration addressed the outcome, quite the opposite.

DR. BORER: Steve.

DR. NISSEN: Could you put up slide 105, please.

This is probably more of a rhetorical

question than a question, but these data here were available to the Steering Committee when they redesigned the trial. They knew what the precedents were for choice of endpoints, and yet they didn't choose those endpoints.

I think it is important that we understand that, that they chose a different set of endpoints, yet, these data were in the public domain, all but I think EPHESUS were in the public domain, and so just so we have the record straight, you guys could have chosen this group of endpoints or any constellation of them when you redesigned the trial, but you didn't do so.

You need not respond unless you want to, to that maybe rhetorical question.

If I may continue and then I will yield, unless you want to say something.

DR. FLEMING: Before you do, I had a similar thought. It is easy after the fact to say, well, these other endpoints are the ones that obviously matter the most and look at how significant we would expect, but why did you not consider these?

DR. DARGIE: Well, it is certainly very salutary. I mean had we chosen death and MI, then

perhaps we wouldn't be having this discussion, however, I think I should just go through the process of why we chose that particular endpoint for cardiovascular hospitalizations.

If I could have backup slide D42. This is our way of summarizing exactly why we chose that endpoint for cardiovascular hospitalization. Now, the original protocol didn't pay a huge amount of attention to the definition of a cardiovascular hospitalization because it was originally a secondary endpoint.

The Steering Committee, and I as the chairman of it, assigned the responsibility for defining the cardiovascular hospitalization, what a cardiovascular hospitalization was to an Endpoint Committee. Dr. Jonathan Sackner-Bernstein here, who is a member, is here if there are any supplementary questions.

Now, our Endpoint Committee defined cardiovascular hospitalization, I am sure you will agree, in a very broad and strict way, which was a hospitalization for which there was no definite known cardiovascular cause, and it didn't target or specify components of that, that previously weren't or thought might be influenced by beta blockade.

You may consider that to be a tactical problem.

That is how the Endpoint Committee defined cardiovascular hospitalizations, which is not an unreasonable definition for something which is a cardiovascular hospitalization.

The further issue was at the time of changing the primary endpoint, I suppose there was another opportunity at that point to make a further change in the endpoint in order to perhaps better characterize what the effect of carvedilol was doing in this population.

But I have to tell you quite honestly and openly, at the time the Steering Committee and I were reluctant to make too many changes. We had already made a significant change in the primary endpoint, which Dr. Fleming and others have alluded to, is a relatively unusual thing to do and one that is only done for the most compelling of reasons, which we have discussed.

So, when we changed the primary endpoint, and we simply elevated the secondary endpoint, we were reluctant to change the definition of that endpoint. We stuck with it. That is the history of the endpoint.

DR. NISSEN: If I may continue, I wonder

if you could put up slide 109. I just had a question. I am surprised that 300-plus of these patients had no increase in cardiac enzymes. I would have thought that would have been part of the definition of an acute myocardial infarction for purposes of the trial.

So, now I am really confused. What I am saying is, Jeff, even if you have got thrombolytics, whatever you get, how do you diagnose an acute MI if you don't have elevated enzymes, I mean does that mean it was only diagnosed by electrocardiographic criteria? Is that what happened?

DR. DARGIE: You and other members are fully aware that the new definition of myocardial infarction depends, first of all, on there being an elevation in enzymes, but we use the WHO definition of acute myocardial infarction, which was at the time the standard way of defining myocardial infarction, which was two out of three count.

One was a typical clinical presentation, one was a typical change in electrocardiogram, and the third was cardiac enzymes, which of course by definition means that you can diagnose a myocardial infarction by that definition without cardiac

enzymes.

Of course, in the early phase of myocardial infarction, ST segment elevation, and so on, one obviously proceeds to treatment before knowledge of the cardiac enzymes, but that is an aside.

But that was the definition we used, and as a result, for those patients entered into the trial, this number of patients were diagnosed without enzyme change.

DR. NISSEN: I accept that, but I guess that would mean then that those no cardiac enzymes patients, did they all have to have ST elevation or could they also just have ST depression?

DR. DARGIE: Good point. I am not sure. But, nevertheless, that wouldn't be necessarily the reason why it wasn't done. You simply adhere to the definition, which was the WHO one.

DR. NISSEN: A final question was slide 114. Again, this is maybe more of a rhetorical question than a question, but to me, this is not discovery, this is data mining. I mean you have taken two endpoints, put them together, that were never prespecified, and show us a bunch of p values for them. I can't let that go unchallenged.

When you are talking here about discovery today, this is not what discovery means. The term for this, the nomenclature is not discovery. It is called data mining. It just doesn't contribute here, to me, in my view, to our thinking process.

DR. DARGIE: Essentially, the reason for doing this was to explain why the definition we used of non-fatal cardiovascular events didn't succeed, and also it demonstrates, I believe, excellent concordance with previous trials.

We are not suggesting that this was not in any way a post-hoc trial, but also describes what I say happened in the trial.

DR. NISSEN: But you see the label that is being asked for is for death and recurrent infarction, and this is the data to support that, but to buy this, we have to allow you to take two endpoints from a bunch of endpoints, put them together, and say, well, these are the two that worked, so that is the label we are going to give you.

We will get to the discussion later, but just so we all understand how these things came to be.

DR. BORER: Paul.

DR. ARMSTRONG: I have got three lines of questioning, Mr. Chairman. It will take a little time, but before starting them, Steve, the definition of infarction in the trial design on page 40 actually indicates that ST elevation or evolving Q would be the ECG criteria if enzymes weren't present, just on a point of clarity.

My first set of questions relates to definitions and, in particular, the definitions of reinfarction, unstable angina, and heart failure, the extent to which there was concordance between the investigator ascertainment and the Endpoint Committee with particular emphasis on reinfarction because you, of course, are emphasizing it and we will be discussing it later, so could you clarify those definitions and the extent to which there was concordance with the investigator and the committees?

DR. DARGIE: Yes, I can do that. I don't know whether Dr. Bernstein might feel that he could be in a better position to do that as a member of the Endpoint Committee.

DR. SACKNER-BERNSTEIN: Hi. Jonathan Sackner-Bernstein from Columbia.

In terms of the definitions, it is

reported in the briefing document how we defined myocardial infarction. Unstable angina was similarly defined in the--

DR. ARMSTRONG: Would you just remind us what your definition of reinfarction was, please?

DR. SACKNER-BERNSTEIN: Reinfarction was the two out of three criteria as has been previously cited, and in terms of the clinical presentation, enzymes with elevation at least two times the upper limit of normal, and the third criteria was the EKG changes.

The EKG changes could have either been ST segment elevation or EKG changes with evolution including Q waves, could also have been a new left bundle branch block if the patient went to Angiography and an intervention on an acute lesion was performed.

So, you needed two out of three.

DR. ARMSTRONG: Sorry, the definition that I have in front of me is the definition of acute myocardial infarction, which was the index event.

My question is what was the definition of reinfarction?

DR. SACKNER-BERNSTEIN: I am sorry I wasn't clear. That is what I was just defining.

Reinfarction was when a patient was hospitalized for more than 24 hours and met two of three of the criteria consistent with the WHO criteria.

So, it was the clinical presentation was one of the three components, the increase in cardiac enzymes, a CPK greater than two times the upper limit of normal was the second component. The third component was ECG changes, which I described, either with the ST segment elevations or other EKG changes that included development of new Q waves, or also, part of that could have been a bundle branch block, a new bundle branch block that was associated with an acute intervention at that time.

So, that is the definition of reinfarction. The definition of unstable angina was the typical ST Q wave changes along with parenteral therapy in a hospitalization that lasted 24 hours.

DR. ARMSTRONG: And the definition of heart failure, worsening heart failure?

DR. SACKNER-BERNSTEIN: Typical symptoms or signs of volume overload associated with parenteral therapy for an admission that lasted more than 24 hours.

DR. ARMSTRONG: And the concordance between the information you received and your ultimate decision?

DR. SACKNER-BERNSTEIN: I actually don't think we have that analysis here looking at those endpoints. So, that is something that we would have to perform, that analysis.

DR. ARMSTRONG: Then, honing in on reinfarction, since about 75 percent of reinfarction that is hospitalized is within the first 72 hours, help us understand what the frequency of reinfarction in this population was after their index infarction, before they commenced therapy, and whether it was balanced.

DR. SACKNER-BERNSTEIN: Well, the way that non-fatal events were adjudicated was as follows. The patient had their index MI, they were stabilized, they were randomized.

While they were still in the hospital between randomization and before they went home, any non-fatal events weren't counted as part of this reinfarction and other endpoint event analysis, so that mortality was counted as soon as people were randomized, but these non-fatal cardiovascular events, particularly reinfarction,

were counted, were adjudicated, were analyzed from the point in time when the patient left the hospital, because part of the definition was a hospitalization for an event.

DR. ARMSTRONG: So, do we know or do we not know the frequency of reinfarction prior to commencement of study drug after the index infarction in this population? That is the question.

DR. SACKNER-BERNSTEIN: I do not know the number or nature of infarctions that occurred while the patients were still in the hospital after being randomized, but there is a relatively small period of time between randomization and commencement of therapy, if that is the period you are trying to hone in on.

DR. ARMSTRONG: Well, the day 10 was the average time to commencement of therapy, which is after the majority of reinfarction, which is the point I am honing in on.

DR. DARGIE: Could Dr. Lukas comment?

DR. LUKAS: I certainly understand the concerns about the time frame. I just wanted to point out--which I believe it states in the briefing document--that even given the time frame,

80 percent of patients were randomized while they were still hospitalized, so that to Jonathan's point, we cannot tell you today how many of those 80 percent of the patients may have had an extension of their index MI, I guess would really be the best way to characterize it, after they were randomized, before they went home.

DR. ARMSTRONG: Without wanting to perseverate on this point, Mr. Chairman, we are going to be asked about an indication for reinfarction in a population whose major risk of reinfarction will have passed before the study drug was commenced, and I just want to be clear about my understanding of the population that we are looking at and our knowledge of the intercurrent likelihood of the event of interest from the time of the index infarction to the time of commencement of study therapy. That, for me, remains a black box.

DR. LUKAS: I apologize if I misinterpreted your question, but we would have to go back and see if the information was available to answer that specifically.

DR. ARMSTRONG: My second line of questioning relates to slide 107, if we could see that, please.

I think, Dr. Dargie, when you presented this slide, you suggested that the only subgroup of interest to drill into, that looked like it was heterogenous, was the Killip III, but I was attracted to the patients with the inferior myocardial infarction, a rather larger sample than the patients in Killip class III, which impressed me as being somewhat to the opposite of the others.

You obviously had a reason for prespecifying this subgroup. I wondered to what extent your examination of that subgroup led to better understanding of why they might have had a different response.

DR. DARGIE: I think we prespecified it in order to define the population as clearly as possible into inferior, anterior, and others. As you say, there appears to be less a response in the inferior group than in the others.

DR. PACKER: Mr. Chairman, if I could just clarify the answer on this?

DR. BORER: Do you want further clarification?

DR. ARMSTRONG: I would be delighted.

DR. PACKER: Paul, I actually had exactly the same question that you did and asked further

about how this, you know, what could explain this.
The other category includes a substantial number of people with inferior other, inferior lateral, inferior, posterior, you know, this is pure inferior, the other is a hybrid category which includes many inferiors, so that one could, in fact, if one wanted to go back and look at the inferiors by pulling out the inferior combined with something out from the other, and if you look at the point estimate, my sense is that the point estimate will shift back to the left. I don't know if that helps.

DR. ARMSTRONG: We have heard some discussion about hypotension as a potential marker in an inferior MI, issues around bradycardia, block, hypotension, that we are all familiar with, whether the time course and the events in these patients would shed any light on it, but it does strike me as being somewhat heterogenous with the other population although I recognize the confidence limits are wide.

My third line of questioning. All of us who have shared your opportunity to enroll patients in large trials--if you could leave that slide up because it's germane--from Russia recognized that

these patients are different, and you obviously were concerned about that because you prespecified a look at these patients.

I presume, but I don't know, that you capped them at 600 or 30 percent of your population, that is why there is an exact number of 600 from that part of the world.

Could you tell us a little bit about the frequency of their events and their behavior as it relates to some of these issues that relate to surveillance, concomitant medications, and outcomes, and how homogeneous versus heterogenous they were?

DR. DARGIE: I could just begin with a description of what went on in Russia and the fact that as the chairman of the Steering Committee, I visited a number of the countries to hold investigator meetings.

I would say that the investigator meeting experience in Russia, that was held in Moscow, was an extremely valuable one because I was extremely impressed by the interest and knowledge of the investigators from Russia who were at that meeting.

Perhaps that was one of the most interesting experiences in the trial, going to

Russia. We, because of this issue, because again it is your right to prespecify, do we have concerns about it and how would it would be extrapolated to the rest of the world, indeed, to the U.S.

We did carry out an audit in the Russian patients, and it appears that good clinical practice in the Russian centers was excellent. Really, here in this slide, one doesn't really see any sense of a difference. The confidence interval is perhaps a little bit wider, but looking at the same analysis for hospitalizations, we have the same effect, i.e., no obvious difference between the Russian centers and elsewhere.

So, I am not saying I was necessarily very surprised, but the visit to Russia was extremely valuable and one had the impression and confidence that the trial was going to be carried out okay there. That was backed up by our audit.

DR. ARMSTRONG: Could you just--last point--clarify what was the mortality rate and the reinfarction rate amongst the Russian patients as opposed to the others?

DR. DARGIE: I think I would have to get that number for you.

DR. BORER: Henry, there is one issue that

was highlighted by the FDA reviewer, and I would appreciate your comment about it.

That is, that the time to hospitalization, to cardiovascular hospitalization, in the carvedilol group was shorter than the time to hospitalization in the comparator group, which might be counterintuitive.

Can you discuss this possible inconsistency?

DR. DARGIE: I don't think I can. The time to hospitalization in the carvedilol group was shorter than in the placebo group.

DR. FORD: Can I comment?

DR. BORER: Sure.

DR. THROCKMORTON: I think that we are referring to something that we had actually sent a correction around to the committee about, Jeff. If you didn't get a chance to look at it, that was an analysis that the FDA conducted.

We had a discussion with the sponsor about it, and I think in the fairness of time, I think in brief we concluded that our analysis was, in fact, not appropriate, we were misunderstanding a bit of it, so I don't think that is a thing that we need to really go any further on.

DR. BORER: I will withdraw that question then.

Marc.

DR. PFEFFER: I have one point I just want to make sure I understood the answer to Dr. Armstrong. So, all the non-fatal events that occurred--now, I am talking about after randomization--and were not part of the non-fatal events, so when Dr. Lorell is concerned about worsening the heart failure, we are not seeing that when we are looking at the non-fatal events, if they occurred during the initial hospitalization, just a clarification.

DR. SACKNER-BERNSTEIN: You have that correct. Non-fatal events that are included in the analyses that you are seeing and that are in the documents are events that occurred after discharge from the index hospitalization.

DR. PFEFFER: And a follow-up on Dr. Armstrong, one of the differences across countries is the lengths of stay. In some of the countries where you are doing this, there is a rather protracted length of stay, which is just their standard of practice. They monitor patients longer. So, we are not seeing events during a

period that I don't know.
Now, there are two safety issues that came up that I didn't see in either the FDA's report or the sponsor's. One is the 30 percent of the people that were on a beta-blocker. So, do we have that subgroup the beta-blocker yes, beta-blocker no? That is one subgroup.
The other subgroup I would like to see came up in the discussion today is a function of time of randomization. There was a wide window to randomize. Some people could have been randomized in the early period, some people in the late, so whether it be the median or tertiles of time to enrollment, I would like to see those as safety issues.
DR. DARGIE: We do have the first of those analyses, which is just coming.
DR. BORER: While we are waiting for that, I am going to peremptorily cancel the break that is listed here and we will stop a little earlier than is scheduled for a lunch break in the interest of keeping the committee together as long as we can, so that we can complete the deliberation as a committee because we have one non-U.S. member who needs to leave at a certain time.

DR. PACKER: This is the analysis that was requested. This is a subgroup analysis based on whether patients had received an oral or an I.V. beta-blocker during the index MI or whether they hadn't. You see the number of patients in each group. You see the hazard ratios. They are almost superimposable for both co-primary endpoints, and you see the number of events that are analyzed in each of those subgroups in brackets.

DR. BORER: Are there any other questions for Dr. Dargie?

DR. PFEFFER: Will we get the time to randomization after lunch?

DR. BORER: I am sorry, the time to randomization.

DR. DARGIE: We will get that after lunch.

DR. BORER: We can go on to the discussion of safety issues then. Thank you very much, Henry.

DR. DARGIE: Thank you.

Safety and Concluding Remarks

Milton Packer, M.D.

DR. PACKER: I would like to conclude with some brief remarks about safety and end with some brief concluding comments.

The committee has already seen the strong

concordance of the effects of carvedilol in the CAPRICORN trial with the effects of other beta-blockers in other post-infarction trials.

You have seen this with respect to all-cause mortality including the pattern of subgroups effects, which is very parallel to that seen in earlier studies, the mode of death, the risk of recurrent infarction in cardiac arrhythmias.

It therefore is appropriate to ask whether such concordance also exists with respect to the safety of carvedilol in the CAPRICORN trial.

This slide lists the safety issues that were identified in earlier post-infarction beta-blocker trials. In these earlier studies, patients randomized to timolol, propranolol, or metoprolol had an increased risk of heart failure and pulmonary edema, hypotension and dizziness, bradycardia and heart block, and peripheral vascular symptoms.

Exactly the same pattern was seen with carvedilol in the CAPRICORN trial. In fact, neither the sponsor nor the FDA identified any new safety issues with the use of carvedilol in post-infarction patients that had not been

previously identified in earlier post-infarction beta-blocker trials or in earlier trials with carvedilol and heart failure.

In addition, in the CAPRICORN trial, there were many adverse cardiovascular events specifically those related to worsening of the underlying disease, which occurred less frequently, less frequently with carvedilol than with placebo.

In fact, if one focuses only on adverse events deemed to be serious by the investigator, nearly all such events were less common in patients randomized to carvedilol.

These safety data, together with the data on non-fatal events that you have just heard about, strongly reinforce the concordance of the results of CAPRICORN with the results of earlier trials.

First and foremost, we have a mortality finding of unquestioned clinical importance observed in the trial designed to find it, and in addition, we have many different dimensions of both internal consistency and external confirmation.

The mortality finding is supported within the CAPRICORN trial by the effect of the drug on non-fatal events. The pattern of benefits is identical to that seen with other beta-blockers in

the same disease state and specifically with carvedilol later in the same disease.

I think it would be fair to say the totality of available data make it extremely likely that the benefits of carvedilol would be reproduced if it were evaluated in a confirmatory trial.

But even if the committee were to agree that the mortality finding in the CAPRICORN trial were credible and persuasive, it might still be wondering why it should recommend incorporation of the results of CAPRICORN into current labeling for carvedilol. After all, carvedilol is already approved for the treatment of post-infarction patients albeit those with a remote history of a myocardial infarction and after they have developed symptoms of heart failure.

Other beta-blockers are already approved for use in survivors of acute myocardial infarction, and these other beta-blockers could be used in the immediate post-infarction period, and patients could be switched to carvedilol if deemed appropriate when the acute phase has passed and heart failure has become apparent.

This may all be true, but I think it would be important to remember that there are

insufficient data to recommend the addition of any beta-blocker currently approved for infarct survivors to an ACE inhibitor or to other treatments, such as thrombolytics, aspirin, or lipid-lowering drugs, in patients who have left ventricular systolic dysfunction following an acute myocardial infarction.

All beta-blockers currently approved for use in infarct survivors carry a contraindication for use in patients with heart failure, and as a result, the frequency of use of any beta-blocker in patients with left ventricular dysfunction following acute myocardial infarction is low especially outside of academic medical centers.

My sense is that such use will remain low unless physicians are educated about the earlier administration of beta-blockers in patients likely to require treatment with a beta-blocker in the future.

I think there is a real need to start treatment with these patients as early as possible, and perhaps the best opportunity that we have is when patients are in the hospital after they have been stabilized following their acute infarction, and of all the beta-blockers currently approved for

use, I think it would be fair to say the most persuasive data in post-infarction patients with left ventricular systolic dysfunction receiving an ACE inhibitor exists for carvedilol.

So, I believe based on the totality of available evidence that there are very good reasons, both from the point of view of strength of evidence and from the point of view of public health, to allow description of the results of the CAPRICORN trial to be incorporated into current labeling for carvedilol.

I would be pleased to take any questions the committee might have.

DR. BORER: At this point, we will limit the questions specifically to issues of fact about the safety. We can get into the more general philosophical issues a little bit later.

Are there any specific questions about safety concerns for Dr. Packer? Beverly.

DR. LORELL: Going back to the issue that Dr. Armstrong raised, I just want to make sure I am very clear and others on the committee may have this query, too.

Adverse events were reported completely from the time of randomization?

DR. PACKER: Yes.
DR. LORELL: So, that the sort of black box period that Dr. Armstrong was referring to in terms of adjudication of endpoints, that period between randomization and leaving the hospital would include adverse events.
DR. PACKER: Yes. The data that you have seen is complete from the point of randomization with respect to mortality and with respect to adverse events. The blackout period that you are referring to, maybe that's not the right term, applies only to the adjudication of hospitalizations that could have contributed to the combined endpoint.
DR. LORELL: So, that does afford us an understanding in totality.
DR. PACKER: Yes.
DR. LORELL: Including very early start time.
DR. PACKER: Absolutely.
DR. LORELL: About risks including bradycardia, hypotension, and acute pulmonary edema.
DR. PACKER: And we have complete data sets from the point of randomization for all of

those.

DR. LORELL: Thank you.

DR. BORER: Alan.

DR. HIRSCH: I have two questions for you, Dr. Packer. One, I just want to bore into two of the adverse effects a little more deeply because I do believe that beta-blockers are helpful in this class of patients in general from the totality of the data.

The first one is bradycardia. Obviously, there is increased incidence when the drug is administered early in about 6 1/2 percent of the population. Nadir heart rates, need for pacing, major bradycardic episodes, can you make a comment beyond what we have seen in the packet?

DR. PACKER: Actually, I have a little bit more information, but probably if you need it, we could get more information. The bradycardia generally resulted in a reduction in dose without the need to stop treatment, so the AE's that you see are AE's that were reported, that then led to a dose reduction, didn't lead to discontinuation of therapy if you look at the withdrawals.

The withdrawals, bradycardia was not a feature that led to withdrawal with any imbalance

between the two groups, and literally, the issue of bradycardia was almost absent if one looked only at serious AE's.

DR. HIRSCH: The second question relates to a small subgroup, which may not surprise you from my perspective, which was the peripheral vascular symptoms group with beta-blockers. I keep looking at this small group.

I presume that the peripheral vascular symptoms, usually ignored in these hearings, were--well, seriously, were potentially one of three things. They are either a complaint of claudication, development of critical ischemia or potentially even amputation, not usually measured in a heart failure trial.

The reason it comes up is because there is a signal again of an increase that is twofold in this group. In a global database of beta-blockers, which is not adverse when these drugs are administered in chronic disease states, patients with arterial disease are going to be increasingly part of these heart failure and ischemic event arenas in the future.

So, my question is, do we know anything more about what these peripheral vascular events

really were, my concern being that without defining that, there may be a small population that really is at some risk.

DR. PACKER: We obviously could try to explore that better. I don't have any more detail other than what you have seen. We could go back and look at the actual descriptions. What you see here are code terms that get translated from what the patient says.

Again, there is no evidence that these led to serious problems like amputation or anything like that, but what you see is really pretty much what I can provide information about in terms of this. We can go back and get the actual descriptors.

DR. HIRSCH: I realize descriptors are often quite vague in these trials, I have participated, as well.

Do we know, as well, the population with pre-existing lower extremity arterial disease entered into CAPRICORN?

DR. LUKAS: We do have that information, but I just wanted to comment on your first question.

In agreement with what Milton had said,

among the hospitalization endpoints that were recorded, there were a group called Other. There were about 34 to 40 in each group. We went back and looked specifically--it's backup E5, I believe it is, just to provide a little bit more information--that among the others, Dr. Sackner-Bernstein was able to provide us more information on the classification.

Five in the placebo group and 2 in the carvedilol group of the actual endpoint were related to peripheral vascular disease, and they were exactly what you said, claudication, one or two amputations, one of two fempot bypasses, et cetera. So, that is the totality of information that we have.

Then, in terms of were these patients included, peripheral vascular disease was not an exclusion criteria unless they had disabling symptoms.

DR. HIRSCH: I know it was not an exclusion criteria, but it did represent 2 percent of the inclusion population at 30 percent if were to amplify this in a more real-world setting.

DR. LUKAS: Right. We will go back and look into that.

DR. HIRSCH: At the end of the day, these symptoms dividing them into claudication or loss of leg are just as important as infarction/worsening angina, it is too vague.

DR. BORER: Paul.

DR. ARMSTRONG: In the interests of clarity, as the sponsor tries to get some of these timing issues back to us early this afternoon, in their document on page 48, I have just come across a paragraph which states, "It should be noted that although some patients were randomized and received their study medication one day following their qualifying infarction, patients generally were initiated on treatment with placebo or carvedilol more than one week following their qualifying event."

So, as we try to get clarity, if you could give us the information on when patients were randomized relative to their index MI, and what the window of time was between randomization and the commencement of study medicine, was that, in fact, symmetrical or asymmetrical, and how did it play out across these issues, because I think it really is quite germane to some of the questions that are being addressed, so I have just appreciated that

there is some ambivalence here in this paragraph that we need clarity on.

DR. PACKER: Just to provide one point of clarification now, and we will try to get some more information, we will try to get as much information as we can on the precise distribution in the patient populations in both treatment groups from the point of index MI to the point of randomization.

With respect to the point from the time of randomization to the commencement of therapy, in almost all patients, it was the same day, and we have some data on it, it was fractions of a day essentially, and it was the same in the two groups.

DR. BORER: Mike.

DR. ARTMAN: I am still a little confused about the issue of recurrent MI. As I understand it, and correct me if I am wrong, to count as a recurrent MI, that had to happen after hospital discharge, after your index MI, yet myocardial infarction was also recorded as an adverse event.

So, what I am trying to get at I guess is back to what Paul was alluding to. I am trying to understand how much of this MI as an adverse event occurred early in that initial hospitalization.

Do you have that information or can you get that for us?

DR. PACKER: Yes, actually, we do have that information. We need to just find the slide. Do we have the early AE's in the first 30 days?

While we are trying to find this, it is not unusual to have a discrepancy between an event reported as an endpoint and an event reported as an AE. One of them is a directed event, the other is a spontaneous event.

It is very common in clinical trials to see discrepancies between those two ways of recording events at the end of the study, but it is a particularly relevant question in this study because of the "blackout" period, for better or for worse.

Can we have slide S7.

This is all adverse cardiovascular events with a frequency more than 1.5 percent, greater or equal to 1.5 percent during the up-titration phase. Let me emphasize this is from the point of randomization, there is no blackout period here.

You can see what is happening early. Let me just direct you to MI, 28 in the placebo group, 13 in the carvedilol group, and part of the

up-titration phase is in hospital, part of the up-titration phase is post-hospital. If you would like, we can go back and see how many of these were actually in the hospital, but you can see the early events are going in the right direction, and this is from the point of randomization.

DR. BORER: JoAnn.

DR. LINDENFELD: Just a quick question about the hospitalizations. You can help me a little bit with this.

The hospitalizations for MI clearly were more in the placebo group, but hospitalizations for unstable angina, chest pain or angina, and other cardiovascular reasons were pretty much exactly the same.

Do you find that at all unusual? I know it is back and forth, but there is such a big difference in MI, I would sort of think that unstable angina and angina and chest pain would follow the MI.

DR. PACKER: I personally wondered about that myself. It is interesting if we could have--

DR. LINDENFELD: It is table 21 in the briefing book on page 68.

DR. PACKER: Let me just hold on, if I

might. Could we have--well, let me just summarize it instead of looking for it. JoAnn, you may remember a finding, a slide in Henry's presentation that looked at the frequency of angina, claudication in other trials, other beta-blocker trials, including angina, including, by the way, although it is not broken up in the slide, unstable angina.

For whatever reason, in all other post-MI beta-blocker trials for which there are data, the frequency of angina and unstable angina is the same in the placebo group and in the beta-blocker group. Let me clarify my own thinking process here.

When you look at these tables, the only thing that you are looking at is the proportion of patients who report an event. One is not looking at when these events occurred and one is not looking for how often they happened in an individual patient, so it is perfectly conceivable that a beta-blocker could be anti-anginal, and not be picked up by that kind of analysis.

DR. BORER: In that regard, the FDA reviewer did an interesting analysis on page 11, because I was caught by that same observation, JoAnn, and it turned out it seems that the initial

cardiovascular hospitalization, the non-fatal MI's tilted in favor of carvedilol by a margin of 18 events, and the unstable angina or angina was the other way by 18 events, so the two types of problems actually showed no net gain, but if you looked at causes for all hospitalizations rather than the initial hospitalization, the apparent skew was less apparent.

Angina still, for whatever that is worth, was less frequent as a cause for hospitalization in the placebo group, but unstable angina, the margin narrowed a little, an MI was very much more frequent in the placebo group, so the net, the total cardiovascular events, if they are considered just as angina, unstable angina, and MI, were less frequent in the carvedilol group.

I don't know if that helps very much because it is the same issue that Steve raised earlier, looking at smaller and smaller subgroups to find something, but it is interesting that if you look at all hospitalizations rather than the initial hospitalization, the intuitively inappropriate result seems less than appropriate.

DR. PACKER: Can we have a backup slide just to illustrate that, I think it is E39. It is

total number of hospitalizations E39.

Jeff, this is what you are referring to?

DR. BORER: Something, that shows those data, yes.

DR. PACKER: Again, this is not considering which are first events, and Ian was just going to come to the microphone and make the point that sometimes in a time to event analysis, time to first event analysis, a minor event will trigger the Kaplan-Meier tick and suppress the occurrence of the event that occurs after the minor event.

So, one way of trying to get information about all events is to look at the total number of hospitalizations for various reasons, and these are the total number of hospitalizations. This is, by the way, where the 60 and 37 came in, what we showed you earlier, and you can see all the others on your own.

In order to make this kind of table, one has to make some arbitrary decisions as to what the hierarchy is. If someone comes in with an MI and heart failure, like which one counts more. You can see the arbitrary decisions that were made here. MI counted above heart failure, unstable angina.

This is not supposed to be a clinical judgment. This is just a classification scheme.

DR. BORER: Were there any other issues, JoAnn? Okay. Tom.

DR. PICKERING: Yes, I have a question related to that actually, if you could leave that slide up, please.

It seems that what screwed up the revised primary endpoint was the hospitalizations. If you compare CAPRICORN and COPERNICUS, the number of patients was approximately similar and the follow-up length of time was a little bit longer in CAPRICORN.

The COPERNICUS patients were sicker, they had lower ejection fraction, they all had heart failure, so I would have guessed that the hospitalization rate would be higher. Yet, for COPERNICUS in the paper, you have, in the placebo group, 395 cardiovascular deaths and 432 hospitalizations for any reason. In CAPRICORN, you have I think 139 cardiovascular deaths and here you have 693 hospitalizations.

There seems to be a disproportionately higher number of hospitalizations in CAPRICORN from what you would expect. Again, I wonder if this has

anything to do with Russia, was Russia part of COPERNICUS. When I went there 20 years ago, I had the impression that patients actually rather liked being in the hospital because it was nicer than being outside.

So, was the hospitalization rate higher in Russia than elsewhere?

DR. PACKER: Russia, Poland, and several other countries in Eastern Europe participated actively in COPERNICUS. There was no heterogeneity of the response in those countries in a manner similar to what you saw in CAPRICORN. I am talking about the COPERNICUS study.

Ian Ford and I were talking about this last evening. The only explanation that I think is credible as to why the frequency of hospitalizations is higher in a patient population that is earlier in their disease state. Again, one has to be careful because the duration of follow-up is different and the way these are calculated are somewhat different, is that when patients are further on in their disease state, they tend to be hospitalized for more and more disease-specific related reasons.

Whereas, patient following an acute

myocardial infarction, the sensitivity to bring them back in the hospital for relatively minor reasons, atypical chest pain, can be very, very high. One is almost never hospitalized for atypical chest pain when one has severe heart failure.

I think that accounts for a big difference in what you are observing.

DR. HIRSCH: Can I follow up on that? Another thing that happens is that we give people medications earlier in the disease state, which also cause hospitalization, so it is both a disease and what we do to patients, both things that are part of the protocol, things that aren't part of the protocol.

Are early hospitalizations again different? Have you broken this up by the first, one week, two weeks between the two groups? I haven't seen that data.

DR. PACKER: We do have that. One moment, please.

DR. HIRSCH: While you are pulling that up, you know, one of the things that Tom said earlier which struck me was, you know, we are really looking at the use of beta-blockers early in

this disease state, which I think we believe is probably a good thing, but the question is when is early appropriate.

The drug effects obviously, the beneficial ones, accrue over months to years. I think as we reach towards the discussion, the question here is are there signals that are beneficial from the very beginning of randomization or is there again this blip in dichotomy, does it really matter whether we start at day 1 or day 10, parallel to the discussions we had years ago about ACE inhibitor initiation.

DR. PACKER: I am very sorry. We do have that slide. I need to go and find it for you, and I am afraid I didn't hear the second part of your question.

DR. HIRSCH: The second part is simply to look at that data vis-a-vis the time course of rehospitalization, looking at that as a risk-benefit analysis for time of initiation of study drug.

DR. PACKER: The only thing I would say is that--and I need to perhaps pull up that slide--but for issues related to, for example, recurrent MI, et cetera, what is seen in the first 30 days is

what is seen later on.
If you want, I can try to find that slide, but I just don't have my index right now that would allow me to do it immediately.
DR. BORER: We can see it after lunch.
JoAnn.
DR. LINDENFELD: Milton, the thing that we are a little bit worried about are the events that weren't counted in the index hospitalization.
Can you reassure me that the time of the index hospitalization was the same in the placebo and carvedilol groups?
DR. PACKER: Yes, it was identical in the placebo and carvedilol groups. The slide that shows that, which I think I can pull up in a second, is D33.
This is a breakdown in two ways. One is the duration of the index hospitalization, and the second is the number of patients who had an event that prolonged their index hospitalization. This was specifically asked for. You can see there is no signal that causes concern with respect to carvedilol.
DR. BORER: Milton, I want to perhaps close this session on safety with one--I am sorry,

did you have something to add, JoAnn?
DR. LINDENFELD: I would just add 17, almost 18 days, that's a long time.
DR. PACKER: This was not a trial that was carried out in HMO-guided therapy in the United States.
DR. NISSEN: It is absolutely astonishing to me, I mean almost unbelievable. I can't for the life for me understand this--third, fourth day typically.
DR. THROCKMORTON: Do you have the distribution?
DR. PACKER: It is pretty impressive, isn't it.
DR. NISSEN: Do you know the median?
DR. PACKER: I think that's a mean.
DR. NISSEN: If anybody has the median, we would be interested.
DR. LORELL: I think it would be interesting to have, if you have it, you might not, the U.S. data because there clearly are profoundly different practices.
I think many people in Eastern Europe would consider our discharges--
DR. PACKER: I know we don't have it

broken down, but I would be very surprised if the U.S. data looked like this.

DR. PFEFFER: To follow up on that, I just wanted to hear the reason that there were 83 U.S. patients, and usually, Canada outdoes the U.S. by a factor of 2 and 5 in Canada. Is that because it wasn't an emphasis in the trial here? I would just like to know the reason for that.

DR. PACKER: I think it would be fair to say that the biggest emphasis in this trial was on Europe. The Steering Committee was primarily a European Steering Committee. This was really a European trial, and that includes Eastern Europe. The number of sites in the United States was very, very low.

DR. BORER: Milton, if this drug were going to be made generally available for patients post-MI, I want to come back to the issue of the Killip class III patients and the titration schedule.

Can we have some sense of what your thought might be about directions for use of the drug or limitation of use of the drug given the apparent problem in patients with Killip class III - obviously, a small number of events, not

significant, but a concern that is biologically or clinically plausible, and a relatively rapid up-titration schedule of this drug compared with how it is has been used clinically in the past?

DR. PACKER: I want to echo what Henry said because I think he said it very well. I think it would not be appropriate for a patient who had rales more than halfway up to be initiated on therapy with this drug even if there were no subgroup with Killip class III that went in the wrong direction.

This is a clinical judgment, it is not a data-dependent judgment. In COPERNICUS, we didn't allow patients who had rales related to heart failure in the trial even though that was a very sick patient population. We required patients to be euvolemic.

The present label for carvedilol, the present package insert which is approved for carvedilol clearly instructs physicians that patients should be euvolemic prior to initiation of therapy. I think that applies very strongly in this sense.

I do not think that patients who have pulmonary Killip class III pulmonary rales, I think

they should be diuresed or treated in whatever way is needed to stabilize them and then considered for long-term therapy.

DR. BORER: If there are no other questions about safety, we will break now for lunch and come back exactly at 12 o'clock, which is 45 minutes from now.

[Whereupon, at 11:16 a.m., the proceedings were recessed, to be resumed at 12:00 Noon.]

AFTERNOON PROCEEDINGS

[12:06 p.m.]

DR. BORER: We are six minutes over our limit here. We are never going to stay on schedule if we lose six minutes.

DR. LUKAS: Dr. Borer, I have three answers for you.

DR. BORER: Dr. Lukas, why don't you go ahead and present those pieces of data, and then we will move on.

DR. LUKAS: Thank you. There may be a few things that were asked for that we were not able to provide in the time since we broke up the meeting.

The first thing I would just like to tell you is that in terms of the duration of the index MI, what you did see were the mean values of 18 and 17. The median values were 14 in the placebo group, 15 days in the carvedilol group. The standard deviations were comparable. They were 14 in the placebo group and 11 in the carvedilol group.

So, there were clearly some outliers which contributed to this. What I don't have is a histogram showing how many people had a normal length of stay and how many had an extended length

of stay, but we can certainly provide that to the Division.

The second thing that I have an answer for is Dr. Lindenfeld's earlier question about how many people had the relatively short exposure to the trial medication after the amendment.

In the placebo group, it was less than 12 percent of patients who had a follow-up that was 42 days or less, so that is as exact as I can get right now. So, on the order of 10 percent of patients were limited to 1-month follow-up.

For the 6-month follow-up, we have 9 percent in the placebo group and 9 percent in the carvedilol group. So, in the middle there is the 3-month data that you were asking for, so about 10 percent of patients were limited to a follow-up of about 3 months.

The only last piece of information regarding the time from index MI to the date of randomization, 35 percent of the placebo patients, 39 percent of the carvedilol patients were randomized between day 1 and day 7 after their MI, with 46 percent of placebo, 42 percent of carvedilol randomized in the second week, day 8 to day 14, and the remainder randomized between day 15

and day 21 in the groups.

The only other thing we want to ask Dr. Borer is Dr. Dargie has one thing he would like to share with the committee related to the DSMB before you reconvene, if that is all right.

DR. BORER: Sure.

DR. DARGIE: Thank you, Dr. Borer. The question of the letter from the DSMB was raised and I wasn't certain whether I had it with me, but I did. Although I can't distribute it because it hasn't been made public, I would like to read the essential paragraph, which I think will help.

There was considerable concern with the implications of the beta-blocking trials, such as CIBIS II and MERIT-Heart Failure, both because of the ethical issue of giving placebo rather than a beta-blocker to patients with heart failure, but also because of the possibility that investigators would be less likely to recruit patients and more likely to discontinue trial therapy.

The committee noted the relatively slow rate of recruitment, the low event rate, and the somewhat higher than anticipated discontinuation rate. It seemed most unlikely that the target number of events, 630 all-cause deaths, would be

reached within a reasonable period of time. It therefore suggested that the Steering Committee should consider making the first secondary endpoint all-cause death and cardiac hospitalization a co-primary endpoint.

Thank you.

DR. BORER: Thank you very much.

DR. PACKER: Essentially, I think Tom's point on this issue was that the Steering Committee could have, in fact, allowed the trial to continue, and not only allow it, but perhaps even encourage or even mandated the use of open-label beta-blockers when people developed heart failure, essentially, therefore, in some ways converting the trial from what it was designed to be, which was a placebo-controlled trial of carvedilol post-MI, to an early versus late intervention trial.

I think that was the point that Tom was trying to make, and I think it is clear that the investigators didn't do that because that wasn't the trial that they had, in fact, envisioned doing, that the trial they envisioned doing was a post-MI, placebo versus carvedilol, not an immediate versus late intervention.

DR. NISSEN: I would have phrased it a

little differently. I would say that it would become a committed early beta-blocker versus usual care, because what happened was when those other trials became available, it became usual care to give a beta-blocker for heart failure, so the test would have been to giving beta-blockers before heart failure had occurred, to waiting until it occurred and then starting beta-blockers.

DR. PACKER: I totally agree. I just wanted to make the point that that is a different trial than the one that was envisioned, and it was a trial given the fact that the treatment effect would be smaller, would be a much larger study in the trial that was already having considerable difficulties.

DR. FLEMING: It has been stated, but it might be worthy of being reiterated one more time. A clinical trial should be designed to evaluate an experimental intervention against a standard of care where the control regimen is delivered in a way that is within a range of what would be an ethical acceptable standard of care.

If the Data Monitoring Committee or an IRB or anybody else that has oversight responsibility for a trial at its initiation or during its conduct

has serious ethical concerns, then, it is, in fact, their responsibility, and it would be the Data Monitoring Committee's responsibility, to note such and make recommendations.

On my part at least, there is no concern about how this process was carried out in that regard. The issue is does that require a change in the primary endpoint and was it the Data Monitoring Committee's responsibility to initiate such a change.

It may be the sponsor's or the Steering Committee's perspective that if standard of care does, in fact, require sufficiently early access to beta-blockers, that it is not plausible to achieve the targeted reduction in mortality, it is then within their purview to determine whether or not mortality could remain as the primary endpoint.

The study was designed, by my calculation, for a 23 percent reduction in mortality by the sponsor's indication of 20 percent reduction, and what I am perplexed about is it seems to me, at this point, the sponsor is still of the perspective that it is not only plausible to achieve a 23 percent reduction, I think they are claiming they have established such a reduction, hence, it seems

difficult for me to understand why, at mid-course in the study, they backed away from that as being something they thought they could achieve. That is the concern.

DR. HIRSCH: Let me speak to that with a contrary view, Tom, and this idea that you get one trial result, whether it is CIBIS or MERIT, and you have to immediately adjust because the standard of care instantly changed I think is problematic, whereas, we are always obliged to make sure we change our trial design in response to clear, unambiguous data, there is this moral obligation.

When you have a multi-center trial in many countries, there are problems that arise when you immediately change trial design because you assume the standard of care is instantly changed in every country. Sometimes it is best to stick to one's guns with a trial design that is ideal and to prove the point more unambiguously as one originally had designed the trial.

I have one more question, though, if I can, before we move on.

You presented the data for time from the index event to randomization and I appreciate that. I was one of the members that asked for that.

Do we have efficacy and safety broken down again in tertiles by those times, one week, two weeks, three weeks, to know whether there is equal benefit and risk?

DR. PACKER: No, but obviously, that could be done.

One last comment. I think this trial, this post-MI beta-blocker trial is a lot closer to present standard of care than any previous post-MI beta-blocker trial, and that is a very important point because if one is talking about bringing this up to current standard of care, this is a lot closer than anything that exists in the past.

Second, although the mortality effect of 23 percent was an observation in this trial, Tom, it is not clear that would have, in fact, been the result if this trial had continued all the way and there had been large-scale use of open-label therapy.

DR. FLEMING: And, in fact, because you are right about that, there is a lot of uncertainty as to whether this agent should be approved because we don't know if this had been carried out to its proper numbers of events, would we still see what we are seeing now. You are right, Milt.

DR. BORER: JoAnn.
DR. LINDENFELD: Maybe my numbers are wrong, I did this quickly, but I am still bothered by the endpoints in this, what has been called blinded phase, this hospitalization phase, because as Paul said, we would expect three-quarters of MI's to occur early.
So, there were 60 MI's that were counted after the hospitalization. That would mean that we ought to have seen a total of 240, and yet in that early in-hospital period, there were only 2 percent or about 18, so clearly, there was a huge discrepancy in the MI's that were picked up in the hospitalization, I mean as adverse events.
DR. PACKER: Let me just emphasize, if I remember what Paul said, I think the point that Paul made was that a substantial number of reinfarctions occurred within the first 72 hours of the initial MI at periods of time that was not even part of this trial.
This is not a blackout issue. This is the fact that the patients were randomized on the average of 10 days later, so that the largest period of reinfarction, the first 72 hours was never even studied. It was pre-randomization, it

wasn't even part of the trial, so the trial missed its greatest opportunity to have an impact on reinfarction because it didn't start therapy in the first 24 hours.

DR. LINDENFELD: Right. I overestimated, but 35 percent were randomized day 1 to 7, so that is still a fair number of patients in that 72-hour time period.

Committee Discussion and Review

DR. BORER: I am going to set a couple of ground rules here as we enter the committee discussion. First, is that at 1 o'clock we are going to take a pause of public comment if there is any.

Second, is that there is a great temptation when an issue as important as the one raised by this supplemental NDA comes up, there is great temptation to try to define rules for dealing with this kind of situation.

That is not what we are here for today. Today, we are here to determine whether this supplemental NDA in the opinion of this committee is approvable, to give advice to the FDA.

The questions are written such that one might draw more far-reaching conclusions and that

may be reasonable, but we are not going to spend a great deal of time discussing those philosophical issues today and I would strongly suggest, because they are so important, if the FDA wants the opinion of this committee about those issues in a really comprehensive fashion, that we schedule a workshop meeting as we have on some other issues in the past.

DR. THROCKMORTON: Jeff, before we leave that--

DR. BORER: We haven't left it yet, but go ahead.

DR. THROCKMORTON: We do need some of that discussion today.

DR. BORER: We will, we will get it. I will get to that. I am concerned about that in part because one of the comments that was made earlier today as a precedent for the current deliberation was the approval of losarten in a setting of prevention of renal dysfunction for an indication of prevention of renal dysfunction.

In fact, that approval was not based on the data from the irbesarten trials. There were a number of data that were considered, and the approval was highly circumscribed and a strong

statement was made by the committee that this should not be considered a precedent for approval of future drugs, that we had to consider each on its own merits.

In any event, with that in mind, because I understand what Doug is saying, and I think of course he is absolutely right, these questions were written for a reason, and there does need to be some understanding of how each of the committee members thinks about these issues in order to understand the advice that we give when we come to voting for the record on Question 6.

We will have some comments, but I am going to request at least at the outset on Questions 1, 2, 3, and 4, that we limit our comments to relatively succinct statements from each of the committee members and that we move on to the voting issues and then we can come back and speak more broadly if we want to or we can wait and have a really broad discussion at some later date.

With that having been said, we will begin with discussion of the questions. Our committee reviewer is Marc Pfeffer, and he will take the lead in discussing the responses to these questions and particularly for some of them, I think it would be

very important to have Tom Fleming's opinion because there is an important issue of replicability that underlies some of these issues.

The Cardio-Renal Advisory Committee is asked whether an observed mortality difference can be a compelling finding far out of proportion to its place in a study's formal hypothesis testing.

Carvedilol is indicated for the reduction of mortality and the reduction of hospitalization in patients with mild to moderate heart failure. With the results of the CAPRICORN study, the sponsor seeks to extend the indication for carvedilol to patients with left ventricular dysfunction subsequent to myocardial infarction.

In CAPRICORN, 1,959 subjects with left ventricular ejection fraction less than or equal to I think it is 40 percent and no heart failure, within 21 days of myocardial infarction, were randomized to placebo or to carvedilol 6.25 mg/bid, titrated as tolerated to 25 mg/bid over several weeks, and then followed for a mean of 15 months.

I would like a clarification there to start with. It was not my impression that the people had no heart failure, but rather that their heart failure had been reasonably stabilized within

the hospitalization, so this study did include people with heart failure. In fact, 47 percent in one group and 49 percent in the other had heart failure at the time they were randomized, which I think is important in considering the primary question here.

The primary endpoint was overall mortality, but as a result of a protocol amendment late in the study, there were two primary endpoints, time to cardiovascular hospitalization or death from any cause, assigned alpha of 0.045, and time to death alone, assigned alpha of 0.005.

After a single interim analysis conducted after the change in endpoint, the final results were as follows, and we have the chart and, of course, we have seen these results several times today in the briefing book.

Basically, the finding, as we know, was that death or cardiovascular hospitalization sort of tended to favor carvedilol with a hazard ratio of 0.92 and a p value of 0.297, whereas, death alone favored carvedilol with a hazard ratio of 0.77 and a p value of 0.031, neither coming close to the alpha that had originally been allocated.

So, our first question. Studies are

designed to test a formal hypothesis. We usually, but arbitrarily, say a study is successful if the null hypothesis is rejected at p less than 0.05, meaning that on average and without considering other internal data from this study or data from other studies, no more than once in 20 times, or once in 40 times for a favorable result--I am not sure what that is meant to mean--will we be misled into believing a result that is not reproducible.

Can you tell us what you meant by "once in 40 times for a favorable result?"

DR. FLEMING: I would like to add to that.

DR. TEMPLE: Going the wrong way doesn't count.

DR. FLEMING: Right. What has traditionally evolved as the standard for strength of evidence for a single trial to be considered positive is a two-sided 0.05, but we know that the false positive error rate with a two-sided 0.05 is 2.5 percent. You are not going to approve an agent that hits two-sided 0.05 in the wrong direction.

So, what we are really doing in most settings is a one-sided 0.025. So, what we recognize as the standard for strength of evidence of a positive study is something that would occur

by chance alone only once in 40 times. That is essentially the standard.

DR. BORER: So, no more than once in 20 times or once in 40 times for a favorable result will we be misled into believing a result that is not reproducible.

Furthermore, to consider a finding to be compelling, we usually expect evidence equivalent to more than one study successful at p equals 0.05.

Let's define discovery, that is our definition here, as any opportunity to declare a finding to be compelling outside of formal hypothesis testing. Discovery comes at the cost of increasing the false positive rate, therefore, how much are you willing to inflate the false positive rate in order to enable discovery?

For every potential discovery one can make in a study, the risk of a false positive result increases. How many opportunities should a study have for discovery?

When should a discovery be confirmed in a separate formal hypothesis test?

Do you believe it is always possible to discover something about mortality, i.e., is mortality always a primary endpoint? If so, of

what value is making it a formally tested hypothesis?

Interesting questions. Marc, do you want to begin?

DR. NEYLAN: Mr. Chairman, could I ask for a point of clarification?

DR. BORER: Yes.

DR. NEYLAN: In the early portion of this, it states that the endpoint was changed from overall mortality to two primary endpoints, time to cardiovascular hospitalization or death from any cause, and time to death alone.

I just want a clarification. Is that indeed time to the event or are these the summations of those events? My understanding was that it was the latter, it was overall mortality and cardiovascular hospitalizations rather than time to.

DR. BORER: We would have to look back. Tom?

DR. FLEMING: It was the log-rank test, I believe, Cox regression. It is time to.

DR. NEYLAN: It is time to, thank you.

DR. TEMPLE: But that is a point that is frequently obscured. I mean one describes the

endpoint as if it is the total number of events, but what is usually looked at is time to. That is probably something for another discussion sometime.

DR. FLEMING: Yes, and there are settings where a fraction of people with events may be preferable to time to events. We often say if it is an acute setting, what I really care about is the fraction of people that have the event. Severe sepsis, I don't care if you delay time to death over 28 days if you are going to be dead anyway by 28 days, but in a longer chronic setting, time to carries a lot more relevant information than just percent with.

While we often represent in deaths the number that died, the summary statistic is the relative risk and the confidence intervals and the p values, and those are all from time to analyses.

DR. TEMPLE: I mean I must say this is for a different discussion. I am not sure that is necessarily optimal, and I think the disparity in presentation comes because it is easier for clinicians to deal with the total number of deaths than to look at those curves and try to figure out what they mean.

So, we measure one thing and we translate

it in something that is easier to understand, which is sort of funny, but another day.

DR. PFEFFER: These comments have nothing to do with this study. These questions have nothing to do with this study.

I think, in general, the sanctity of a clinical trial is just that, that you define things before you start and you define how you are going to make your test and what you are going to make these tests on, so, in general, I think to continue clinical trials as we know and love them, and to make them better and better, we need to keep the standards.

To allow discovery would erode some of that confidence you have in a clinical trial. Now, the mortality issue is a very big one because a data safety monitoring committee and now that we have more and more trials comparing active therapies, looking at combined endpoints, data safety monitoring committees in general are saying we will monitor mortality even if your endpoint is the combination of four different things.

So, I think we have to be cognizant of monitoring plans before studies start, asking what the Data Safety Committee said they would monitor,

and if they said they are monitoring mortality, then, we do have to use that because they have the authority to call a halt to a trial if they reach some prespecified limits, some of which Tom has very importantly defined.

So, I think it is very important to keep trials within the confines. I also believe trials have to have some breathing room. A chronic study that will go over the course of five years is going to run up against changes in the outside world, and that is what you have leadership for.

Leadership has to be able to work with that and make an adjustment as needed, but make an adjustment as needed that doesn't hurt the integrity of the trial.

DR. BORER: Let me go to Tom Fleming next and then we will go back around the table, and maybe you can make specific comments about the specific questions here in the context of your remarks, Tom.

DR. FLEMING: Yes, I think maybe there are two or three main issues within this first question that I wanted to address. Milt Packer said something that I would like to reinforce. I think he said, in principle, what we would like to do is

work in a way that we don't inflate the false positive error rate, and I would endorse that, that in principle, we should be doing the best we can in design, conducting, analyzing, and interpreting data in a way to try to maintain the integrity of the study, both false positive and false negative error rates should be controlled.

So, the standard for strength of evidence of a single positive study is a 2.5 percent false positive error rate, and typically, we allocate alpha to the primary endpoint and say if we achieve that, the study is positive.

Does that leave some room for judgment? Absolutely. Statistical measures should be guidelines and obviously, they don't make decisions about whether a study is positive or negative solely on whether you achieve that statistical strength of evidence.

There has to be judgment, but that judgment has to be very carefully implemented in a way to maintain these error rates. What that means, I believe, is that we should have prespecified in the trial, not just the primary endpoint and the primary analysis of that endpoint, but what would be the key, most important

supportive results, so that the study is largely confirmatory even though there is an exploratory element, any trial, it is important to distinguish the confirmatory element from the exploratory element, but that cannot be perfectly done in any setting, even in the best planned trial.

So, we have to use judgment. Secondary endpoints clearly have to be taken into account and especially those that are profoundly important. Survival clearly comes to mind as the classic example. Debilitating stroke might be another good example of a profoundly important endpoint.

Generally, I would like to see those as the primary, but there are reasons that are legitimate in cases not to make them the primary. If you don't make them the primary, clearly, they should influence your judgment.

Now, my belief is there are settings when you can achieve a conclusion of positivity on a secondary endpoint such as mortality, but it has to be done extremely cautiously. Now, doesn't that inflate your error rate? I would say no, not necessarily if you are doing this in a very careful manner in the following sense.

If I have a non-mortality primary

endpoint, and mortality looks unfavorable, I am not going to call that study positive even if I hit significance in my primary endpoint. So, I am not spending all of my alpha on the primary in that sense. I am using judgment that could go in either way.

As I look at the totality of data, there are settings where I may hit my primary, but judgment says totality of evidence on benefit to risk does not provide conclusive evidence that I have established benefit.

In the same sense, if you have not achieved significance on the primary endpoint, I believe that there are settings where you could, in looking at the totality of the data, judge that favorable benefit to risk has been conclusively established. At the same time, I think this has to be done extremely cautiously.

Now, the last part of this question relates to the specifics of mortality itself. I have already mentioned, I think, even if mortality isn't a primary endpoint, I think it is an endpoint that does merit very special consideration.

I would agree--I think again Milt had said this--that saying mortality automatically gets a

two-sided .05, hence, 2.5 percent false positive error rate allocated to it, is a gross oversimplification of what should be the case.

Generally, my own personal sense is if mortality hasn't been allocated to the primary endpoint, it is going to have to be much stronger evidence if it were a secondary endpoint than if it had been the primary endpoint.

My own personal sense about this is--again, this is just a general guideline--is if it took a two-sided .05 for mortality at the primary for the strength of evidence of a single positive study, I am generally looking at a two-sided 001 to 005, i.e., at least 10-fold more in terms of strength of evidence if this is a secondary endpoint.

Now, if I am going to be using this as the basis of judging positivity, that is just a gestalt that, in fact, is not always the case, but a general sense of what it would be in order to address the first issue that I mentioned, which is if we are going to go beyond the primary, we have to do it in a way that addresses, as Milt said, the goal of still maintaining the overall 2.5 percent false positive error rate.

So, in summary, my sense is we should be maintaining the error rates. It does require, however, judgment in looking at benefit to risk. Secondary measures are important particularly those that are profoundly important, and it is entirely possible that mortality could be of such a nature that it could be a basis for concluding positivity of a trial, but it requires much stronger evidence than if it had been the identified primary endpoint.

DR. THROCKMORTON: Tom, if I could, I want to ask a couple things.

First, I would like you to comment just a little more and then I will ask sort of for other people to comment. This question was framed around mortality and what I heard you say was there are other things, and you gave a single other example of a thing that was so hard or debilitating I think is the word you used, that they could also potentially be discoveries, if you will, something so fixed that you might allow a finding from a single trial to form the basis of adequate evidence.

The second part of it, the second question I had for you is regarding that aspect, that is,

that this first question revolves around a single trial providing the sole basis for a decision of efficacy on a particularly hard endpoint.

You will be asked later about other things, but were the comments that you made, were they directed at the trial and its sufficiency to form the sole basis for a decision, or were they mixed in some way or another?

DR. FLEMING: Doug, I am delighted you asked for that clarification. I should have made that. I was referring to the strength of evidence from a study that would give this, what I call the strength of evidence of a single positive trial.

There is a whole additional set of issues here that have to be considered in general - is the strength of evidence of a single positive study adequate for approval. Generally, we strive toward achieving strength of evidence of two adequate and well-controlled trials, and that leads to some of us saying what is 025-squared as a two-sided p value 001.

If, and this is an if, if we said for mortality we require the strength of evidence of two positive trials, then, as a primary endpoint from a single trial, you would be talking the 005

to 001 just for the strength of evidence of two studies as the primary endpoint.

What I was referring to in my comments, Doug, was what if mortality wasn't the primary endpoint in a trial, what would be the result you would need to see to judge this as a positive study, the strength of evidence of a single positive study, and I am saying basically, you are going to need, in my own heuristic judgment, an additional zero in front of that p value because you didn't designate it as the primary endpoint.

Now, if you are saying do I need the strength of evidence of two studies, then, obviously, a much stronger criterion would be required. This is another entire discussion, and that is, for mortality for debilitating stroke, for profound endpoints, could something less than 025-squared be adequate.

In my judgment, the way we proceed is frequently we would consider that, we would require stronger evidence for something like hospitalization, two positive studies, but in my experience there has frequently been accommodations made for mortality, so that it didn't have to have that strength of evidence. But I am glad you asked

for this clarification because all of my initial comments related purely to what it would take to judge this study as meeting the standard for strength of evidence of a single positive study.

DR. BORER: John, do you have some opinion about this?

DR. NEYLAN: Sure. I would be happy to chime in on the questions if you so desire. Taking this from a clinical background rather than a statistical, I would look on the issue of discovery in a perhaps more narrow and slightly less regulatory definition to encompass the opportunity to advance understanding in science.

With that definition, I would consider that discovery should not be constrained, but, in fact, be unbridled, but taking that a step further and using that as the basis for forming new regulatory opinion.

I would agree with both of the preceding speakers, as well as Dr. Packer, that one would not do so at the risk of increasing the false positive rate, so my answer to No. 1 would be none.

Then, following on what I said about the importance of discovery in advancing clinical understanding, certainly I would see that there

should be as many opportunities as is practical and feasible for studies to make explorations, and so again I am speaking a bit more narrowly in my definition of discovery.

For that answer, then, I don't set a limit, but then going to No. 3, when should discovery be confirmed, if you will, as a pilot observation, I think in most cases it should always be confirmed in some sort of separate analysis that is typically done as a prospective trial.

Finally, do you believe that it is possible to discover something about mortality and the value of making that a formally tested hypothesis, and I defer to I think the very cogent arguments that Tom has made, that one can't underestimate the importance, but I draw the line at making this a de facto component of each trial.

DR. BORER: Tom, do you have any additional thoughts about Question 1?

DR. PICKERING: No, really, I would just say that if discovery is an unanticipated mortality finding that is going to lead to approval that otherwise wouldn't be there, I would say it should be very much the exception rather than the rule, and it should be judged in the light of the numbers

involved and the plausibility as in this case.

DR. BORER: Steve.

DR. NISSEN: Just a couple of additions. I think Tom was implying this, as well, that obviously, the answer I am about to give is out of the context of any specific application because, you know, one of the things I have learned from this committee is there often is ancillary information available that allows us to modify up or down how much strength of evidence we require, and that is always changing, that is always different for everything that comes before the committee.

There is some other precedent or something we know, and so out of context, I would argue that 05 is not stringent enough, and the reason I would argue that it is not stringent enough is that at the very least, I would propose that, at a minimum, if you look at another endpoint, at the very minimum you have got to split the alpha between the originally designated primary endpoint and some new endpoint.

I mean I don't think you can go below 025 very safely because the minute you add a second endpoint, you have got to make a correction, it

seems to me, statistically. But I also don't want to tie one on behind our backs and say that we are going to be a slave to statistics.

The reason I say that is that ultimately, our job as physicians and regulators and everybody else is to save lives and reduce suffering, and sometimes that means that the rules have to be shaded a bit.

So, you know, I think if we say implicit in every trial that an 05 p value for mortality is approvable, that is just too low a standard, but how much lower we are willing to go will depend a lot on the context, and I would argue that going below 025 is very risky just because it really does increase those error rates substantially.

DR. BORER: Alan.

DR. HIRSCH: I think most of the important points have been made, but just to re-caution the balance of what Dr. Pfeffer stated, that respecting the benefits of a pre-hoc, well-defined hypothesis is worth keeping in mind because it avoids, as you said earlier, Steve, the difficulty of discovery being data mining.

So, the same thing, I don't know how to balance exactly which alpha to confer to more than

one multiple hypothesis, but that caution is obviously always kept in play.

DR. BORER: Beverly.

DR. LORELL: I agree with what has been said and I also would like to emphasize that interpreting mortality, I think one should be very influenced as to whether it was a predefined hypothesis or derived very late after the fact.

Secondly, as Steve emphasized, the context in which that observation is made, and that includes not only the context of whether there are other well done studies that are consistent and supportive, but also the data from within the trial as to whether other endpoints, which are also of great clinical importance and merit, go in the same direction.

DR. BORER: Mike.

DR. ARTMAN: I really don't have anything else to add other than the fact that as I am listening and thinking about this, I think we do this discovery thing a lot when we look at safety data, and when we are looking at safety data, sometimes there are signals, they are not part of formal hypothesis testing, but there is something there that worries us and concerns us.

I would sort of think about this--and perhaps this is all upside-down--but kind of in the same say, so that yes, maybe there is a signal here, but I think we have to then verify that, we have to confirm it, and I think we have to be very rigorous in these standards.

So, I would agree with the other members who have answered these questions.

DR. BORER: Susanna.

DR. CUNNINGHAM: I really do believe it all has been eloquently stated, so I will just agree.

DR. THROCKMORTON: Jeff, I am going to just break off with this. Everybody has been talking about mortality, that is, that the only thing available is mortality, and that is fine. I mean obviously, you could make an argument that other things, or an argument has been made in the past that other things are less final, let's say, so that, in fact, you are in more equipoise and that you can potentially want to have to repeat it to minimize your risk of a false positive or drawing a false conclusion.

Other things, stroke, something like that, are there other examples of things that are so

fixed or irrevocable that anyone on the committee wanted to sort of put those forward, it is just a request for some help.

The other thing is, I guess we are going to get to this in Question 2, but it seems to me that the difference between looking at safety, at data in safety assessments and what we are calling discovery here is that when we are looking in the safety, we are sort of bringing our own priors, if you will.

In some sense, we bring to our priors the things that we see there and we apply that to whether or not a signal that may or may not show up is a relevant thing, a thing to be sort of paid attention to. I am not sure about that.

DR. HIRSCH: Doug, just to quickly answer your question. You keep asking us what is like mortality. Any irreversible end organ function is like mortality, so stroke, which Tom mentioned, amputation, I tried to bring up earlier. When you have lost part of your body, that is irreversible, is equivalent. There are probably others.

DR. BORER: Two things before you comment, Bob.

With regard to the safety issue, I am not

sure I could fully agree with what you have said, Doug. I mean I see the safety concern as being the potential for doing harm where we actually have statistically a less stringent standard because we certainly don't want to do harm as opposed to the standard for showing benefit of an intervention compared with not intervening where the standard might be different.

I don't want to state what the standard should be in the benefit category yet, but I think there is a difference.

DR. TEMPLE: I think you are absolutely right. We have sent drugs back for more work on the basis of evidence that if it were presented as effectiveness, would never pass muster because we feel we have no choice, you don't want to hurt people.

I just have one question for everyone about all of this. It may be that the way of dealing with mortality findings usually involves data like we are going to discuss in 2 and 3, so it doesn't turn out to be a problem, but I still have a question for Tom and others.

Imagine a finding that was not particularly expected and is not supported by other

trials and things like that, and it is a 0.02. I take it you all feel that you could actually invite people to be in another placebo-controlled trial in that setting and that everybody would feel comfortable, the patients fully informed about the results would be willing to enter.

I just wonder if you think that is really true.

DR. BORER: Let's continue around the table and then we can come back to everyone else.

DR. TEMPLE: I just want to make one point. Milton showed vesnarinone, and I don't believe he represented it entirely. There was great suspicion about the results of that trial, not because the numbers were small, the difference between treatments was almost as large as we are talking about here, but because there were other data that went the other way and there was a lot of concern about whether it was true.

That is different, that is not the same. What would one feel if one really thought it was true and there were no reservations, could you really get people to enter this thing? It seems like a fix problem.

I would just be interested in comments.

DR. BORER: Paul, in your response, maybe you can incorporate an answer to that question.

DR. ARMSTRONG: Maybe a slightly different perspective. On 1.1, my openness to discovery depends very much on the natural history of the disorder that one is evaluating, what available therapy exists.

We have heard about orphan diseases and other circumstances, the risk of the new therapy that is under investigation, and the weighting of the endpoints vis-a-vis this issue of splitting alpha and how to handle the statistical issues that Tom so eloquently has discussed.

So, my threshold under 0.12 would depend on those issues and might be quite liberal under selected circumstances. As it relates to No. 3, again, the risk of therapy, the existence of external validity, and the potential for disconnect as opposed to connect regarding surrogates and more defined endpoints would modify my thinking.

Under 0.14, the answer is most certainly yes. I am involved in trying to understand the disconnect between a reliable surrogate and mortality at the moment that will probably end up here, so I would put those other things on the table.

DR. BORER: JoAnn.

DR. LINDENFELD: Again, I agree with most of what has been said. I would add to this p value that Tom talked about in mortality, that it is not just the p value, it is numbers, and Dr. Packer showed us data, so it is critical that it can't just be a p value. There have to be a reasonable number of events.

In terms of hard endpoints, I think mortality is the one that I am most confident with. A p value that we might acquire in discovery seems to me to be larger, that is more significant, the harder it is to document the event.

So, mortality is very easy, but as events become more difficult to very clearly document, that that p value has to get smaller. For instance, I know Alan mentioned amputation, but we had a discussion several years ago. Amputation is not nearly as hard an endpoint as we might believe.

So, I am not sure I would be willing to give amputation as an endpoint. I think disabling stroke, though, would be an important one.

DR. BORER: To cover that last point first, because you have specifically asked about it, Doug, I would agree that mortality is an

overwhelmingly important endpoint and it is very difficult to argue about its definition, but I would be hard put in the context of an off-the-cuff discussion like this to give you a strong statement, a firm conclusion about other endpoints that might be equally important because as JoAnn just said, every single one of them that I can think of as I am sitting here is open to some interpretation.

Disability depends upon the perception of the disabled person, so I don't think any other endpoint can have the weight for me that mortality has as an irrevocable problem, but in certain situations, others might depending upon how the definition was constructed.

With regard to the other aspects of this specific question, just like everyone else, I don't think that it is appropriate to inflate the false positive rate and therefore, for endpoints in general, I don't think that the opportunities for discovery should be very wide if the result of discovery is to recommend approval of a drug for remediation of what you have discovered the problem to be.

So, virtually, in every situation, what

you have defined as the discovery should be confirmed in a separate formal hypothesis test, virtually every one except perhaps for mortality, and there I completely agree with Steve and with Tom and with everybody else around the table, that the standard, if the mortality benefit is to be discovered, that is, it comes out of a single trial and hasn't been declared the primary endpoint, then, there has to be a stronger group of evidences to support a belief that this finding is correct than merely a p value of 0.05.

Having said that, I think that Beverly's point is very important. If the mortality endpoint was prespecified, well, if you expected it, that would be important. How important I don't know, I don't want to put numbers on this.

If the mortality benefit was unexpected, if it wasn't prespecified, then, I would give very little weight to a p value of .05. So, with those things having been said, Steve, you have the last word and then we will move on to the next.

DR. NISSEN: I wanted to directly answer Bob's question, which as I think a very tough one. I mean suppose an unexpected finding of reduced mortality without a lot of other supporting

evidence, and an 0.01 level of significance were found, could you get physicians and patients to enroll in a trial that would be the definitive trial with that as a prespecified, and I think it has to be looked at on a case-by-case basis.

There will be cases where we might agree that the statistics are not strong enough to support giving that label to a drug, and yet the definitive trial is just impossible to conduct. I hope we don't get caught in that, we probably will some day, and if we do, I think we are going to have to really think it through very carefully because the fact is it is one thing to prove something, it is another thing to actually be able to then conduct such a trial, and some trials are not conductible.

DR. TEMPLE: Just one last observation. This question, quite appropriately, is artificially narrow. It really says you have got no hint from anywhere else, you have got no priors, you didn't mention it in your protocol. It is not that you thought you couldn't quite do it, you really didn't think it was going to happen.

So, for that case, it all sounds pretty sensible, but most cases aren't like that, which is

why the next two questions come up.

DR. BORER: I was going to say all my answers and I think everyone's answers with regard to 1.4, would depend in part on how much additional information we might have from other sources about this drug, about other effects of this drug, et cetera, et cetera.

Tom.

DR. FLEMING: Yes, just briefly to add that I agree that Bob's question is a very important one that regulatory authorities, sponsors, and the scientific community would have to carefully discuss, which also I think brings us back to gee, it would be great to avoid getting into this situation.

So, as we plan trials, thinking ahead to what it would be that we would like to have, because if we get in a position of having equivocal results, it can be very difficult to know how to proceed.

It definitely would require consideration of the strength of evidence as to whether or not this is something that we could replicate. We can give examples.

What comes to mind immediately to me is in

my own experience, the 5-FU/levamisole and levamisole colon adjuvant trials that were done in the early 1980's showed survival differences for both levamisole and 5-FU/levamisole, and yet we started over with a completely confirmatory trial that took another six, seven years. Nice that we did, because 5-FU/levamisole was proven to be effective in a confirmatory way, and levamisole was proven to do nothing in that confirmatory trial.

So, it is certainly possible to do so, but the likelihood that we can do so depends on how strong the results are in that first trial and what the global sense of uncertainty is in the clinical population about this intervention's effects.

DR. BORER: Marc.

DR. PFEFFER: Well, Tom is using cancer examples. It is a little different because those drugs were not generally available, they were used in protocols only. Now, we are talking about agents that are on the market, so it is much harder to do trials when the every-day physician has access to these drugs. It makes it much different.

DR. TEMPLE: There is another difference. Most cancer drugs delay death by a month or two on a good day. Here, you are talking about death

yes/no.

DR. FLEMING: But the example I gave, granted it was cancer, but it was reducing death rate by a third from 50 percent down to 33 percent in a curative fashion, so that is pretty profound.

DR. TEMPLE: Okay, I will buy that.

Open Public Hearing

DR. BORER: Let's go on to No. 2, but before we do that, it is 1 o'clock, so I want to ask if there is any comment that any member of the public wants to make at this meeting.

[No response.]

DR. BORER: If not, then, we will go on.

Continuation of Committee Discussion and Review

DR. BORER: I think No. 1 has generated probably the longest discussion we will have before we get to the vote, so let's go on to No. 2.

Without formally specifying how we do so, and that is important, without formally specifying how we do so, we may be comforted or discomforted about a finding by other information derived from the study.

In considering the mortality effect discovery in CAPRICORN, how do the following affect your confidence?

The effect on cardiovascular hospitalization.

Consistency of the mortality effect across prespecified groups.

Consistency of the mortality effect across non-prespecified subgroups.

Other secondary endpoints suggestive of a mechanism for the mortality effect.

Marc, why don't you give us an answer and then we will see if there are any additional opinions.

DR. PFEFFER: So, now the blinders are just for within the study information, this question, so you can't know about anything outside.

Okay. I would say let's not talk about this study for a second, but if you were overwhelmed by the consistency of non-fatal events, that would help you in terms of looking at a discovery of fatal events.

I would have to say in this particular study, although the trends were all there, it wasn't an overwhelming, the non-fatal endpoint, so I am neither comforted nor not comforted. I feel kind of neutral about the support from that.

The consistency across the subgroups, I

felt best with the additional one of the beta-blockers because I was very worried about a withdrawal of beta-blockers, and that was helpful to me to see that that was there. It did make me feel better.

The mechanistic studies, we had more mechanistic studies presented in our brochure than presented here. In general, I think these are important, discovery, new studies, but without having the protocol, you have to look at a mechanistic study the same way you did the overall one, and all too often, clinical trials, and I don't know if that is the case here, have 16 mechanistic studies with outcomes that have multiple outcomes and you don't know what you are seeing.

So, I don't know how to evaluate some of the echo studies that weren't presented here, but were in our booklet. It would have been helpful to me if there was a rigorous echo study and I knew how many people were randomized, they intended to be randomized, what the one primary endpoint was, how many people actually had the measurements.

That would have been helpful to me, but what I had in the packet was not.

DR. BORER: Let's go to our statistician again next and then we will go around the table.

Tom.

DR. FLEMING: Looking at supportive evidence, I try to follow the directions that the study team and the protocol laid out by their intentions, and we had co-primary endpoints and we had two secondary endpoints.

We obviously have talked a lot about survival. Survival certainly shows a favorable trend, not hitting the specified strength of evidence, cardiovascular hospitalization, death shows a very modest trend, but a p value of 0.297, and the two secondary endpoints were 0.1 and 0.276, so the negative view of all of this is we failed on the two primaries, so we failed on the two secondaries.

However, there certainly are some favorable sides. The secondary endpoints and the mortality endpoint were favorable trends and suffered from sample sizes or overall amount of evidence that was in inadequate to discern whether these trends were chance trends or whether they were, in fact, a true signal that we were simply unable to conclusively establish because of

inadequate sample size.

Other supportive measures, which I would have given a lot more credence to, in the spirit of Steve's earlier questions, endpoints such as death, MI, arrhythmias, et cetera, those actually showed more signal. They are certainly clinically relevant.

I run into a lot more trouble, though, in understanding how to weigh those when they hadn't been specified as either primary or secondary, so essentially, what were some of the more interesting positive signals were tertiary endpoints.

DR. BORER: Let's start from this end this time. Mike.

DR. ARTMAN: I really don't have anything to add to that. I think that Marc summarized my feelings, so I have nothing to add.

DR. BORER: Susanna.

DR. CUNNINGHAM: The only thing I have to say is that the effect on hospitalization is hard to evaluate when the systems are so different, so that we are looking across many different countries and obviously very different from ours, so I don't really know how to read that.

DR. BORER: Paul.

DR. ARMSTRONG: I would agree on the hospitalization and I would also have had greater comfort if the Killip III and the inferior MI's had been on the other side of unity.

DR. LINDENFELD: I don't think I have anything to add to those points.

DR. BORER: John.

DR. NEYLAN: The mixture of internal consistency was not sufficient to provide comfort. I would also add the length of stay for the index hospitalization raises questions in my mind about applicability to U.S. practice.

DR. BORER: Tom.

DR. PICKERING: I agree. Obviously, the incorporation of hospitalization was a very unfortunate choice in retrospect. I was somewhat reassured that when the COPERNICUS criteria were used, there would have been, had they used the COPERNICUS criteria, there would have been a significant primary endpoint, I believe.

DR. BORER: Steve.

DR. NISSEN: For 2.1, I don't find the effect on cardiovascular hospitalization at all persuasive. As I said earlier, I just don't accept that you can post hoc pick those endpoints that

went in the right direction and lump them all together and say that worked.

So, to me, it has no effect on my thinking at all. It is almost really a neutral one. I do think, however, for 2.2, there appears to be pretty solid consistency of the mortality effect across subgroups, so 2.2 is reinforcing and 2.3 is reinforcing.

I actually think the secondary endpoints are also actually really tertiary, if you can use Tom's language here, you know, the issue on sudden death and arrhythmias, and the things that one might expect that carvedilol would have an impact on, all seem to kind of consistently go in the right direction.

So, I do think they are tertiary, but I do think they are reinforcing.

DR. BORER: Alan.

DR. HIRSCH: It is hard to add much more than what has been said, but I think for the cardiovascular hospitalization, it is intriguing how popular that has become as an added-on outcome variable, so here is the study where it actually hurt the study outcome.

It is worth reflecting on that. It is

important. We have added it to many, many cardiovascular trials because of both the real quality of life impact, as well as cost impact, but I think future steering committees will take heed of this.

Just regarding the other things, like Paul, I always like internal consistency across the other prespecified, nonspecified subgroups, but the IMI, low blood pressure, and Killip class III groups, I found somewhat discomforting in the whole framework. I have nothing else to add for 4.

DR. BORER: Beverly.

DR. LORELL: Yes, I agree with what has been said about cardiovascular hospitalization. I think it was extremely unfortunate that it was such a gamisch of components.

I found some mild comfort in the breakdown data about hospitalization for worsening heart failure in non-fatal myocardial infarction. I was comforted by the consistency of the mortality effect across prespecified subgroups and actually I differ a little in my interpretation of the Killip class data.

To me, that data is actually supportive of consistency. It makes sense in what we know about

giving beta-blockers in heart failure and in patients who have acute and still decompensated heart failure. So, I actually found that data reassuring.

As with I think Dr. Pfeffer, I was reassured by the data breakdown that we saw that wasn't in our original pamphlet of information regarding the previous beta-blocker use.

I thought that not so much in secondary endpoints, but actually in the adjudicated breakdown of causes of sudden death, and here I am going to bring in what I know about other heart failure trials, that it was reassuring that the data consistently went in the right direction for sudden death and death due to worsening heart failure since I think a huge concern raised by previous beta-blocker trials, early post-MI, was that there might be a risk of worsening heart failure including death from worsening heart failure.

So, that is what I have to add.

DR. BORER: I don't have anything major to add to what has been said. Just to summarize, I have some slight differences. I didn't find the effect on cardiovascular hospitalization to be

particularly comforting because I am concerned, as Steve articulated earlier, about the potential for data dredging with the subanalyses that were done.

On the other hand, all the subanalyses were consistent with what I would have expected and even the overall effect sort of tended in the right way, so while I wasn't particularly comforted, I wasn't discomforted at all and at least there was a little bit of support there.

The consistency of mortality effect across prespecified groups was certainly an important point to me and I agree completely with Beverly about the Killip class.

I would have been a little surprised to see a benefit in the Killip class III patients, and I think an important safety issue has been raised, but I am not concerned with regard to the effect of the drug because the Killip class III's dissimilarity and the inferior MI doesn't bother me quite so much either because I can't possibly understand it, and there were many, many comparisons done in that subgroup chart, so that one of them might go the wrong way unexpectedly doesn't bother me as much as perhaps it might.

I, too, believe that the secondary or

tertiary endpoints are supportive and I would add to that I was happy to see that the beta-blocker distribution, the non-protocol beta-blocker administration, skewed in the direction of more being given to people on placebo.

I am sorry there is no explanation of it. It certainly can't be used as strong evidence of anything, but I would have been very unhappy if more beta-blocker were given to the carvedilol group than the non-carvedilol group.

So, in general, there are some comforting findings here and some neutral findings, nothing particularly negative.

Without formally specifying how we do so, we may be comforted or discomforted about a finding by information derived from other studies. In considering the mortality effect discovery in CAPRICORN, how did the following affect your confidence?

We have a list here - COPERNICUS.

How relevant and supportive are the COPERNICUS data for establishing a mortality effect on the post-MI population given the relationship between the two populations? The types of deaths apparently affected by treatment in two settings?

The time course over which the effects on mortality were manifest? How concordant are the findings on cardiovascular hospitalization?

Also similar questions for CHAPS.

Again, Marc, maybe you can summarize a response to that.

DR. PFEFFER: Now, we are broadening it and allowing prior carvedilol experience, not just COPERNICUS, I guess, so that reminds me of being on this committee when the U.S. carvedilol program was first here, the first time, and it is very much like the first question, because they found a mortality difference combining, so we are almost ignoring history here with this particular agent.

I was not particular comforted with that until COPERNICUS, and COPERNICUS was a very well done trial which indicated in the syndrome of heart failure with LV dysfunction that the drug had benefit and rather profound benefit, so that is very helpful to me to now talk about the carvedilol experience and then as we move into the infarct population, I have to step back and say this had to be a very difficult study to do.

There was a little window of opportunity of who could be studied. If you actually read the

ACC AHA guidelines from '99 and for the beta-blockers it was probably the same in the '92 edition, there is a little schizophrenia there where people should be on beta-blockers, but not the really low risk people and not the really high risk people.

That is what this trial was trying to do. Tom, as opposed to the cancer trials, and beta-blockers are out there, so physicians could use them, so it was really a tough niche shoehorn to put a trial in, and I guess maybe that is why it was difficult to do in the United States. I don't know that.

Having said that, you then have the information and I think it is very consistent with--I won't use the other beta-blocker trials until the next question--I think it is very consistent with what you had with COPERNICUS and the carvedilol experience, that in people with an impaired heart, this did lead to improved outcomes.

Then, if you look at the relationship of the two populations, it is somewhat arbitrary. Most heart failure trials have these people, after they raise their hand and convince their doctor that they have heart failure, you know, the patient

two days before, they convinced their doctor that they had heart failure, this is the same human being.

So, I think we have that distinction we make and trials have to live within that. The modes of death reductions appeared quite similar and I think the time course didn't particularly help me. The cardiovascular hospitalizations we talked about. The beta-blocker trials in general have difficulty, sometimes this, sometimes that, but mortality is clearly reduced.

So, overall, I was very comforted by the prior experience. CHAPS, single-center, interesting observation is again a safety experience with even earlier use with the intravenous, so I would use that as a safety experience, so overall we are getting more safety information and we are getting efficacy information which is consistent in people with impaired LV function.

DR. BORER: Tom.

DR. FLEMING: Let me just briefly add to CHAPS. I think what we are getting here obviously as it relates to mortality is clearly very limited. We have what I think a six-month control time frame

and when we look at CAPRICORN, the survival differences don't emerge until roughly after that time point.

The relevant information here to me as I look at it is deaths, cardiac deaths, 4 versus 2, heart failure 7-6, MI's 8-5, strokes 1-1, so it is obviously very limited additional evidence, so the essence of what would be relevant external information is what Marc was referring to coming from COPERNICUS.

DR. BORER: Let's start with Beverly and go back around the other way.

DR. LORELL: I agree with what has been said about COPERNICUS. I would add that in contrast to Dr. Nissen's point about data dredging, as if one were looking for an indication for cardiovascular hospitalization, the separate issue of concordance of findings on cardiovascular hospitalization, looking at the COPERNICUS indications in comparison with the CAPRICORN data experience, I did find reassuring.

I think it is worth mentioning that one important difference between the experience in COPERNICUS and CAPRICORN that takes Marc's comment one stage further is that to my knowledge, this is

the first large prospective trial that has actually looked at patients who haven't raised their hand, without clinical symptoms or signs of the syndrome of heart failure and low ejection fraction that has been tested and shown a benefit, so in that sense I would say this is an important difference and may be an adjunctive piece of information.

I would also say I actually found CHAPS helpful only as a safety experience. I thought the efficacy data is really not comparable because if I understood CHAPS correctly, and correct me if I am wrong, ACE inhibitor use was not permitted in that study, so that that study is really not relevant to current best practice in the United States.

DR. BORER: Alan.

DR. HIRSCH: Well, I found COPERNICUS and CAPRICORN to be two chapters in the same book and I think that how the sponsor laid these out was clear in that we are trying the same disease with the same intervention that alters the natural history in a comparable way, so I will just jump and say that to Item 3.1.1.3, looking at the time course data, I think there are implications of that, which is that treatment with a beta-blocker obviously must be sustained over a long enough period of time

to accrue benefit, so assuming that we look favorably at these two trials as showing evidence of beta-blocker benefit, I think my caution, when this is translated to practice, is that we find ways of maintaining adherence, so that those benefits really are accrued in real life as they are in clinical trials. Very helpful, they are concordant.

DR. NISSEN: Yes, this is where we really get down to the crux of it. I mean was this finding a bolt out of the blue, you know, something one just wouldn't have expected. I mean that is what discovery is a little bit all about.

I would be the first one to say that the development program for carvedilol has been exemplary. I mean it has been really an outstanding one and I think that the whole advance of using beta-blockers in heart failure, I mean 10 years ago, none of us were doing it and now we are all doing it, and I think all of these trials that contributed to this have played a huge role in improvement in the standard of care for patients with cardiovascular disease, but they have also contributed to a comfort level with this particular drug carvedilol that you can give it to pretty sick

people and they actually get better.

So, I think COPERNICUS is relevant, it has the impact of what Tom and I were talking about earlier of beginning now to shade the requirements in terms of how much strength of evidence we want for a discovery in another trial.

It begins to have a real impact on my thinking, so I consider it highly relevant, CHAPS perhaps a bit less relevant, but it is a second trial. I mean no matter how you cut it, whether it is in fact contemporary standard of care or not, it nominally sort of looks like a second trial which has some impact also on kind of lowering the threshold, so I think the two together have pretty significant impact on my thinking about how high one sets the threshold for the discovery of this finding in CAPRICORN.

DR. BORER: Tom.

DR. PICKERING: I would say this is sort of filling in the missing pieces of a jigsaw puzzle, that if you take all the data on beta-blockers post-MI in heart failure and carvedilol, that this is consistent with the other data, and I found COPERNICUS very reassuring and I guess with CHAPS, they got lucky.

DR. BORER: John.
DR. NEYLAN: I do find comfort, the external consistency here is very strong. I think the sponsor should be commended for doing a landmark study with COPERNICUS and CAPRICORN is certainly a logical extension of the development program.
CHAPS is a supportive study that, by and large, is useful for its safety data.
DR. BORER: JoAnn.
DR. LINDENFELD: I agree. I think that COPERNICUS is very comforting here and really lowers my requirement for a p value for CAPRICORN.
DR. BORER: Paul.
DR. ARMSTRONG: COPERNICUS is helpful to me, as well, and notwithstanding the erudition of my two distinguished colleagues, the Killip class III issue, these were sick patients in COPERNICUS and although I still don't know when beta-blocker therapy was started in CAPRICORN in sick patients, I am still troubled about what has happened and what would be reasonable expectation there.
I was, in fact, looking for benefit and stretching it from COPERNICUS and wondering when the therapy was started.

CHAPS actually reassures me on two points, since the therapy was started early, that both re-MI and unstable angina go in the right way in therapy that started within 24 hours of the index event, so I felt that was helpful from a timing issue.

DR. BORER: Susanna.

DR. CUNNINGHAM: I have really nothing extra to add except I am about maxed out on acute acronyms, although I guess it does make discussion more straightforward.

DR. BORER: Mike.

DR. ARTMAN: Well, I agree that COPERNICUS was supportive and reassuring, and the issue from COPERNICUS to me was really the time course, and sort of supported my interpretation of the CAPRICORN data, as well.

It is at about three months that I think things begin to happen and the curves begin to diverge. It gets to this issue of timing, you know, do you need to start it early or not, and I think the studies are concordant in that the effect begins at about three months, where you begin to really see differences.

The CHAPS study I pretty much discounted.

I really saw that just as a pilot study that showed you it probably wouldn't hurt a lot of people if you gave them carvedilol.

DR. BORER: Bob.

DR. TEMPLE: The study is interesting because it is a study of two things that have been separated to a degree in the past. The previous beta-blocker post-infarction studies for the most part didn't study people with heart failure although some were included. They studied people who were characterized as having had a heart attack two or three weeks ago.

COPERNICUS, of course, didn't study people who had a recent heart attack although they had a distant one. That studied people with heart failure. It is not so easy, I guess, to say what this is a study of. It is a study of people with sort of incipient heart failure who have also recently had a heart attack.

What I am hearing people say--I just want to confirm this because we have got to grapple with all of this--is that you find COPERNICUS helpful at least on the aspect of the trial related to poor ventricular function and heart failure, but presumably not particularly informative with

respect to people who have had a recent infarction because they didn't, although the next question may get at that.

So, maybe I am being arbitrary and trying to break things into pieces that really are a continuum, but I would be interested in comments about that. But I take it COPERNICUS seemed supportive in a population of people with poor ventricular function and therefore it makes some sense. Is that right?

DR. BORER: Since I am the one left here, I was going to agree with everybody about COPERNICUS, but now you have focused the question. I was happy to see that the benefit of carvedilol for people with heart failure wasn't lost in the CAPRICORN study.

I would have expected a benefit of some sort in people with heart failure. Because of COPERNICUS, people who enter with severe heart failure were benefited, I was happy to see that there was some consistency about that, but COPERNICUS, by itself, wouldn't be sufficient support to cause me to say that CAPRICORN was, by itself, sufficient for approvability.

I must say I agree with what I think that

Steve and Paul were both saying about CHAPS. I find that more comforting than perhaps some of the other people on the committee found it.

I think it certainly does suggest, as has been said, it does provide some additional safety comfort with regard to the early administration of the drug, but I was happy to see that for all its inadequacies as a definitive trial, it was small, it was a pilot study, it didn't give this, didn't give that, that the results of benefit in a global sense looked the same as the global benefits that one sees from COPERNICUS.

So, forgetting for a moment about the specific issue of mortality, in a setting of acute myocardial infarction, I was happy to see that there was a second experience that suggested benefit from giving this drug early in the course of acute myocardial infarction.

Steve.

DR. NISSEN: Yes. There is also implicit in what you just asked, a question that I was a little surprised that you didn't ask in here, and that is the question of how much weight do we put on the prior knowledge from trials albeit 15 years ago and older on the use of beta-blockers in the

post-MI setting. Oh, I see, it is coming up, I haven't seen that yet.

DR. TEMPLE: It's all in a perfect order, you will see.

DR. NISSEN: I did not read that No. 4 in that way. That is why I missed that. But just to answer your question, what we have coming to the table is we have COPERNICUS, which tells us something about the population who developed overt heart failure, and we also know something about the patients that have had a recent infarct from those older trials, so there is prior knowledge for those two populations albeit from very different sources that allow us to think about this.

DR. BORER: Okay. Without formally specifying how we do so, we may be comforted or discomforted about a finding by information described from studies of related drugs.

If one were to do that with post-MI use of carvedilol, would one include any drug with any of its pharmacological properties - beta-blocker, alpha-blocker, free radical scavenger, antihypertensive, or only drugs with all of these properties?

Would one be interested in survival trials

only, any trials with survival data, or other endpoints, as well?

Are there relevant results with other drugs?

Marc.

DR. PFEFFER: Following the line of questioning now, we are allowed to go even broader, and I think this is very important especially in the context of discovery and the context of what could be done.

So, I want to just step back for a minute. The past beta-blocker trials are now almost, well, they are over 20 years old, from the time they started, a quarter of a century. The rules have changed. The concomitant medications have changed, but the lessons have stood up, that these are good therapies in the patients that were studied, which in general were the lower risk patients.

Discovery was made in those trials by looking within those at the risk groups, and it was found that even though the highest risk patients were excluded, the discovery was that the most benefit was seen in the fringe of patients at the higher risk.

Now, that was not approvable, that is

discovery, and medical practice actually was driven by that without coming through this agency, without a new trial, but that was always speculation, and that was before the ACE inhibitors, so we really didn't know if these findings would be redundant on top of an ACE inhibitor.

Then, you get, during this 25-year period, the development of ACE inhibitors, which were used first in hypertension, but then in severe heart failure, and then post-MI.

In the post-MI studies, there were about 30 percent of people on a beta-blocker, add all the studies together, those people did better than the others, highly selected for who got a beta-blocker, but the effects of the ACE inhibitor that was randomized was about the same in the beta-blocker or not.

So, there was the beginning of some comfort in saying they are both producing benefits. Then, enter the beta-blockers in heart failure on top of an ACE inhibitor showing benefit, so we have got that type of picture emerging that these are two therapies that work independently and give additive benefits to the best that we can show within the realm of clinical trials.

Then, that little area that was understudied is studied in this particular trial. Now, we can talk about how well it was studied, we can talk about what did they do with their endpoints, but this is the study, there won't be another, and it did show what we have been talking about all day. Within the alpha level, we will have to argue about.

But I do think it is a very important piece to a very difficult puzzle that says the question we have with the therapy for human beings is not is this a good therapy or not, but can it improve upon what we are already doing, and that is the most difficult thing in a clinical trial.

I found some comfort in that, and I think it falls into place. Somebody used the analogy of a puzzle. This piece does fit in the puzzle of 25 years worth of work. So, that was helpful.

Would you be interested in survival trials only? Basically, if we agree, I think it would be very difficult to do a beta-blocker trial post-MI in this population. Is this one of the properties? Well, you know, this is where I think--

DR. BORER: Can I just add? I think the importance of that particular clause, 4.2, is if

you are looking at other studies, would we be interested in survival trials only or can we look more broadly.

DR. PFEFFER: Maybe you can help me. What other studies would we be--in this field of beta-blockers post-MI? Give me an example.

DR. BORER: Of anything post-MI.

DR. PFEFFER: Of anything post-MI.

DR. BORER: Studies of related drugs. There are maybe alpha-blocker studies, free radical scavenger studies, antihypertensive studies, any studies you might refer to.

DR. PFEFFER: I think any other studies I might refer to out of the context of what is approved therapy for people as of now, I think would have to start from scratch and show that it is of value over and above what we should be doing including revascularization procedures and things like that, aspirin, lipid-lowering. Maybe I missed your question.

DR. BORER: It may be the way the question is worded. I think what the FDA is asking here is if we have a trial, a single trial with the limitations that we have talked about all day, can we derive any comfort by looking at trials that

have already been done using some other drug that somehow we perceive as being in some way relevant to, or similar to, carvedilol.

Carvedilol has beta-blocking properties, alpha-blocking properties, free radical scavenger properties, antihypertensive effects. To gain comfort, can we look at studies of beta-blockers, can we look at studies of alpha-blockers in acute MI, free radical scavengers, antihypertensives in people with acute MI or any other related disease?

DR. PFEFFER: I now understand your question, Jeff. I was answering this as a beta-blocker without intrinsic sympathomimetic activity. That was the answer I was giving.

DR. THROCKMORTON: Jeff is exactly right. We are now giving you full flight. You have an opportunity to bring in whatever pieces you feel like. It is just a matter of defining of what pieces you think you can bring in. What I am hearing you say is that this puzzle is beta-blockers.

DR. PFEFFER: I was only using the beta-blocker/ACE inhibitor experience and both experiences.

DR. THROCKMORTON: So, beta-blockers and

ACE inhibitors.

DR. PFEFFER: Yes, ACE inhibitors and beta-blockers adding value in heart failure. Now, beta-blockers adding value on ACE inhibitors.

DR. THROCKMORTON: How about ARB's?

DR. PFEFFER: I was not using that at all. I think that would have to be proven.

DR. TEMPLE: I still didn't understand that. Were you looking at the effects on beta-blockers, but noting that some of the studies, people were already on ACE inhibitors, as well, or were you actually looking at post-infarction ACE inhibitor data?

DR. PFEFFER: I was using both, and I went historically that in one field, one started with the ACE inhibitor and added the beta-blocker, and the way trials were done in the other field, post-MI, you started with the beta-blocker, and ACE inhibitor trials were done with a background of beta-blocker therapy, and the results have been consistent.

Now, this is one that tests specifically beta-blocker, I am calling it a beta-blocker on top of an ACE inhibitor, and gives consistent findings.

Now, it is discomforting to me, but the

sponsor didn't start with that this is a unique antioxidant. You know, if they did that, I would have had trouble, but that isn't what they were presenting today.

DR. TEMPLE: I mean how many documented benefits of antioxidants do we actually know about?

DR. BORER: We will get to that.

JoAnn, why don't we start with you and we will go around in a totally different direction.

DR. LINDENFELD: I, as Marc, are comforted by a number of other studies, ACE inhibitors with beta-blockers, in this sense. The other thing I think that I find comforting is that we all want to know if beta-blockers in the current era with all this new therapy that we do are important, but there isn't any reason to believe that they wouldn't be.

There is nothing to make me think no, gosh, I don't think beta-blockers will work today, so I find all of that data and even the older data with beta-blockers comforting in this sense.

DR. BORER: Paul.

DR. ARMSTRONG: I think there is some comfort in knowing some of the information from other trials, indeed, I failed to point out that in

CHAPS, there was uniform reperfusion, and one of the central issues of the day is whether all infarcts are the same, and they are not, and the notion that this apparently applies to both those who did and didn't get lysis.

Only about 50 percent of the population that we have been asked to look at received some form of reperfusion, and as Steve brought out, we know that over 3- or 400 of them didn't have an enzyme elevation, so the issue of heterogeny within the trial is to some extent handled by reassurance from some of the other trials. So, that would be my additional comment.

DR. CUNNINGHAM: I think there is comfort from the other studies. I think, though, one thing I would say is there is a continuum of similarity, and the more similar the drugs were that were used in the other studies, the more comfortable I am, and the more you get out in the dissimilar, if they only have one property in common, then, I am much less comforted.

So, I think if we get out to the free radical scavengers, I would be very uncomfortable, so there is no absolute answer.

DR. BORER: Mike.

DR. ARTMAN: I really don't have anything to add.
DR. BORER: John.
DR. NEYLAN: Yes.
DR. BORER: Tom.
DR. PICKERING: One point. We have generalized a lot from results of other beta-blockers that have beta-1 blockade, but not intrinsic sympathomimetic activity. I think if it is approved for this particular population, we should be cautious that the findings are not generalized to other beta-blockers that don't have the additional properties like the vasodilation that carvedilol appears to have.
DR. BORER: Steve.
DR. NISSEN: Let me just slightly disagree with JoAnn and say that in this contemporary era where everybody is getting reperfused, and so on, I mean something that I actually hear is people say, well, in the reperfusion era, we are not so sure beta-blockers have much to offer.
So, one of the reasons why I viewed this trial as so terribly important is to understand whether, in the ACE inhibitor era with thrombolysis, statins, aspirin, and all the

therapies that weren't even thought about back in the early 1980's, whether or not, in fact, there was an additional benefit.

So, while the prior information is very useful, this trial obviously adds to our understanding, and that is why it is incremental information.

DR. LINDENFELD: I agree with that, and you can correct me if I have the data wrong, but even prior to lytic therapy, half of people reperfused at two weeks. With lytic therapy, we agreed that there is not 100 percent reperfusion, so I think that difference in who really reperfuses is actually quite small.

DR. NISSEN: Actually, at the Cleveland Clinic, everybody gets reperfused.

DR. LINDENFELD: But that is not this trial, I mean it is not angioplasty.

DR. NISSEN: Sorry, just had to say that.

DR. LINDENFELD: This trial was thrombolytic based. But I think that the difference is at two weeks, in the absence of thrombolytic therapy, 50 percent of people are open again.

DR. NISSEN: But I am talking about the

myocardial salvage era.

DR. LINDENFELD: Right.

DR. NISSEN: In the myocardial salvage era, there is still something to be gained--we are trying to ask that question--is there still something to be gained by giving, you know, beta-adrenergic blocking agents, and it is a very important question.

DR. BORER: That reminds me of 20 years ago when I was stupid enough to answer a question posed to me by Mason Sones on a big public panel, which was, "How much does it cost to do a catheterization at New York Hospital," and when I gave a number, he said, "Everybody should come to Cleveland, we do it cheaper."

Paul, did you want to make another comment about this?

DR. ARMSTRONG: I just wanted to pick up, and you may want to wait on this, but Tom Pickering really signaled for me an issue which I don't think we can let pass, those of us who are lumpers or splitters on this beta-blocker issue.

I think we have accepted that ISA is off the board here, but at one point we talked about the special properties of carvedilol. Today, we

have lumped it with metoprolol and with propranolol, and, in fact, the sponsors made a key point that it is very like propranolol.

Tom has suggested that he is not prepared to extend the observations today to metoprolol, and I would have a different view, so I guess at some point we are going to have to return to that discussion.

DR. BORER: Alan.

DR. HIRSCH: I concur with what has been said before. I will make it simple.

DR. BORER: Bob.

DR. TEMPLE: We would certainly not lump in the sense of giving this claim to a drug that hadn't been studied, but I do want to ask about some of the things people have just said.

Carvedilol has alpha-blocking activity in addition to beta-blocking activity. Why would anybody imagine that that is a good thing? There have been formal studies in heart failure of alpha blockers. They don't help at all.

The results of drugs post-infarction, as was just shown totally, seem very similar perhaps if you don't have ISA for drugs that don't have these extra properties and drugs that do. It looks

like it is the beta blockade that seems to be doing most of the job.

So, I am not sure why everybody is so worried about it.

DR. BORER: We will get to that. Hold your response to that, Steve, and let's finish up with Tom.

DR. FLEMING: Just to reinforce some of the general principles here. Philosophically, in answering Question No. 4, I would say I would certainly give attention to results on studies evaluating members of the same class in the targeted setting that we are interested in.

Under 4.2, I would find relevant, not just studies that are primarily focusing on survival, but any study that would provide substantial survival information would be relevant.

Having said that, what I worry about, and I know all of us have thought about this, is the relevance of such information depends heavily on how confident we are that the other agents that are being studied would not have any favorable mechanisms of action that our specific agent in this case, carvedilol, wouldn't have.

You would want to avoid overestimating

survival benefits because other agents have mechanisms that carvedilol doesn't, and similarly, you would want to make sure they wouldn't have any unfavorable mechanisms that carvedilol would have that could influence survival.

In my own view, this is what leads me to be thinking at least in focusing on members of the same class, but even within that, you are not fully reassured that those criteria are met.

In the targeted settings, I go back to the sponsor's penultimate slide where they said there are no data on any beta-blocker currently in infarct survivors being provided ACE inhibitors where these people have had LV dysfunction following acute infection.

So, we don't have any perfect situation here even with members of the same class studied in exactly this manner, so we are left with need for some extrapolation and yet that extrapolation in this setting obviously, as Milt has summarized, there is considerable experience, more so than we would typically have.

My own sense, though, is that each of these cases have to be individually considered, and I am reluctant to have certain actions by this

committee viewed as precedent-setting, and I would like to just thank Jeff for pointing out that the losarten example in the renal trial in type II diabetic renal disease that this committee had considered over the last year certainly shouldn't be viewed as a precedent.

I certainly didn't look at the irbesarten data and view that to be particularly substantive in that decision, and I worry a little bit about what views will come forward in the future as this committee considers this specific application and I would just urge that the principle is indeed other experiences with sufficiently closely related agents studied in sufficiently closely related settings should be considered, but that is very much on an application-by-application basis in terms of how much weight that would be given.

DR. BORER: Beverly.

DR. LORELL: I have nothing to add to the previous comments that experience with this drug seems to be very congruent and to fit into a continuum of experience of the use of beta-blockers in heart failure, as well as the use of beta-blockers in the context of ACE inhibitors from ACE inhibitor trials where one looked

retrospectively at beta-blocker use.
I think Question 4.1 is a very important one and I think this trial in the context of other studies provides no data about the helpful negative or neutral effect of alpha blockade. I mean to my knowledge, there are no other large trials that have tested the addition of alpha blockade on top of either beta-1 selective or nonselective use in myocardial infarction.
Similarly, I think this experience does not speak in any way, nor can any prior trials be used to raise conclusions about free radical scavenging or antihypertensive effects.
So, I wanted to answer that a little more directly than others have.
DR. TEMPLE: There is a big study of alpha-blocker alone.
DR. LORELL: About what?
DR. TEMPLE: Of an alpha-blocker alone.
DR. LORELL: Yes.
DR. TEMPLE: But not on a beta-blocker.
DR. LORELL: To my knowledge, there is no experience whatsoever of adding alpha blockade to beta blockade in this setting.
DR. TEMPLE: Can I mention one other

thing? The timolol study actually had about a third of its population with acute heart failure at the time of the infarction although by the time they were randomized, they no longer were.

I don't think anybody had ejection fractions on those people or anything like that, but there is some experience in a group that at least was at somewhat higher risk, and the effects were the same in that group or better perhaps in the rest.

DR. BORER: I gain some comfort from other trials using drugs that have beta-blocking properties, but not a heck of a lot. It helps me a little bit and as Tom said, in the parallel of irbesarten and losarten, it may have helped a little bit there, but that wasn't the basis for a decision, nor would it be the basis of a decision for me here.

I have said this many times before and I may be a bit of an iconoclast in saying it, but I have heard both Toms and Paul say something very similar just now. This is a unique molecule, carvedilol.

When we were hearing about this drug for its approvability for treatment of patients with

heart failure, the sponsor presented a great deal of information suggesting that the uniqueness of the molecule, because of its alpha blockade and because of its free radical scavenger properties, that these properties were very important in mediating the benefits that we saw.

Now, I didn't think much of that then, and I don't think much of the argument that it's a beta-blocker and other beta-blockers do this, therefore, this one works. I don't think all that much of that now.

I think that provides me with some comfort, but this is a unique molecule. I doubt very much that we know all of its pharmacological effects, in fact, I am sure we don't, and I am sure that nobody in this room can tell me the mechanism by which other drugs with beta-blocking properties have improved mortality after myocardial infarction. That is not known.

There aren't even a whole heck of a lot of good hypotheses. So, this provides me with some comfort, but the reason for my going through that discussion a moment ago is to support exactly what Tom said and exactly what Beverly said and exactly what Tom Pickering said, that is, that I think that

we have to look at the body count here and decide whether we believe it or not.

We will get some comfort, more or less, from all of these other sources of data, and then we are going to make a decision about this drug, and it shouldn't be widely extrapolated to other drugs.

Now, Steve, you wanted to make one other comment?

DR. NISSEN: No, I just wanted to respond to Bob. Bob asked a theoretical question, why might it be beneficial.

I mean at least hypothetically, when one gives a beta-blocker in a setting with a depressed LV function, the problem, of course, is the negative inotropic effects may, in fact, make patients worse before they make them better. At least theoretically, a drug that has some inherent vasodilator properties might reduce wall stress, unload the ventricle, you know, mitigate against the adverse effects.

Now, whether that happens here or not, I have no idea, but you asked theoretically, could the alpha blockade have any therapeutic implications, and the answer is it might.

DR. TEMPLE: But I am just pointing out that in a heart failure study done by the VA, prazosin did not have any benefit.

DR. NISSEN: Say that again.

DR. TEMPLE: There is a major heart failure study with prazosin, and it didn't show any benefit. It's an alpha-blocker.

DR. NISSEN: No, but I mean I think there are other things that happen when you give more of a pure vasodilator.

DR. ARTMAN: And that is a different question.

DR. NISSEN: Yes, and also I think there is all kinds of issues about reflux increases and sympathetic tone when you give vasodilators. I mean it is very different to give a mixed beta-blocker or alpha-blocker than it is to give a pure alpha-blocker.

DR. TEMPLE: No one has documented that one is actually better than another at anything. It is all speculation.

DR. NISSEN: I agree, but you asked is there any theoretical reason. You asked for a theoretical reason, and I can tell you there is a theoretical reason why one might expect that.

DR. BORER: Let's move on. May I, Doug and Bob, combine 5 and 6? It doesn't appear that there is an important difference between 5 and 6.

We are going to get to the point where we actually have to vote for the record.

No. 5 is: All things considered, how likely is it that the mortality effect in CAPRICORN represents an effect attributable to carvedilol, which is another way of saying should carvedilol be indicated to reduce mortality in patients with left ventricular dysfunction after myocardial infarction.

May I request that we refine that just a little bit. It is not left ventricular dysfunction, it's left ventricular dysfunction the way it was defined here, which is an ejection fraction of less than or equal to 40 percent. That is moderately severe or however you want to qualitatively define that term. It was with or without heart failure.

But given all those caveats, should carvedilol be indicated to reduce mortality in patients with left ventricular dysfunction. We don't have to go into all the reasoning, we have done that already.

Marc, you are the committee reviewer.

DR. FLEMING: I don't know whether Doug or Bob will wish to provide any clarification, but in the event that you would, I would be interested in hearing FDA's perspective on strength of evidence that we would generally like to have on a mortality endpoint.

I had mentioned earlier on we talk about two adequate and well-controlled trials, and we talk about 025-squared, and we realized that for an endpoint such as mortality, that is something that might not be required.

I realize, of course, lots of issues will have to be taken into account as we think through is this the strength of evidence of two studies, one study, it doesn't just have to be the evidence from this trial as we have discussed in Questions 3 and 4, it could be evidence from other studies.

As FDA looks at this, when we look at the totality of evidence that is relevant to a given consideration, are we talking about the strength of evidence of 1.5, two studies, anything in general you want to say about this?

DR. TEMPLE: These questions are all bound up together, that is the difficulty, however, just

a couple of observations. You saw data on what it took to get metoprolol a claim for post-infarction beta blockade.

The p value wasn't as long as your arm, it was a one-study value, so the strength of evidence that was needed there probably, although I have to say not explicitly in light of previous experience, was that one study would confirm what you sort of thought about the class.

We presented to you what we have done with ACE inhibitor heart failure claims. It is very clear we are using one study at a reasonable p value standard even though I would say we were not explicit in thinking that through, but the weight of evidence from SOLVD on made us think that one confirmatory study that was reasonably persuasive was good enough.

It depends on how you think of that here. As I was trying to point out, you have got a little bit of heart failure and you have got a little bit of post-infarction here.

So, my view would be that you need a total amount of evidence that is as persuasive as usual, but that you can get it from more than one place, one piece of which comes from the study at hand,

the other comes from the other studies of the same drug, the other comes from the studies of the other drug, all of which should add up to approximately the usual standard.

But as I have pointed out for metoprolol, we thought it met the usual standard, but it did it with one study at a p of 0.02 or whatever it was, because we thought we had other relevant information. You know, we are all being bayesian here, but we are not admitting it.

You saw similar behavior with the irbesarten/losarten. Each study was a reasonable study, nobody had any doubts about that, but it was the combined data that made the persuasive case, and I think that is the situation you are in here.

Is that too squiggly or is that good enough?

DR. THROCKMORTON: I guess I will just add one thing. I think we are in a place we are not going to find ourselves a lot when we think about the sort of strength of evidence that we have for this class of drugs, for these classes of drugs versus other sorts of therapeutic areas. I mean you can think of other places like, I don't know, GP2B3a antagonists where we have had surprises when

we tried to extend what we thought we understood from single trials.

Here, we have a relatively robust effect seen across a lot of different drugs and a lot of different therapeutic areas, the patient populations that makes it an uncommon place, I think, with regard to most of the therapeutic areas we think about in cardiovascular medicine.

DR. BORER: Marc.

DR. PFEFFER: Well, I found the leading from the agency helpful in this case. Sometimes it is not, this time I think it was. Really, it boils down to there were some other issues that came up, do you think you could do another study in this, or do you think we have enough information now to apply to people.

I don't think I could personally be involved in a beta-blocker post-MI trial unless it were a very small group that we still have yet to define, and that is what I think we also need to say of the few places that more information is needed, I think we need an answer to Dr. Armstrong's question about these Killip class III patients, what were they like at the time they were randomized, were they cleared and then randomized.

The onset, we have now heard that there was a long period and even within two weeks could be divided. I would like to see some information about the safety, so I am now talking about harm, potential for harm of giving this very early. I just don't know enough about that, and that is what is happening in post-MI especially beta-blockers.

So, I would hope we can have the agency dissect out the information on day 1, day 2, randomization and events in those people.

But overall I think we have a benefit here that will help patients, and I think getting this out, regulations will talk about this drug, but guidelines will then talk about beta-blockers, and I think that will help people.

DR. BORER: So, that's a yes.

DR. PFEFFER: That's a yes.

DR. NISSEN: I have to make a few comments before I answer. First of all, notwithstanding the nearly heroic efforts of the sponsor to shoot themselves in the foot, which continued right up through today, and there are some things I have to say.

First of all, Tom and I are, I think, and he will speak for himself as I know he will, you

know, I don't think the Data Safety Monitoring Board acted entirely properly here and I think it ought to be said for the record, that, you know, there are roles for each of the constituencies involved in the trial, and those roles should be carefully defined and observed.

There is a penalty to be paid for not following those rules. Now, it turns out the rules weren't broken as much as it seemed, and this is where some more shooting in the foot occurred. I mean when I read this statement in the executive summary that said the Data Safety Monitoring Board strongly recommended that they change the primary endpoint, I was extremely uncomfortable, and then you read the letter, and that wasn't what the letter said.

The letter didn't say that. It said consider. It didn't say do this, it said you ought to think about this, and that is a little bit, you know, it made me more comfortable, but I think we ought to say from the beginning what the roles are of these various committees, the charters ought to say them, and they ought to follow those rules, and the extent that those rules are not followed undermines the credibility of the trial process,

and it is something we ought to be careful about in the future.

Similarly, I think the Steering Committee acted somewhat unwisely in the whole way that the study was redesigned and not sort of thinking more carefully about what endpoints they wanted to choose, so we got into this data dredging problem later on where now we are talking about which cause for hospitalization, how you define that, and those are avoidable problems potentially.

So, I think that it is important that we say that. Having said that, I think that this is an important observation, that, you know, beta-blockers are largely forgotten, they get forgotten periodically. You know, every time we get a new therapy, everybody is focused now on the angioplasty era on how fast the door to balloon time is now the thing that counts the most about how you treat a myocardial infarction, and they forget about the fact that the patients have this period of time afterwards where they are very vulnerable.

The use of beta-blockers post-infarct in America, and I don't know what it is like in the rest of the world, it is just abysmal, and we

didn't really know before CAPRICORN, we didn't have really compelling evidence of what happens in the reperfused patient that has done very well and gets ACE inhibitors and gets statins and gets aspirin, and all the contemporary therapies, and I would bet you there are a lot of people out there that think that in this era, beta-blockers are passe, and what CAPRICORN teaches us is that they are not passe.

So, the reason I am voting yes is not because the conduct of the trial was exemplary. I think there were some terrible dilemmas that you had to deal with. I am not sure you dealt with them in the best possible way, but the fact is that I think that, by and large, lives will be saved if this label is granted and if the message is aggressively pursued that even in the contemporary era, there is still a lot to be gained by giving beta-blockers post-MI.

So, I vote yes because I think the public health considerations here and everything else make this a mandatory yes.

DR. BORER: Alan.

DR. HIRSCH: You know, it is very hard to follow Steve, but I will make an effort here. I will start with humor, but try to make a clear

point.

For humor, obviously, the sponsors shot themselves in the foot. The FDA, according to Marc, occasionally leads one way or the other. I think our committee can sometimes opine in more than one direction, and it gets all very confusing.

When I came into this meeting, we talked about discovery, are we finding something new that was unique, that wasn't part of a pre-hoc hypothesis, and I really don't think that that encompasses where I am going to lead you with my vote.

I don't think that this was about discovery. What happened here is that we have demonstrated, I think, that carvedilol has a positive effect in this somewhat mixed post-MI heart failure state.

We found a gem in a mine discovery here that has come up with many, many precious stones as part of a tradition of like-minded beta-blocker related positive outcomes in a consistent pattern. So, this isn't discovery to me.

It gets back to how Tom looks at spending alpha, I think there is little doubt that we have carvedilol causing a positive beneficial health

effect in a very specified population. I think it is also true it is unlikely that if we had any doubt about that, we could perform a second trial in the real world to better confirm that.

So, the evidence base we have overall, this isn't discovery, this is I think good data confirming a reality. My vote is yes.

DR. BORER: Tom.

DR. FLEMING: In leading up to an answer, let me begin by thinking about CAPRICORN and strength of evidence from this key pivotal study.

The sponsor presented this and said this is a mortality trial and very appropriately it should have been. It was initially a mortality trial, but a very thought-out decision was made in mid-course to back away from that mortality endpoint based on what I as best can understand a judgment that the plausibility of achieving a mortality effect of sufficient magnitude in this setting was not sufficiently high in the context of the size of the trial that was being conducted, and as a result, there was a shift to an alternative endpoint.

Hence, prospectively, mortality wasn't the primary endpoint, and that matters. It matters a

lot when we are looking at whether this is a confirmatory trial or an exploratory trial, and, of course, life is a continuum, it is not simply that dichotomous, but clearly, there was a backing away from the thought that yes, this is an endpoint that we believe is obviously profoundly important, highly clinically relevant, and one that we believe is going to be of sufficient magnitude that in the context of this size of a trial, we can establish benefit.

So, it does leave me in the position of interpreting strength of evidence from this study in the context of this being an endpoint that wasn't the primary endpoint. Nearly all of the alpha was assigned to an alternative measure.

The target for what was viewed as sufficient evidence to conclude that mortality has been proven with the strength of evidence of a single positive study here was the 0.005, and as the FDA review indicated, we are about a factor of 6 or 8 away from that.

So, I am going to become very quantitative here for a moment. As a statistician on a log scale, that is the strength of evidence of two-thirds of a trial. Okay. I have to be

quantitative in a moment because I do think external data is relevant here, and I have to try to think of how that is to be considered.

My own view, what does it take for mortality? In my own view, if we are talking endpoints such as hospitalization, I strongly endorse the concept that we should have two adequate and well-controlled trials for the concept of replication, as well as strength of evidence.

For a profoundly important endpoint like mortality, I have long believed that somewhat less strength of evidence is acceptable in view of the profound importance of that endpoint, and have subjectively in my own mind over time thought of it in terms of roughly 1 1/2 trials if it is a mortality endpoint.

So, two studies, one of which achieves an 0.03 and a second study that doesn't achieve significance, but it is close, that is an example, or one trial where mortality is the primary prespecified endpoint that achieves an 0.005, that is also of that strength of evidence.

So, we are left here with, in my own view, we are halfway there roughly in terms of what strength of evidence I would have wanted to have

seen.

The external data here are very relevant and as Milt Packer had described in his presentation, I believe this is, I think he called it a unique situation in terms of the magnitude of evidence that you have from, first, the agent at hand, carvedilol, in related settings where the COPERNICUS trial is particularly important, as well as the magnitude of evidence for other members of the class.

This part is unavoidably very subjective - does this get us the rest of the way. In my own view, I think it is very rare to have that much strength of evidence from supportive studies, but I think in this case we are in that rare circumstance.

So, with that overall summary, I think this is a situation where overall evidence is sufficient to conclude that mortality benefit has been shown, but I would really emphasize that this is, in my own mind, a fairly uncommon or I call it rare circumstance, and not one that I would consider as precedent setting that would lead to the expectation that in the future, if studies that are designed to address the right issue, mortality,

are, in fact, redesigned, and don't achieve unfortunately the real evidence that we would need to see, that they can be salvaged by looking at other supportive evidence.

I would say, and I know the FDA does this extremely well, I would just reemphasize the important role the FDA does play in working with sponsors creatively prospectively in designing trials and ensuring that the right designs are in place, and this also is relevant when the studies are redesigned, that if ultimately, we expect mortality as an issue that we want to address, that when the study is initially designed or redesigned, we do whatever we can to avoid this type of circumstance where we end up getting data that is much less than what we would really want to see to answer the questions.

DR. BORER: That is a yes?

DR. FLEMING: That was a yes.

DR. BORER: Beverly.

DR. LORELL: Thank you. I have nothing to add regarding the issues of trial redesign. I think they have been addressed very well.

I do vote yes. My vote is based on really three things. One is that mortality was predefined

as a major and initially, the primary endpoint.

Secondly, I think this experience, as was said by others, as well as Tom, fits into and in congruent with other data regarding the use of this drug, as well as other beta-blockers, in moderate and severe heart failure.

Third, I think these data are supported by other studies looking at the use of beta-blockers after myocardial infarction.

DR. BORER: I vote yes. I have nothing to add to everything that has been said about why, but I would just reemphasize what Tom said a moment ago about the extrapolability of my vote, like his, to any other situation where it just happens that mortality is considered and there has been one trial. I think we have to look at the specific circumstances.

That having been said, I vote yes.

JoAnn.

DR. LINDENFELD: Yes, I also vote yes. I think that mortality was a prespecified endpoint and although it wasn't the only endpoint, that was changed. I don't see any malintent here. I think just a goof was made.

So, I tend to shade this more toward a

single good trial, not the two-thirds of a trial that Tom discussed. I think it moves more toward that way because I think it was just a little bit of a goof.

This was designed to show a mortality benefit. It showed exactly the mortality benefit that was prespecified. So, I would shade this more toward one trial and vote yes.

DR. BORER: Paul.

DR. ARMSTRONG: I will vote with the caveats that I thought Marc Pfeffer brought out very well, and I would like to reemphasize. I think there is a lot of work yet to be done with the sponsor and the agency in terms of what the label will say if, indeed, they decide to approve this, so that caveat.

The second thing I would like to say, Mr. Chairman, as someone who has been both the chair of a DSMB and a member of a DSMB, is a somewhat contrary view to what has been expressed. I am satisfied based on the presentation of the chair of the Steering Committee and the excerpts from the letter, that the DSMB here acted appropriately.

Like many of you, I get a lot of advice in life and I take some of it, and I think that the

DSMB has a responsibility after assuring patient safety to provide an informed opinion and suggestions to a steering committee, which they may or may not take.

The issue of blinding, I think has been much discussed. Tom and I have a different view about that. I think there is healthy reasons to think differently about this, but I don't have a problem with the way the DSMB acted or the Steering Committee responded in this particular instance.

DR. BORER: Susanna.

DR. CUNNINGHAM: I am going to vote yes and I am going to second Bev's very well-stated reasons.

DR. BORER: Mike.

DR. ARTMAN: Yes.

DR. BORER: Did you want to make a comment?

DR. TEMPLE: I just wanted to support what Paul said. We have recently written guidance on what a data monitoring committee is supposed to do, and one of the things, difficult as it is that they are supposed to do, is keep a watchful eye on the world and on the rate of events, and things like that, and give advice that might in some cases

salvage the study.

They plainly tried to do that, but the outcome was contrary, which we now know, but it is not illegitimate for them to consider those things or at least we didn't think so when we wrote the guidance.

DR. FLEMING: Just to follow up, my only concern with the action of a monitoring committee is given that I believe they should be unblinded because that is I think critical to being able to fully carry out their role of safeguarding patient interests, if they were, if they were then to make any recommendation about changing an endpoint clearly is inappropriate.

Given they weren't--

DR. TEMPLE: Absolutely.

DR. FLEMING: Given they weren't, I see no problem with what they did. My concern is not with the Data Monitoring Committee, it was with the Steering Committee and in particular today with the presentation that indicated it was the Data Monitoring Committee that said we had to do this.

The other thing, something for further discussions is how conservatively they apportion their alpha. We have had a lot of discussions of

these things. I believe they could have gotten away with saying 0.03 for both of them and might have been much better off to have done that, because they are not entirely separate endpoints, but that is a discussion for a different time. This was a very conservative choice for a very important endpoint.

DR. TEMPLE: Because of the correlation, if we are talking two-sided p value, of course, they wouldn't have needed 0.025, 0.025. It probably would have been close to 0.03, 0.03, as you said, or because they weren't given it equally, where they were saying 0.045, 0.005, it could have been probably 0.047, 0.009.

DR. NISSEN: Bob, what I was reacting to was the implication here in the original document that it was somehow coercive, that basically, how could we possibly, in the face of this very strong recommendation not do this, and that was the way in this document it was stated.

Now, it turns out that is not what they did, and that is why I backed off on that, but if you read what was said in here, it doesn't look like it was done the proper way, and the letter actually, it turns out, is to say we think you

ought to consider this, and I don't have any problem with that at all.

But if they had been unblinded, that would have been inappropriate, and I don't think anybody should leave the room without understanding why Tom and I feel so strongly about that, you know, that is off the table.

DR. BORER: Okay. We have one final question and then we can discuss DSMBs if the FDA wants us to.

The final question is: Regarding the fact that the sponsor also seeks a claim for reduction in recurrent MI, based on the observation of 45 adjudicated events on placebo and 27 on carvedilol, of which 16 and 12 were fatal, do these data support a claim?

Marc, let's have your answer first and then we will go to the other side of the table.

DR. PFEFFER: My answer would be no, and I was a little disappointed that it was not quite clear in the document that there was this relatively long period of silence in terms of non-fatal events, the patients couldn't express themselves, and also in terms of the prespecified criteria for the event itself. I think those

things weren't as robust as I would have liked to have seen.

DR. BORER: Mike.

DR. ARTMAN: I would agree with that. I was really disappointed with the data on recurrent MI. I thought it was murky and not very clear, and I don't think that what we have seen supports this claim in any way.

DR. BORER: Susanna.

DR. CUNNINGHAM: No.

DR. BORER: Paul.

DR. ARMSTRONG: A clear no for the reasons that have been stated.

DR. BORER: JoAnn.

DR. LINDENFELD: No, for the same reasons.

DR. BORER: I vote no.

Bev.

DR. LORELL: I vote no for the reasons that have already been said.

DR. FLEMING: No.

DR. HIRSCH: No.

DR. NISSEN: No.

DR. PICKERING: No.

DR. BORER: Unanimous no.

I think the reasons behind that decision

should be clear from what has been said about why the yes vote was given for the mortality claim.

Do you need further clarification from any of us? Do you want us to discuss anything else? Do you want us to discuss DSMBs?

DR. THROCKMORTON: Please do not discuss DSMBs.

DR. TEMPLE: We are all done with that. We wrote a guideline and Tom wrote a book.

DR. BORER: I continue again to suggest to the FDA that for a more complete discussion of this committee's opinion about how to deal with data about primary endpoints that are seen in only one trial, we might have a workshop.

That having been said, if there are no other comments, we will adjourn.

DR. THROCKMORTON: Thank you very much.

[Whereupon, at 2:23 p.m. the meeting was adjourned.]

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