DEPARTMENT OF HEALTH AND HUMAN SERVICES

CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

98th MEETING

Monday, January 6, 2003

8:30 a.m.

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Jeffrey Borer, M.D., Chairman

Jayne 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

John Neylan, M.D., Acting Industry Representative

Thomas G. Pickering, M.D., D.Phil., Consultant

FDA:

Robert Temple, M.D.
Douglas Throckmorton, M.D.
John Lawrence, Ph.D. (Presentation Only)

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P R O C E E D I N G S

Call to Order and Introductions

DR. BORER: Good morning. We will begin the 98th meeting of the Cardiovascular and Renal Drugs Advisory Committee. We will introduce the committee members who are sitting around the table. Mike, why don't you just state your name and, for everyone, when you want to speak turn the microphone on so that we can see the light, and turn it off when you are done.

DR. ARTMAN: My name is Mike Artman. I am with the New York University School of Medicine.

DR. CUNNINGHAM: Susanna Cunningham, University of Washington.

DR. ARMSTRONG: Paul Armstrong, University of Alberta.

DR. LINDENFELD: JoAnn Lindenfeld, University of Colorado.

DR. PETERSON: I am Jayne Peterson. I am the acting executive secretary of the committee. I would remind you when you get done talking, you have to remember to turn the mike off.

DR. BORER: Jeff Borer. I am the committee chairman.

DR. LORELL: Beverly Lorell, from Harvard

Medical School and Beth Israel Deaconess Medical Center.

DR. FLEMING: Thomas Fleming, University of Washington.

DR. HIRSCH: Alan Hirsch, University of Minnesota Medical School.

DR. NISSEN: Steve Nissen, from the Cleveland Clinic Lerner School of Medicine.

DR. PICKERING: Tom Pickering, from Mount Sinai Medical Center in New York.

DR. NEYLAN: John Neylan, from Wyeth Research. I am the industry representative to the committee.

DR. BORER: I want to announce that Tom Pickering is an adjunct member of the committee. He is an SGE consultant for this meeting. John Neylan, the acting industry representative, who is a non-voting member--Tom will be voting--is sitting on the committee as an industry representative for the first time. That is, we have not had an industry representative on the committee before so this is a new situation for us.

Do we have a conflict of interest statement, Jayne?

Conflict of Interest Statement

DR. PETERSON: I will read the statement. 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. Susanna Cunningham has been granted a waiver under 18 U.S.C. 208(b)(3) and a 505(n)(4) waiver for her ownership of stock in the sponsor. The stock is valued between $25,001 to $50,000.

Dr. Thomas Fleming has been granted a waiver under 18 U.S.C.(208)(b)(3) for his consulting for a competitor on an unrelated matter. He receives less than $10,001 a year.

Dr. Alan Hirsch has been granted a waiver under 18 U.S.C. (208)(b)(3) for serving on a speakers' bureau for a competitor on an unrelated matter. He receives less than $10,001 a year.

Finally, Dr. JoAnn Lindenfeld has been

granted a waiver under 18 U.S.C. (208)(b)(3) for serving as a consultant to a competitor on an unrelated matter. She receives less than $10,001 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, Parklawn Building.

In addition, we would like to disclose for the record that Dr. John Neylan, a full-time employee with 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: We will proceed with the presentation. This presentation is relevant to supplement NDA 20-386/S-032 for Cozaar, losartan potassium, tablets made by Merck and Company. The company is proposing a new indication for the reduction in the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy. The sponsor's presentation will be introduced by Dr. Jeffrey Tucker, the director of regulatory affairs of Merck.

Sponsor Presentation

Introduction

DR. TUCKER: Mr. Chairman, members of the advisory committee, FDA, ladies and gentlemen, my name is Jeff Tucker, in the Department of Regulatory Affairs at Merck Research Laboratories.

Thank you for the opportunity to present Merck's data on the efficacy and safety of losartan in reducing the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.

This morning we are discussing the results

of Merck's cardiovascular outcome study LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study. The agenda for Merck's presentation is as follows: After my introduction, Dr. Jonathan Edelmann, the medical monitor of the LIFE study, will present the background and rationale and then describe the efficacy and safety results of the LIFE study. Finally, Dr. William Keane, vice president of clinical development, will provide interpretation of the data from the LIFE study and summarize the evidence that supports our proposed new indication.

LIFE was an active-control, double-blind, multicenter study conducted in 945 sites in seven countries, and 9193 hypertensive patients with left ventricular hypertrophy were enrolled in the study and were followed for four years for occurrence of cardiovascular endpoints.

We believe the results of the LIFE study merit modification of our product label to support the following new indication: Cozaar is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left

ventricular hypertrophy. You will see in our main presentation that the single study provides compelling evidence to support our proposed claim.

As you know, in 1998 the FDA issued guidelines entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." This included the agency's thinking about approval of new claims based on data from a single study. As noted in the document, relying on a single study is generally limited to situations in which one is dealing with serious outcomes where performing a second confirmatory trial is not ethical or practical. We believe the LIFE study results represent just such a situation.

The guidelines document also points out that additional data from within a study or from other sources can provide evidence to help independently substantiate the results of the single study. During today's presentation we will provide confirmatory evidence from within the study and external to it that substantiates our results.

When evaluating the LIFE study to support the proposed indication, it is important to consider that the LIFE study compared losartan to atenolol, an active antihypertensive medication

that is known to reduce cardiovascular morbidity and mortality in hypertensive patients.

The primary hypothesis of the LIFE study was that compared to atenolol, losartan reduced the incidence of cardiovascular morbidity and mortality in patients with essential hypertension and LVH. In the LIFE study the primary endpoint was a composite of the combined incidence of cardiovascular mortality, stroke and myocardial infarction.

The study evaluated whether a losartan-based regimen would reduce the risk of cardiovascular morbidity and mortality more than an atenolol-based regimen in the face of comparable blood pressure control in both treatment groups.

As you will see in Dr. Edelmann's presentation, the LIFE study demonstrated that compared to atenolol losartan reduced the risk of the primary composite endpoint. Both the atenolol- and losartan-based regimens reduced blood pressure to a comparable level. Losartan was well tolerated. No new clinically significant adverse experiences were uncovered in the LIFE study. In fact, the safety profile of losartan was consistent with the currently approved U.S. product circular

for Cozaar.

Merck has invited several consultants to the meeting. These experts are available to facilitate the advisory committee's discussions and deliberations. Here today are Dr. Bjorn Dahlof, of Sahlgrenska University Hospital in Goteborg, who served as chair of the LIFE steering committee; Dr. Richard Devereux, of the Cornell Medical Center in New York, who is vice chair of the LIFE steering committee; Dr. John Kjekshus, from the University of Oslo, who is chair of the data and safety monitoring board; Dr. Stevo Julius, from the University of Michigan in Ann Arbor, who is the U.S. national coordinator and a member of the steering committee; and Dr. Peter Kowey, from Jefferson Medical College in Philadelphia.

Our statistical consultants are Dr. James Neaton, from the University of Minnesota, Minneapolis, and Dr. Scott Zeger, from Johns Hopkins University in Baltimore.

The advisory committee members have previously received a briefing document from Merck that provides more detailed information than time allows us to present here this morning. I would now like to turn the podium over to Dr. Edelmann.

Background and Rationale; Study Results

DR. EDELMANN: Good morning, ladies and gentlemen. My names is Jonathan Edelmann and I am senior director in clinical development in Merck's US Human Health Department. As Dr. Tucker indicated, I have been the medical monitor for the LIFE study since its inception in 1995.

My presentation this morning will include a discussion of the background and rationale for the LIFE study during which I will try to highlight the issues that we considered in arriving at the final study design. I will then review the LIFE study population and study results for efficacy and safety before turning the podium over to Dr. Keane, who will conclude with a review of the evidence to support our proposed claim.

As you well know, hypertension is a major public health concern. It is the most common cardiovascular condition in the world and a risk factor for the development of complications of the heart, brain, kidney and peripheral vasculature. Over the course of the last 50 years or more we have come to understand that the systemic manifestations of hypertension derive not just from elevations in blood pressure but also from adverse

morphologic and functional changes in these organ systems including, for example, changes in the wall of the left ventricle and the blood vessels.

Data from the Framingham Heart Study help to highlight the fact that patients with hypertension are at increased risk of cardiovascular disease compared to normotensive patients. This slide shows the age adjusted risk per 1000 patients on the vertical axis for normotensives, shown in white, and hypertensives, shown in green. You can see that in both men and women the risk of cardiovascular disease is more than two times higher in hypertensives.

These epidemiologic observations were confirmed in a series of prospective, randomized, controlled hypertension treatment trials during the 1970s and '80s which show that lowering blood pressure in hypertensive patients with pharmacologic agents resulted in reduction in the incidence of cardiovascular morbidity and mortality.

In 1993 Rodgers and MacMahon summarized the results of five studies, involving more than 12,000 patients over the age of 60 years, which compared the effects of diuretic- and

beta-blocker-based regimens to placebo or no treatment. In these five studies antihypertensive treatment lowered blood pressure by about 14 mm Hg systolic and 6 mm Hg diastolic more than control. This slide shows the number of vascular deaths, strokes and coronary heart disease events among patients treated with blood pressure lowering medication in green and control patients in white. For all these manifestations of cardiovascular morbidity and mortality treatment was associated with a lower risk, and with the same 15 mm Hg reduction in systolic blood pressure the magnitude of benefit varied depending on the endpoint. From this analysis, it was noted that the benefit of treating hypertension was greatest for stroke and less for coronary heart disease.

When the LIFE study was conceived in early 1994 it was intended to ask a simple but important question about the consequences of treating hypertension in patients at high risk of cardiovascular morbidity and mortality, namely, does the mechanism of lowering blood pressure matter in reducing the adverse cardiovascular consequences of hypertension? We were specifically interested in asking that question in terms of

angiotensin II receptor blockade with losartan in comparison to conventional antihypertensive therapy when peripheral blood pressure was similarly controlled.

In order to answer this question the LIFE study was designed with specific choices in terms of the primary endpoint to be measured, the patients to be studied and the comparator against which losartan would be evaluated.

First, a composite cardiovascular endpoint was chosen in recognition of the systemic effects of hypertension on multiple organ systems, and in order to describe the effects of blocking angiotensin II with losartan on the heart and brain the composite endpoint included the occurrence of cardiovascular death, stroke and myocardial infarction.

Next, we chose to study patients with hypertension who were at increased risk of cardiovascular events because of the presence of left ventricular hypertrophy. We focused on LVH for three important reasons: First, LVH is known to be a consequence of long-standing hypertension as well as a manifestation of the systemic effects of angiotensin II throughout the cardiovascular

system. So, these patients were expected to benefit from angiotensin II receptor antagonism.

Second, LVH could be easily detected using the electrocardiogram and was known to have a prevalence of between 10 percent and 25 percent depending on the age of the population. This graph shows the increasing prevalence of LVH with increasing age among U.S. hypertensive patients from the NHANES III database. The average prevalence in those aged 55-80, as in the LIFE study, is around 20 percent which made it feasible to recruit patients into the study.

Third, LVH had been established as a marker of high risk of developing both cardiac and non-cardiac complications of hypertension independent of blood pressure level, as shown on this chart from the Framingham Heart Study. This chart compares the risk of CHD and stroke events in elderly patients with ECG-LVH, shown in green, and patients without LVH, shown in white. You can see for both men and women a three- to five-fold increase in the risk of an event in patients with left ventricular hypertrophy. So, hypertensive patients with ECG-LVH were expected to be at increased risk of experiencing stroke and

myocardial infarction in the LIFE study.

Finally, in designing the LIFE study it was necessary to utilize a comparator agent that would provide effective blood pressure lowering by a different pharmacologic mechanism of action than losartan, and one that itself had an established track record in reducing cardiovascular morbidity and mortality in hypertensive patients. At the time the LIFE study design was finalized in 1995, only beta-blocker and diuretic based regimens had demonstrated through controlled clinical trials benefits on cardiovascular morbidity and mortality.

The available evidence for the benefit of diuretic and beta-blocker regimens, including the studies I just reviewed in the analysis by Rodgers and MacMahon, were summarized in JNC V in 1993. To paraphrase, because diuretics and beta-blockers are the only classes of drugs that have been shown to reduce morbidity and mortality, they are recommended as first-choice agents. This was the first time in the JNC document series that any class of agents achieved a preferred status. Thus, the obvious comparator regimen was one that included beta-blocker and diuretic therapies and we were left to decide which agent would be the anchor

compound. As you well know, we chose atenolol as the comparator agent in the LIFE study and this was for a variety of reasons.

First, as I mentioned, beta-blockers were recommended as appropriate first-line antihypertensive agents because of their demonstrated benefit on cardiovascular morbidity and mortality. Among the many antihypertensive trials, five have used a beta-blocker as the anchor compound in the treatment regimen. We have summarized these trials in a meta-analysis which is presented in this plot.

The diamond represents the odds ratio and the 95 percent confidence interval for a cardiovascular event from the pooled data. The odds ratio and 95 percent confidence intervals for the individual studies are shown below in green. The size of the dot is proportional to the number of patients in each study, which is listed to the left of the dot. The number of cardiovascular events in each study is shown next to the study name. Points to the left of the line of unity favor antihypertensive therapy; to the right of the line favor the control group. The majority of these trials used atenolol as the beta-blocker.

You can see that beta-blocker-based therapy was associated with an odds ratio of 0.79, or a 21 percent risk reduction in cardiovascular events, compared to control.

In addition, although there were no specific data for the use of beta-blockers in hypertensive patients with left ventricular hypertrophy, beta-blockers were known to be effective in the prevention of myocardial infarction and, more recently, in the treatment of heart failure patient populations with a high prevalence of antecedent LVH. Atenolol had been shown to be effective in combination with diuretics and, importantly, had demonstrated comparable antihypertensive efficacy with losartan.

By making atenolol the anchor compound in the comparator regimen the study could be designed to allow the addition of diuretics to both arms. This enabled us to use a beta-blocker/diuretic comparator regimen as recommended in JNC V and, at the same time, to ensure balance in the treatment arms with regard to additional treatments for control of blood pressure.

Thus, the losartan intervention for endpoint reduction in hypertension study was

designed as a multicenter, multinational, double-blind, randomized trial to investigate the effect of a losartan-based regimen compared to an atenolol-based regimen on the reduction of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.

The study was conducted under the scientific leadership of a steering committee, chaired by Dr. Bjorn Dahlof of the Sahlgrenska University Hospital in Sweden. Dr. Richard Devereux, of the Cornell Medical Center, was the vice chair. There was an independent blinded endpoint committee comprised of Dr. Daniel Levy, of the Framingham Heart Study, and Dr. Kristian Thygesen, of the Arhus University Hospital in Denmark. The study was monitored by an unblinded data safety monitoring committee chaired by Dr. John Kjekshus, of the University of Oslo in Norway. Merck served as the coordinating and data management center for the 945 sites in seven countries that participated in the LIFE study.

As you have heard, the primary hypothesis of the LIFE study was that, compared to atenolol, losartan would reduce the incidence of

cardiovascular morbidity and mortality in patients with essential hypertension and left ventricular hypertrophy. The primary endpoint was a composite of cardiovascular mortality, fatal and non-fatal stroke and fatal and non-fatal MI.

The components of the primary endpoint were analyzed as secondary endpoints. For both the primary and secondary endpoints we used an intention-to-treat approach. Before I go on with a description of the study design, let me illustrate how we handled patients with multiple events in the primary analysis.

This slide shows two hypothetical patients and the endpoints they experienced in the order in which they occurred. So, patient A was randomized in 1995 and first experienced a non-fatal MI in 1997; then a non-fatal stroke two years later; and then finally died of a fatal MI in 2000. For patient B the first and only occurrence of an endpoint was a fatal stroke around one and a half years after randomization. Both patients would count only once in the analysis of the primary endpoint based on the first event they experienced. I will come back to how the analyses of secondary component endpoints were performed when I review

the efficacy results of the study.

In addition to the primary composite and secondary component endpoints, a variety of other cardiovascular endpoints were collected in the trial and adjudicated by the endpoint committee. These included the cause of death; the occurrence of angina pectoris or heart failure that required hospitalization; the occurrence of coronary-artery or peripheral arterial revascularization events; or the occurrence of resuscitated cardiac arrest.

There were two central reading laboratories in the LIFE study, one for reading ECGs and one for echocardiography. The ECG core reading center was located at the Goteborg University in Sweden and was responsible for assessment of LVH from yearly electrocardiograms on all patients. In addition, the reading center evaluated these ECGs for the presence of silent myocardial infarction.

In a subset of patients echocardiograms were performed to assess left ventricular mass index, and the central reading center for echocardiography was the Cornell Medical Center in New York.

Investigators measured sitting trough

peripheral blood pressure at each clinic visit. At four centers in Denmark ambulatory 24-hour blood pressure was measured in 110 patients at baseline and year one as part of a substudy. Investigators recorded the occurrence of adverse experiences throughout the trial. Investigators also diagnosed newly occurring diabetes according to an algorithm based on a World Health Organization guideline that included multiple measurements of fasting glucose or oral glucose tolerance testing.

Two important disease categories within the hypertensive population were prespecified to be of special interest in the LIFE study. These were patients who at baseline had diabetes or isolated systolic hypertension. In these patients we planned to analyze the primary endpoint and the secondary component endpoints, as well as the cause of death in cases of mortality and hospitalization for angina pectoris and heart failure.

To qualify for entry into the trial patients were required to be between the ages of 55 and 80 years, and have hypertension, as evidenced off therapy by an elevated systolic blood pressure between 160-200 mm Hg, or elevated diastolic blood pressure between 95-115 mm Hg. In addition, all

patients were required to have evidence of LVH confirmed by the central ECG reading center, as measured either by the Cornell voltage duration product or the Sokolow-Lyon voltage.

Patients who had secondary hypertension or who had experienced a myocardial infarction or stroke within six months of the planned randomization date were excluded from the trial. In addition, patients who had angina pectoris that required treatment with either a beta-blocker or a calcium channel antagonist were not permitted to enter the study, nor were patients with active heart failure or known left ventricular ejection fractions of 40 percent or less. Conditions other than hypertension that required treatment with a study therapy, that is angiotensin receptor antagonists, beta-blockers or diuretics, or conditions that required therapy with an ACE inhibitor were also reasons for exclusion.

This diagram shows the planned visit schedule and the study drug titration scheme that was used for the trial. You will notice that the losartan arm of this schematic is in yellow and the atenolol arm is in blue. This is a color code that will continue throughout the presentation.

Eligible patients entered a placebo run-in period during which their active antihypertensive therapy was discontinued and baseline vital signs and left ventricular hypertrophy measurements were obtained.

Qualifying patients were randomized to receive 50 mg of study therapy and over the next six months returned to the clinics for assessment of blood pressure and titration of study drug, if necessary, to achieve a goal blood pressure of below 140 systolic and below 90 diastolic. If patients required additional therapy beyond 50 mg of study drug a low dose of hydrochlorothiazide was added. If further therapy was required the dose of study drug was doubled to 100 mg. If further titration was required, additional antihypertensive medication could be added to achieve blood pressure control, with the exception of ACE inhibitors, angiotensin receptor antagonists or beta-blockers. Once patients achieved blood pressure control, they were maintained on that regimen and returned to the clinic for semi-annual visits throughout the study.

The study was designed to continue for a minimum of four years for all patients and to conclude not before at least 1040 patients had experienced a primary cardiovascular event. Our

intention was to follow patients until death or study termination. In that regard, the study was designed so that patients were to remain on study drug even if they experienced a study endpoint unless it was clinically contraindicated, at which point they would discontinue study therapy. However, even if they discontinued study therapy patients were to continue in the clinic with the semi-annual visits. If it was not practical for patients to come to the clinic telephone contact was maintained between the site and the patient to determine the presence of endpoints in the trial.

If the occurrence of a study endpoint was detected, the investigator gathered the necessary documentation and made a full report to the endpoint committee for adjudication. If at any time it became appropriate for patients to restart study therapy, this was permitted in order to ensure that patient exposure to study drug was maximized throughout the trial.

Investigators were encouraged to report all potential events that might qualify as endpoints in order to allow the endpoint committee to adjudicate them. Merck personnel made regular monitoring visits at each center to ensure that

investigators reported all potential endpoints to the endpoint committee. Each endpoint committee member reviewed and classified each endpoint on his own. If either member felt that more information was necessary to classify an event, this was requested from the site and provided to both members. Differences between the initial classification of each member were resolved at periodic meetings of the two endpoint committee members. Although cases could be referred to the steering committee for final adjudication if there was a persistent disagreement, this was never necessary in the LIFE study. In total, more than 4000 investigator-reported endpoints were adjudicated by the endpoint committee. In every case the committee had sufficient information to permit adjudication.

Approximately 21 percent were determined not to be an endpoint. There were seven deaths for which the endpoint committee was unable to obtain enough information to permit the determination of the cause of death. These seven cases were treated as non-cardiovascular deaths in agreement with the steering committee. Four occurred in the losartan group and three in the atenolol group.

As you can see on this time line, the study commenced in June of 1995 and by May of 1997 enrollment was complete. In March of 2001 the steering committee established the endpoint cut-off date of September 16, 2001, representing four years and four months of follow-up for the last patient in the study. When the endpoint database was locked 1096 patients had had a primary endpoint adjudicated by the endpoint classification committee.

In the next section of the presentation I will provide a description of the study population. Over 10,000 patients entered the placebo run-in period and 9222 were randomized in the LIFE study. Early on in the study irregularities at one site led the steering committee to disqualify that site and instruct that all patients there be discontinued. Further, the steering committee decided to exclude these 29 patients from all analyses. As a result, there were 9193 patients who were followed for the duration of the study. These patients were equally randomization between the treatment groups. Of course, all available follow-up information was included in the intention-to-treat analyses. Complete follow-up

about all endpoints was available for 98 percent of patients, accounting for almost 99 percent of potential patient days. We were able to determine if another one percent of patients were alive or dead at the end of the trial so that follow-up on vital status was available for more than 99 percent of potential patient days. The remaining one percent of patients discontinued follow-up prior to the termination of the study. Approximately 80 of these patients did so by withdrawing consent and 12 patients were lost to follow-up, four in the losartan group and eight in the atenolol group.

We have performed a sensitivity analysis with patients for whom we have only partial follow-up information, and concluded that these missing days of follow-up do not alter the interpretation of the study results.

Investigators in the seven countries listed here participated in the LIFE study. You can see that five are Nordic countries, the other two are the United Kingdom and the United States. The patients were roughly evenly divided among the countries, with the notable exception of Iceland which contributed relatively few patients.

The next several slides show the baseline

characteristics of the patients in the LIFE study. All baseline characteristics were well balanced between the treatment groups. The mean age of patients was 67 years. Slightly more than half of the patients were women. Not surprisingly, the overwhelming majority of patients in the LIFE study were white. Almost all of the non-white patients were randomized in the United States. Black patients represented about six percent of the total population. Other ethnic groups represented one percent or less of study patients.

Blood pressure, as expected, was elevated. Systolic blood pressure was about 174 mm Hg and diastolic blood pressure was about 98 mm Hg. Heart rate was similar between the groups at baseline. The patients were slightly overweight and about 16 percent of them were current smokers at the time of randomization. The patients were also well balanced with respect to preexisting medical conditions like diabetes, isolated systolic hypertension and prior coronary heart of cerebrovascular disease.

Patients were also well matched for the baseline variables that were prespecified as covariates in the primary analysis, the presence of

LVH by both the Cornell product and Sokolow-Lyon methods and the Framingham risk score. The Framingham risk score is a predictor of the five-year risk of new coronary heart disease determined from the baseline characteristics of gender, age, systolic blood pressure, smoking status, ratio of total to HVL cholesterol and the presence of diabetes and left ventricular hypertrophy. This turned out to be a very strong predictor of risk in the LIFE study patients. Despite the small and non-significant difference noted in the baseline score, when it was used as a baseline covariate this parameter had an influence on the analysis. So, when I present the results in just a moment you will see both the adjusted and the unadjusted analyses for the primary endpoint.

Finally, before I present the efficacy results from the trial, I would like to review the distribution of study drug dose level that was achieved during the trial. I described to you earlier the titration scheme that was followed in the LIFE study.

This slide depicts the distribution of study drug in each treatment group at the end of follow-up or at the occurrence of a primary

endpoint, whichever came first. You can see that only a small fraction of patients, around ten percent, remained on 50 mg of study therapy for the entire duration of the study. Most patients required the addition of other drugs to their regimen and about half required an increase in the dose of study drug to 100 mg. At the end of follow-up or the occurrence of an endpoint approximately 25 percent of patients had discontinued study therapy. Most of the patients who required additional therapy received hydrochlorothiazide, but more than a quarter of the patients received other drugs beyond hydrochlorothiazide, largely calcium channel antagonists or other diuretics.

Although approximately 25 percent of patients were off drug at the time of a primary endpoint or the end of follow-up, the mean proportion of time that patients remained on study therapy was in excess of 80 percent of the days of follow-up in both treatment groups. The average dose of study drug was about 80 mg in both treatment groups. Hydrochlorothiazide and other diuretics were taken on approximately 71 percent of the days of follow-up. For study,

hydrochlorothiazide average dose was 20 mg in both treatment groups. On average, patients in both treatment arms received 2.3 antihypertensive agents, counting study drug and hydrochlorothiazide.

Having reviewed the characteristics of the patients enrolled in the LIFE study, the level of study drug and concomitant medication use, what was the effect of treatment on the primary outcome in the life study?

DR. BORER: Can we just hold it for one minute and make sure that everybody is clear on the characteristics of the study design? Are there any specific questions from the committee about the study design? Susanna?

DR. CUNNINGHAM: I wasn't going to ask about the design, I was going to ask for the age of the patients. I notice that some of the patients in the study were actually younger than 55.

DR. EDELMANN: Yes, there was a small number of patients whose age at randomization was below 55 in violation of the protocol, a small number.

DR. BORER: In addition, there seemed to have been a very small number that, if I read the

data correctly, didn't have baseline blood pressures measured per protocol but they were included as hypertensive with LVH. Can you tell us how that happened, or am I misunderstanding the data?

DR. EDELMANN: I guess I am not sure what you are referring to.

DR. BORER: From the way I read the data, it appeared that determination of blood pressure according to when it should be determined in the protocol to define blood pressure was not done in some patients who, however, were followed up.

DR. EDELMANN: That is correct, although those patients were randomized into the trial before it was discovered that their blood pressure regimens were not done exactly in accordance with the protocol. Because of our plan for intention-to-treat, they were continued in the protocol in any case and followed.

DR. BORER: That was a very small percentage I guess.

DR. EDELMANN: Yes.

DR. BORER: Paul?

DR. ARMSTRONG: Jeff, I had three questions, one of which I will need Tom's help with

and you may want to rule discussion later. The first relates to the withdrawal of prior antihypertensive therapy which occurred in a significant proportion of patients. It wasn't clear to me from your presentation or the written material, other than the fact that there was a two-week placebo run-in period, what length of time and what manner of withdrawal strategy was used in the two treatment groups vis-a-vis prior exposure to therapy?

DR. EDELMANN: Sure. Obviously, there was not a different strategy for the two randomized groups because this would have occurred prior to randomization. The discontinuation of antihypertensive therapy before randomization was left to the discretion of the investigator in terms of method. So, if it was appropriate to down-titrate the antihypertensive therapy, that was the prerogative of the investigator.

Then, patients were monitored with frequency specified by the protocol and investigators were free to see their patients more frequently if there was concern. Patients whose blood pressure rose dramatically and too high were excluded. That was one of the reasons for not

being randomized, if blood pressure levels exceeded the upper limit. Likewise, if blood pressure did not rise to the appropriate level patients were supposed to be excluded, and in almost all cases that was true. Does that answer your question?

DR. ARMSTRONG: Do we have information then apropos the two treatment groups as to whether there was a difference in the time of withdrawal of therapy prior to the two-week placebo run-in?

DR. EDELMANN: What we have is the blood pressure at the first visit, which would in most cases have been on therapy, and we have the therapy that they were on and then we have the blood pressure at randomization, which is off therapy. I guess we have the duration between those two but I don't think we have more information particularly about the strategy of withdrawal in patients. That is not something we collected.

DR. ARMSTRONG: My second question relates to your slide 23. That was the meta-analysis of beta-blocker regimens and hypertension. Could you help partition for me the distribution of cardiovascular events vis-a-vis myocardial infarction as opposed to stroke since that, obviously, is relevant to the discussion we will

have in terms of the results? What is the evidence that there was a reduction or not a reduction in myocardial infarction as opposed to the other events within this meta-analysis?

DR. EDELMANN: Sure, I would be happy to. First, this represents a composite of the events that are similar to the primary endpoint of LIFE. So, it is the occurrence as reported in the trials of stroke, myocardial infarction and cardiovascular death. As in the example I showed you from the Rodgers and MacMahon paper among these trials, when you do the meta-analysis of the individual components we see the same kind of distribution with a greater reduction in the risk of stroke and a smaller reduction in the risk of coronary heart disease events. Cardiovascular mortality is kind of in the middle between those two. So, it is very similar to what I showed you from the Rodgers and MacMahon paper.

DR. ARMSTRONG: Maybe I haven't asked the question properly. Just to sharpen the point, if we were to try to impute placebo, as ultimately we will in terms of assessing the study under discussion, what is the evidence that there was any effect on myocardial infarction?

DR. EDELMANN: Sure, why don't I show you the results for the three components individually? Maybe that will help clarify.

DR. ARMSTRONG: Great!

DR. EDELMANN: Let's look at stroke, myocardial infarction and cardiovascular death. Stroke first. I don't know if this is exactly how you want to see it but this represents the composite of all five studies for these three endpoints. Here is what I showed you for all cardiovascular events and this is the pattern that I was describing before. You can see a greater effect on stroke; less of an effect on coronary heart disease; and an intermediate effect on cardiovascular death.

DR. ARMSTRONG: If you recall, the question was about myocardial infarction.

DR. EDELMANN: Yes. Actually, I beg your pardon but myocardial infarction is not explicitly reported in most trials and coronary heart disease events include myocardial infarction, fatal and non-fatal, and in some cases it includes cases of angina and in some cases it includes sudden death. But it wasn't possible for us to parse out specifically myocardial infarction based on those

data.

DR. ARMSTRONG: So we don't have that information?

DR. EDELMANN: Yes.

DR. ARMSTRONG: Okay. The third question--

DR. FLEMING: Would you put that slide back on the screen again before we leave Paul's point? When we talk about all CV events, and you have specifically confirmed we are talking about stroke, MI and cardiovascular death, are there any other events beyond those three included in all CV events?

DR. EDELMANN: I do not believe there are but I would like to just be able to verify that from the five trials. There is a limit in terms of how the trials were reported, but if I am not mistaken, I think all CV events represent just those three. To be clear, this is CHD rather than MI as the label given to it, which may have more than MI in it.

DR. ARMSTRONG: And the third question was in setting up a statistical point on heterogeneity when one is dealing with a primary composite, what are the implications of when that heterogeneity is

found relative to the validity of the composite? I would appreciate some discussion and, obviously, Tom's advice on this point, Mr. Chairman.

DR. EDELMANN: If you will permit me, that is a topic that we will cover so, if it is all right with you, I would just as soon finish with the presentation and then if there is further discussion--would that be okay?

DR. BORER: Sure. Tom, you had some questions?

DR. FLEMING: Could we return to your slide 28? You give a very nice diagram that really gets at one of the issues I wanted to confirm. I think this is one of the strengths of your trial and I would like to confirm it, that is, when you randomize patients you are both managing them and following them until this late 2001 date even beyond the occurrence of the primary endpoints. This first patient that had a non-fatal MI in May of 1997, you continued to follow that patient with exactly the same intensity for other endpoints such as stroke, such that you were able to, in fact, detect and document the February, 1999 non-fatal stroke. Is that correct?

DR. EDELMANN: That is exactly correct.

DR. FLEMING: As you present these results, and this is somewhat related to Paul's point, clearly we are going to be interested in looking at your composite but we will also be interested in looking at the effects on the elements, and not the elements as censored at the time of the primary--

DR. EDELMANN: That is right.

DR. FLEMING: --but, in fact, you can emphasize this as you are presenting. When we look at stroke we want to look at this as all strokes over time.

DR. EDELMANN: Yes, as you will see when I get to the presentation of the data, I have another illustration to actually highlight the point about the secondary endpoints but I can confirm that we have done it just the way you said. I think when I get to it, it will be helpful, and it comes just before the results so it will be a reminder.

DR. BORER: Steve?

DR. NISSEN: Yes, I am still a little confused on slide 23, if you could help me with that? Would you put that up there? There are a couple of things. One, are these all placebo-controlled trials?

DR. EDELMANN: They are either placebo- or no treatment-controlled trials. It varies by study.

DR. NISSEN: One of the things that confused me is after the STOP there is a cross and there is a double-cross. The cross says an atenolol arm; the double-cross says beta-blocker and/or diuretic arm.

DR. EDELMANN: Let me clarify. You are probably familiar with the STOP trial. STOP was a trial in which patients were allocated either to a beta-blocker regimen or a diuretic regimen or no treatment. In the beta-blocker there was a choice of three and atenolol was one of them but there were two others. So, it is not purely data from a beta-blocker anchored regimen because there is a mix. I think about a quarter of the patients got a diuretic, if I am not mistaken.

DR. NISSEN: So, shouldn't that really be in the meta-analysis?

DR. EDELMANN: I guess that is a matter of--

DR. NISSEN: I mean, it was the strongest effect but it wasn't really a beta-blocker versus placebo trial, it seems to me. It sort of violates

the rules of meta-analysis unless there is some homogeneity here, I would think. I just wanted to clarify that.

Then, I have another question about your final slide before we started this discussion, which was slide 48. I would like to see p values, particularly for the off-study drug and the numbers of patients that got additional drugs, other than losartan or atenolol. Are those differences statistically significant and at what level of significance are they?

DR. EDELMANN: I can tell you that the difference between the off-study drug at this time is significant. I have to confer about the exact p value. This bottom 23/27 difference is significant. I can get you the p value in just a second. In terms of the others, is there one particular that you are interested in?

DR. NISSEN: I guess I am interested in the number of patients that got an additional drug. So, I would like to know whether there is a statistically significant difference in the number of patients on combination therapy and losartan and combination therapy and atenolol because this, obviously, has a lot of implications.

DR. EDELMANN: Let us work on that and I will come back when I have the answers. Is that acceptable?

DR. NISSEN: Sure; sure.

DR. BORER: Other questions? JoAnn?

DR. LINDENFELD: In follow-up to slide number 48, I noticed that there was an amendment made in the protocol to be able to decrease the dose of study drug to 25 mg. I wonder if you could show us how often that was done with each of the two regimens.

DR. EDELMANN: First of all, that was an amendment made during the course of the trial because of the desire to maintain patients on study therapy. It was implemented as needed at a site so it wasn't implemented at all sites. It was not a frequent occurrence. It is not a number that I know off the top of my head but it was a relatively small number of patients. I will get you the number of patients.

DR. LINDENFELD: I think it becomes a little bit important. This is an older subgroup and 50 mg of atenolol in a patient group whose average age is 70 is a fair amount of atenolol.

DR. BORER: Other questions? Mike?

DR. ARTMAN: Along those lines, still with slide 48 up there, I had a question. In addition to pharmacologic management were there differences in non-pharmacologic therapy--weight reduction, smoking cessation, exercise, etc.--do you have information on that?

DR. EDELMANN: We have some limited information, for example, on weight and smoking only at baseline so not in trial. There was reasonably good balance; small differences between the treatment groups but nothing substantial. By the protocol, there was obviously no intentional difference in the way the treatment arms were to be managed in terms of weight reduction, smoking cessation and so on. But the kinds of things that you would expect to happen to a population under supervision happened by things that we did measure. Concomitant use of statins, for example, went up. The behavior of patients being actively looked after was apparent in the trial, but not to a different degree between the treatment groups.

DR. BORER: John and Tom?

DR. NEYLAN: I have a question about slide 40. I was wondering if you could provide a bit more detail about some 1500 patients who were

excluded during the placebo run-in period, and speak to their potential differences demographically or with regard to baseline antihypertensive regimens as contrasted to those patients randomized? This gets to the applicability to general clinical practice.

DR. EDELMANN: Yes. Well, to answer the second part of your question first, one of the things we looked at as applicability to general practice was to look at the patients who did qualify for the study in comparison to a similar population, a reference population in the U.S. of hypertensives with left ventricular hypertrophy, which we took from the NHANES database. There we saw very similar--I can show it to you, but very similar characteristics based on the study patients in LIFE and similar patients from this reference database.

In terms of the reasons that patients were excluded, largely that was due to blood pressure reasons. A substantial proportion, and I will have to get the specific numbers, were patients whose blood pressure failed to rise to the right level upon discontinuing prior antihypertensive therapy; some for rising to a level that was too high; and

then there were other patients who were discovered during the process to have had a recent myocardial infarction or stroke which disqualified them. So, those are the kinds of things.

I am not sure that we have--in fact I know we don't have a detailed breakdown of the demographics of those patients, but we may be able to get some information beyond what I have told you about the ones who did not qualify. But that was because our procedure at the time was not to collect a lot of information about patients who were not randomized. You know, there was some information collected but not with the same level of detail as for patients who did get randomized.

DR. BORER: Tom Pickering?

DR. PICKERING: I have a couple of questions about slide 23. HEP is not an acronym with which I am familiar. Could you enlighten me?

DR. EDELMANN: This is hypertension in the elderly so this is the Coope and Warrender study.

DR. PICKERING: All right. In the UKPDS, my memory is that those patients could be on diuretics. Is that correct?

DR. EDELMANN: Yes, they could have a diuretic added to their regimen in the UKPDS. That

is right. I believe that is right.

DR. BORER: Any other issues with regard to the trial design or characteristics?

DR. NISSEN: I was just wondering if we could have those p values before we leave the thought.

DR. EDELMANN: I have made a note of it.

DR. NISSEN: Okay.

DR. EDELMANN: Shall I continue?

DR. BORER: Yes, just make a bookmark and we will get to it later.

DR. EDELMANN: Yes, I have it.

DR. BORER: Why don't you just go right ahead then? I am sorry, one second. Tom?

DR. FLEMING: Just to revisit the meta-analysis that you were showing, if you could put that slide back up for a moment? You refer to the Psaty meta-analysis in your briefing document as potentially one that is especially relevant here because it is looking at, if one is trying to get a sense of what is the effect of the active comparator-- it is looking at diuretics and atenolol. Essentially that focuses on the SHEP study and the MRCII trial. Is that, in fact, your perspective of what would be potentially the most

relevant studies to assess the effect of the active comparator?

DR. EDELMANN: Well, part of the reason that we elected to do our own meta-analysis is because none of the published meta-analyses, and there are several, had accounted for all of the data that was based on beta-blocker specific anchored therapy. SHEP, for example, is diuretic-based with the addition of a beta-blocker. So, I think from our perspective these studies represent the best estimate that you could have, imperfect though it is, of what a beta-blocker anchored therapy does as antihypertensives to reduce cardiovascular morbidity and mortality.

DR. BORER: Bob?

DR. TEMPLE: I am sorry, could you just say what comparison from STOP is shown there because I am still confused? What odds ratio was actually shown there?

DR. EDELMANN: In case you don't know, the STOP trial was only ever reported with active versus placebo so it is not available, at least it wasn't available to us in any of the places we looked to be able to break it out. So, this is the finding of all of the patients in the study, and

there was a mixture of patients whose anchor therapy was beta-blocker or diuretic.

DR. BORER: All of the patients in the study or all of the patients in the study on atenolol whether or not they were getting a diuretic?

DR. EDELMANN: Although we would have loved to do that, it is all the patients in the study because it wasn't ever reported as only the patients taking a beta-blocker.

DR. TEMPLE: There were three different beta-blockers but were most of the people on a beta-blocker?

DR. EDELMANN: Yes, it was roughly evenly divided between the four choices, diuretic was one choice and three beta-blockers. So, I think it is predominantly beta-blocker but it is never broken out as either the beta-blockers together and diuretic or the individual components.

DR. TEMPLE: And did you do a red box without STOP? How much difference does that make?

DR. EDELMANN: Right, that is something we have done but I don't have the numbers right at the top of my head, but it is something that I can give you. We did a couple of different iterations of

this. You know, the bottom line is that it really did not make a lot of difference but you can see that STOP is, I guess, the most positive.

DR. TEMPLE: Yes, but it is still only ten percent of the events.

DR. EDELMANN: Right.

DR. FLEMING: But in the MRCII you are quoting the atenolol results.

DR. EDELMANN: That is right.

DR. FLEMING: In MRCII, if you were looking at the diuretics and atenolol results, if you put them together the relative risk is 6.7.

DR. EDELMANN: That is exactly right. We have done a version of this meta-analysis including the trials that have a diuretic-based therapy with a reasonable add-on of beta-blocker to kind of look at the other side. I can show you that as an example of another iteration of this. Effectively what it does, it reinforces the fact that active treatment with these diuretic/beta-blocker anchored regimens alone and in combination in the face of differences in blood pressure reduction is effective in preventing cardiovascular morbidity and mortality. If you would like, I can show the one that includes the diuretic with additional

beta-blocker added to the overall. If you are interested, I can show that. I don't know if it is in the briefing document.

DR. BORER: Does anyone need to see that? Okay, let's put it up.

DR. TEMPLE: Jeff, I guess you are arguing, at least slightly, that this was a trial of a beta-blocker added to a diuretic because most people had a diuretic so that that is relevant?

DR. EDELMANN: That is right; that is the idea. So, here the five trials are supplemented with a couple more, and they are listed at the bottom here. We used 20 percent beta-blocker concomitant use as our threshold. In other trials the concomitant beta-blocker was less which we elected to leave out. So, that is MRCII, SHEP and OSLO. I guess it is only seven new trials because MRCII was already counted once. In any case, what you see is what I was describing. The benefit shifts a little bit to the left, but it confirms the idea that active antihypertensive therapy with a beta-blocker/diuretic regimen is effective in reducing cardiovascular events.

DR. FLEMING: On this point, I look at this as a comparison against the regimen where the

active comparator regimen is the diuretic and atenolol. So, technically the active comparator effect is the effect of the diuretic and atenolol so this really gets more directly to what the active comparator effect is.

DR. BORER: Doug?

DR. THROCKMORTON: Yes, I wanted to return to slide 40 and just something different. We have been interested for a while in the number of patients that you needed to screen to get your trial under way. Do you have the screening population number and then the number that got into baseline?

DR. EDELMANN: Yes, I cannot give you the screening number specifically but it was substantially higher than the 10,000 who actually got to the point of entering the run-in. The reason is that the centers used a variety of different screening techniques which would not really fairly represent the effort. There were centers that took every ECG they had and sent them in, and those that got a positive reading from the core center, they went forward with. There were others who reviewed their patients and talked to them, more akin to what you would expect would be

an appropriate effort in terms of judging it where the physician or the site is involved with the patient, and then they went forward; sent in a screening ECG and it was, you know, rejected.

So, one way to look at that in our trial would have been to count the number of ECGs that were evaluated at the screening center and it was probably ten-fold that. But, as I said, it had a dramatic influence. With almost a thousand centers there were almost a thousand different strategies and it had a tremendous influence, you know, what strategy was used on the number of ECGs that were looked at.

DR. BORER: Are there any other issues before we go on to the results? If not, why don't you just go right ahead?

DR. EDELMANN: Thank you. If I could move to slide 51, this is the result for the primary endpoint, as is shown here in a Kaplan-Meier presentation. The horizontal axis represents time of follow-up in months and the vertical axis shows the percentage of patients with a primary cardiovascular event. The yellow solid line represents losartan and the blue dashed line represents atenolol. Depicted at the bottom of the

slide is the number of patients by year who were at risk of developing an event.

You can see that the lines diverge for the entire duration of follow-up, representing an adjusted risk reduction of 13 percent favoring losartan, with a p value of 0.021, which was the primary analysis. The unadjusted risk reduction, that is, without adjustment for baseline Framingham risk score and ECG-LVH, is slightly larger, about 14 percent and the p value is 0.009.

This slide depicts the hazard ratio for the primary composite endpoint and its 95 percent confidence interval. The solid line represents the primary adjusted analysis, and the dashed line the analysis without adjustment for baseline Framingham risk score and ECG-LVH. To the left of the vertical line favors losartan; to the right favors atenolol.

You can see that there were 508 patients in the losartan group who experienced a primary cardiovascular event compared to 588 in the atenolol group. This significant advantage of the losartan-based regimen over the atenolol-based regimen was achieved with comparable and substantial blood pressure lowering in both

treatment groups, as you will see in the next several slides.

This figure illustrates the change in systolic blood pressure during the study. Depicted on the horizontal axis is time in months and on the vertical axis is the mean systolic pressure. You can see that beginning with randomization and continuing through the first six months of titration, there was a prompt and substantial decline in systolic blood pressure which was slightly greater in magnitude for the losartan group. Systolic blood pressure was lowered by around 13 mm Hg in each group. However, the reduction with losartan was approximately 1 mm Hg more than with atenolol. This difference was statistically significant.

Here is the figure for diastolic blood pressure. Again, a prompt and substantial decline of around 17 mm Hg in each group was seen over the first six months. There was a slightly greater reduction in magnitude in the atenolol-treated patients for mean diastolic blood pressure, although the difference between the two treatment groups was quite small and did not achieve significance.

Study therapy was titrated to achieve a goal blood pressure of 140 systolic and 90 diastolic. This table shows the percentage of patients who achieved the diastolic goal blood pressure, the systolic blood pressure or both pressure goals for each treatment group. You can see that the majority of patients in both groups achieved the diastolic blood pressure goal. Slightly under half of the patients achieved the systolic blood pressure goal or both targets, more in the losartan than the atenolol group. So, blood pressure was similarly and substantially reduced in both treatment groups, with better diastolic than systolic control.

This slide shows the effect of treatment on heart rate. As expected, atenolol had a significantly greater effect on mean heart rate than losartan of about six beats per minute throughout the study.

To summarize the findings of the primary endpoint of the LIFE study, in hypertensive patients with ECG evidence of LVH, losartan-based therapy was associated with a 13 percent reduction in the combined risk of cardiovascular death, stroke and myocardial infarction compared to an

atenolol-based regimen with comparable levels of blood pressure.

Next, I will review the results--

DR. BORER: May I ask you to just stop for one second?

DR. EDELMANN: Yes.

DR. BORER: Only ten percent of the population was on monotherapy by the end of the trial, and certainly you don't have enough power to look for anything with a reasonable likelihood of finding statistical significance but do you have data to show whether nominally at least the overall results were also seen in patients who were on monotherapy?

DR. EDELMANN: One of the things that we have not done, and specifically not looked at in detail for interpretation, is the assessment within the trial of things that changed by the patient's response and, thus, a non-random comparisons and that is a good example of one. We have looked at this in some cases but I can tell you we did not look at monotherapy because the numbers were so small. But we are hesitant about drawing conclusions from those kinds of analyses in any case because so much of the basis for change of

therapy is response to prior therapy that it barely really makes sense with think.

DR. BORER: Steve and then Beverly.

DR. NISSEN: That is what I was also trying to get at, Jeff, with this question of whether there were differences in number of patients on combination therapy within the two arms. So, to me, that is really a pivotal thing to understand here since this wasn't really a monotherapy trial; it was a combination therapy trial.

DR. EDELMANN: What I would like to point out, and we will come to this in the final presentation, is a way that we did try to look at whether or not differences, even small differences in the therapy that patients received might have accounted for the outcome advantage, which I think is really at the root of the question you are getting at. Again, if you will permit me, that is a little bit later in the presentation and it makes more sense to go through in order, but we will come to it and, you know, if you would like further discussion we can certainly do that.

DR. BORER: Beverly?

DR. LORELL: I think one of the things

that is quite striking about slide 55 in thinking about how this evaluation might relate to best practice in the United States is that less than 50 percent of patients met goal for treatment of systolic hypertension.

So, a couple of questions. Are you going to show us later in the efficacy section how the adverse events were distributed among those patients who achieved a systolic blood pressure of less than or equal to 140 and those that did not? The reason I think that it is terribly important is that if half of the patients in this study were inadequately treated by national standards, it raises the question as to how do we think about this recommendation. I think in real practice what physicians would do with this group of patients would be to add on a beta-blocker if they were not getting it, or an angiotensin inhibiting drug if they were not getting that drug and were still nearly to goal for therapy. So, it would be very interesting to see, I think, in this population how the distribution of adverse events, including stroke, were distributed.

DR. BORER: In fairness, I think that analysis is in the FDA review. I don't want to

misquote it but the events were far more frequent in people who weren't well controlled but the distribution or the relative proportion of events was sort of similar in the two treatment groups.

DR. EDELMANN: Right.

DR. BORER: Steve?

DR. NISSEN: I guess before we move on, you know, on slide 53 and 54 we get the systolic and diastolic and I was very interested in the same graph for pulse pressure and the p values since some folks have suggested that pulse pressure is probably the best predictor.

DR. BORER: That is in the FDA review and it shows what you are suggesting.

DR. NISSEN: Yes, I wonder if you have your pulse pressure data.

DR. EDELMANN: I think I can show you the blood pressure. As you would expect, it is the sum of opposite effect so it is a little bit bigger. It is about 2 mm Hg difference in pulse pressure across the study. I think if you will just give us a second I will be able to pull up the slide for you but it is as you would expect based on the numbers you saw.

Here is the difference in pulse pressure,

wider in the beginning, narrowing at the end. The stars represent time point comparisons of significant difference. So, it is exactly as you would expect. We have looked at this just as we have looked at all of the blood pressure effects, and again that is part of the discussion, to see whether or not these differences could explain the treatment difference and we will cover that.

DR. BORER: Why don't you go ahead?

DR. EDELMANN: As I was saying, will review next the results of the other endpoints in the LIFE study, beginning with the secondary component endpoints. But before I present these results, let me describe how we accounted for the occurrence of multiple endpoints in an individual patient in these analyses. To do that, I will go back to the hypothetical patients.

Again, here is hypothetical patient A and his endpoints. This patient has multiple endpoints, as shown on the slide. For the analyses of the secondary component endpoints each patient was counted if they experienced that component. So, patient A would be counted in the analysis of MI based on the May, 1997 occurrence of non-fatal of MI, the first occurrence of MI. The patient

would be included in the analysis of stroke on the basis of the February, 1999 occurrence of non-fatal stroke. Finally, the patient would be included in the analysis of cardiovascular death based on the September, 2000 fatal MI.

To recap, for the secondary component endpoints we used an intention-to-treat approach. The occurrence of an endpoint of one type did not censor the patient from the analysis of endpoints of a different type and, therefore, each patient counted in all relevant analyses. However, each patient was included only once in any particular endpoint analysis.

This plot summarizes the hazard ratio and 95 percent confidence intervals for the secondary component endpoints. The number of events for each treatment group, for each endpoint is listed on the left side of the slide. You can see that more than 500 patients experienced a stroke, making this the most commonly experienced of the secondary component endpoints. From this plot you will also notice that there is variability in the relative risk reductions observed among the secondary component endpoints, which was evaluated with a prespecified test for heterogeneity which was

significant, with a p value of 0.02. This indicates that the variation in hazard ratios among the secondary component endpoints was more than would be expected by chance alone.

The next several slides will depict the results of the individual secondary component endpoints in Kaplan Meier format. The first graph shows the occurrence of stroke, again with time on the horizontal axis and the proportion of patients who had a stroke on the vertical axis. You will notice that the scale is smaller than for the composite endpoints since fewer patients had this endpoint. This scale will be used for the other secondary component endpoints as well. You can see that the curves separate over the course of the trial. This represents a 25 percent risk reduction for losartan, with a p value of 0.001.

Here is the occurrence of MI which, as you can see, was similar in the two treatment groups across the entirety of the study. Although as an adjusted risk reduction this represents a slight increase in risk for losartan, the p value is 0.05.

DR. BORER: Before you to on to the next slide, did you attempt, just for my information, to break down between the treatment groups for fatal

MIs alone?

DR. EDELMANN: Yes, and I am going to come to that in just a second.

DR. BORER: Okay. Bob?

DR. TEMPLE: Is this category just documented heart attacks? This doesn't include things like sudden death which were included in some analyses of coronary-artery deaths which I found a little confusing.

DR. EDELMANN: That is right. To be clear about this, investigators had the opportunity to report the occurrence of a myocardial infarction and did so on a specific work sheet. The endpoint committee reviewed those data and made a determination of MI, yes or no. If the patient died, in addition to that, the investigator completed a death package. So, the endpoint report of MI is without regard to whether it was fatal or not. When the endpoint committee classified death, one of the choices that they had was a coronary heart disease death, and I will show that in just a second. So, it wasn't precisely reported as a fatal MI, or classified as a fatal MI; just an MI. Both fatal and non-fatal endpoints were reported in exactly the same fashion. In fact, that is true

for fatal and non-fatal stroke, the same thing.

DR. TEMPLE: But this is just documented MIs. It doesn't include other kinds of things that you call coronary deaths?

DR. EDELMANN: On this report, that is correct.

DR. BORER: Steve?

DR. NISSEN: As I understand it, a number of these patients had had previous myocardial infarctions. Is that correct?

DR. EDELMANN: A small percentage had, at least six months prior to randomization, an MI.

DR. NISSEN: So, the thinking here was that it was acceptable to withhold beta-blockers post myocardial infarction for the purposes of the trial?

DR. EDELMANN: Well, that decision was left to the individual practitioner because the patients had a requirement for a beta-blocker that was an exclusion from the trial so only patients who, in the view of the investigator, were appropriate to not be on a beta-blocker were permitted to be randomized.

DR. NISSEN: About 20 percent or so had a prior MI, something like that?

DR. EDELMANN: No, no, it was about six percent.

DR. NISSEN: Six percent? Okay.

DR. EDELMANN: Finally, here are the results for cardiovascular mortality. A separation between the two curves appears to occur by 12 months and continues thereafter through the course of the study, representing an 11 percent risk reduction with a p value of 0.2.

This slide again displays the hazard ratio and 95 percent confidence intervals for the cardiovascular death endpoint which can be further subdivided into death due to stroke, death due to coronary heart disease and death due to other cardiovascular causes like heart failure and aortic disease which are shown here. Among the cardiovascular causes of death, CHD was the most common cause and was not different between the treatment groups. Losartan significantly lowered the risk of fatal stroke by 35 percent. Other cardiovascular causes of death favored losartan although the difference was not significant.

So, the 11 percent reduction in the risk of CV death with losartan appears to be driven by the 35 percent reduction in fatal stroke, with no

difference in CHD death. This pattern of a greater benefit for losartan on fatal stroke and no difference on fatal CHD is similar to that for the other secondary component endpoints of stroke and myocardial infarction, as you can see.

DR. TEMPLE: Not a major point but the other category which favored losartan was mostly driven by events called peripheral vascular disease deaths. I just wondered what that meant.

DR. EDELMANN: It was non-coronary vascular events, and almost all of them were aortic related, aortic aneurysms, ruptured aortic aneurysm and so on.

DR. TEMPLE: I didn't think of that as peripheral.

DR. BORER: Can I ask the committee members sitting around the table, if you want to say something, if you will press your button in addition, or not in addition, to raising your hand that would help because it is easier for me to pick up the red light and the hand. Beverly?

DR. LORELL: Did you do a hazard ratio analysis to be able to give us what that number is on non-stroke cardiovascular death? You have the two components, but if you were to make it even a

little bit simpler as stroke death and non-stroke cardiovascular deaths, what was the reduction?

DR. EDELMANN: So, you are suggesting combining the bottom two?

DR. LORELL: Yes.

DR. EDELMANN: That is not something that we have done but it is something we can do.

DR. LORELL: Thank you.

DR. BORER: Bob?

DR. TEMPLE: It is 172 versus 164, slightly favoring losartan.

DR. EDELMANN: Yes.

DR. TEMPLE: And that difference is mostly driven by these aortic phenomena, whatever they are, because you can see the coronary ones are dead even, so to speak.

DR. EDELMANN: On the next two slides I will review the additional endpoints that were adjudicated by the endpoint committee. The risk reduction with losartan for total mortality was consistent with that for CV mortality but it did not achieve statistical significance. You can see on this slide the individual cardiovascular causes of death, as well as the results for non-cardiovascular deaths which were largely due to

cancer.

The remaining cardiovascular endpoints are depicted on this slide. Angina pectoris or heart failure requiring hospitalization and coronary or non-coronary revascularization were not different between losartan and atenolol. Resuscitated cardiac arrest occurred too infrequently to evaluate.

Next, I will present the results that were obtained from the ECG core center. The core center evaluated yearly electrocardiograms for the magnitude of left ventricular hypertrophy by both the Cornell voltage duration product and the Sokolow-Lyon methods, as well as the occurrence of silent MI. Only 27 patients were detected as having silent MI, 13 in the losartan group and 14 in the atenolol group, so no analyses were performed on this endpoint.

This slide shows the change in ECG-LVH as measured by the Cornell voltage duration product for losartan and atenolol over the course of the study. You can see that there was a significant and steep decline in this parameter for patients treated with losartan that was present by six months and continued in its decline over two years

before it plateau'd. In the atenolol-treated group there was a decline which also continued over two years but was significantly less than that seen with losartan over the course of the study.

In like fashion, as measured by the Sokolow-Lyon voltage, there was a significant and greater decline with losartan treatment that continued over pretty much the entire course of the study.

A similar pattern is seen in the subset of patients who had yearly echocardiography performed. Losartan resulted in a larger decline in left ventricular mass index compared to atenolol.

Let me next turn to the efficacy results in predefined subsets of the population. As described earlier, we defined diabetes and isolated systolic hypertension as disease categories of special interest. In these patients we evaluated the primary endpoint, the secondary component endpoints, as well as total mortality and hospitalization for angina and heart failure.

In addition, we prespecified 23 subgroups of the population based on demographics, disease history and clinical characteristics at baseline. In these patients only the primary endpoint was

evaluated using a test for treatment by subgroup interaction.

First I will review the results in the high risk disease categories of special interest, diabetes and isolated systolic hypertension. As expected, we observed a higher event rate in these patients in the LIFE study. This slide depicts the rate of the primary endpoint per 1000 patient years in the LIFE study on the vertical axes. Diabetic patients, shown in green, and non-diabetic patients, shown in white, are presented in the left panel. Patients with isolated systolic hypertension, in green, and without isolated systolic hypertension, in white, are presented in the right panel.

As you can see, for the diabetic patients the risk of the primary endpoint was twice the rate observed in non-diabetics. In patients with isolated systolic hypertension the risk was increased 1.2-fold as compared to patients without isolated systolic hypertension.

This slide summarizes the results of the primary endpoint in diabetic and non-diabetic patients and patients with and without isolated systolic hypertension. Again, the size of the dot

is proportional to the sample size of the population in this plot. The dashed white line shows the hazard ratio for the total population as a reference. There was no treatment by subgroup interaction in either of these populations, as indicated by the p values to the right of the subgroup results.

The next series of slides will display the individual endpoints in the diabetic and isolated systolic hypertensive patients. This slide shows a Kaplan-Meier presentation for the primary endpoint in diabetic patients. The separation between losartan and atenolol continues through the course of the study, representing almost a 25 percent risk reduction, with a p value of 0.031. Remember that diabetic patients represented only around 13 percent of the entire population.

This plot summarizes the results for the secondary component endpoints in diabetic patients. All of these results appear to be consistent with the primary endpoint result.

Total mortality was reduced by nearly 40 percent in diabetic patients treated with losartan, as was hospitalization for heart failure. Angina pectoris was not different between the treatment

groups.

In patients with isolated systolic hypertension a similar finding of benefit for losartan was present in the primary endpoint. A separation between losartan and atenolol persisted over the course of follow-up, showing a 25 percent risk reduction which approached but did not achieve statistical significance on its own. This population represented about 14 percent of the entire study group.

Here, similarly summarized, you can see the secondary component endpoints for the patients with isolated systolic hypertension. The benefit for losartan among the secondary component endpoints is again consistent with the primary endpoint.

The remaining endpoints in isolated systolic hypertensive patients are displayed on this slide and show a similar pattern as was seen with diabetics.

Now, for the 23 subgroups, demographic, clinical and disease history subgroups, analyses of an interaction with treatment were performed for the primary endpoint. A p value of less than 0.05 was predetermined to indicate a positive treatment

by subgroup interaction. In none of the subgroups did we find a test for interaction that achieved this threshold with a p value of less than 0.05, as reflected in this table.

Please note that the p values are not adjusted for multiplicity. However, I will point out that the test for interaction between treatment and ethnic subgroup had a p value that was close to 0.05 that caused us to look more closely at this subgroup.

This plot shows the hazard ratio and 95 percent confidence intervals for each of the ethnic subgroups. In this plot, again, the size of the point is proportional to the sample size in the subgroup and the white dashed line shows the hazard ratio for the total population for reference. The p value for the interaction test is shown on the right side of the graph.

What you can see is that the white subgroup, which included the vast majority of patients, had a benefit that was consistent with the overall population. In contrast, black patients had an effect that appeared to favor atenolol. Because the test for interaction that was used could be influenced by the small size of

the remaining subgroups, we further evaluated the ethnic subgroup by creating a dichotomization into black and non-black patients and repeating the interaction test, which is reflected in the next slide. As you can see, the interaction remained and, in fact, was highly statistically significant, with a p value of 0.005. We then applied a test for qualitative interaction and found that it was also significant.

To try to understand the qualitatively different response of black patients in the LIFE study we undertook a large number of exploratory analyses. These included looking at and adjusting for differences in the baseline characteristics between black and non-black patients and between the losartan and atenolol treatment groups among black patients.

In addition, we looked at the influence of site and region both in the U.S. and in the overall study. We further explored the treatment effects of losartan and atenolol on the secondary clinical endpoints, as well as for vital signs and left ventricular hypertrophy.

While there were some baseline differences between black and non-black patients, for example,

there were more smokers and diabetics among black patients and there were higher rates of stroke and lower rates of coronary heart disease in the black population compared to non-black patients, adjustment of the analysis of the primary endpoint for these differences did not explain the interaction, nor did adjusting for small differences between black patients randomized to losartan and atenolol.

The next series of slides present the blood pressure as well as heart rate and ECG-LVH data in black versus non-black U.S. patients. As you can see on the left, losartan and atenolol provided significant and comparable reductions in systolic blood pressure in black patients, similar to the findings in the non-black patients. The same finding was present for diastolic pressure, shown on the right.

This slide depicts the effect of treatment on heart rate for non-black patients on the left and black patients on the right. As with the blood pressure data, the black patients responded similarly as the non-black patients.

We next looked at the impact of treatment on LVH in black and non-black patients. Again as

shown in these charts, the black patients appeared to behave similarly to non-black patients, with a larger decrease in ECG-LVH with losartan as compared to atenolol measured either by the Cornell product method, shown on the left, or the Sokolow-Lyon method, shown on the right.

To summarize, black patients behaved differently from the non-black patients in the LIFE study with respect to the primary endpoint as indicated by a significant test for interaction. Black patients appeared to have a greater reduction in risk with atenolol.

This observation was not explainable by small differences in baseline characteristics between black and non-black patients or in differences among black patients randomized to losartan and atenolol. In contrast, black patients behaved similarly to non-black patients with respect to the effect of treatment on blood pressure, heart rate and left ventricular hypertrophy.

So, we were unable to find any explanation for this interaction from within the LIFE study data. Nonetheless, we believe this is important information that prescribing physicians should be

aware of and are recommending that a description of these findings be included in the product circular.

To summarize the overall--

DR. BORER: Excuse me, can you just go back to the results in blacks?

DR. EDELMANN: Yes?

DR. BORER: The FDA review actually identified some baseline differences among the black and white patients that might be important in modifying the results that you found. Have you done an analysis of the baseline data that would confirm or refute that fact?

DR. EDELMANN: This is again a topic that we intend to cover in some detail and that I expect would be part of the discussion afterwards.

DR. BORER: That is fine.

DR. EDELMANN: To summarize the overall efficacy results of the LIFE study, losartan-based treatment of hypertensive patients with electrocardiographic evidence of LVH was superior to atenolol-based treatment as shown by a 13 percent reduction in the risk of the primary endpoint of cardiovascular morbidity and mortality.

Among the secondary endpoints, the risk of stroke was significantly decreased with losartan,

by 25 percent, and there was a non-significant benefit on cardiovascular death that favored losartan, driven by a significant reduction in fatal stroke. There was no difference in the risk of MI or in death due to coronary heart disease.

In addition, there was a significantly greater reduction in ECG-LVH with losartan and these results were obtained in comparison to an established antihypertensive regimen with comparable blood pressure lowering with both treatments.

With the exception of black patients, as I have just mentioned, the benefit of losartan was generally consistent among a wide range of subgroups of patients, including those at higher risk of cardiovascular events, patients with diabetes or isolated systolic hypertension.

Next I will review the results of the adverse event reporting and other safety parameters that were evaluated in the LIFE study.

DR. BORER: Dr. Edelmann, perhaps we can stop here for a moment. I am going to resist the tendency, in view of the Giants horrible collapse in the fourth quarter yesterday, to punish everybody by making them sit at the table but I

have been reminded that we need a break. So, it is 10:15. We will take a 15-minute break and then you can go ahead.

[Brief recess]

DR. BORER: Let's get back and get started again. Dr. Edelmann, before you present any of the safety data, I would like to ask everyone around the table if they have any specific questions about clarification of your efficacy data. I am sure there will be some. Why don't we start on my left-hand side and we will come around the table. John, do you have any questions for clarification here?

DR. NEYLAN: If you will perhaps give me a minute I will come up with a couple.

DR. BORER: Okay, we will come back to you. Tom?

DR. PICKERING: Yes, with regard to how the composite endpoints were determined, in the Lancet paper, in Table 3, it gives the number of endpoints, and there are about between 500 and 600, and yet the total for mortality, stroke and MI is over 1000 per group. So, could you give us a breakdown of which type of events were actually used in the composite endpoints?

DR. EDELMANN: Yes, this is a descriptive analysis that was in both the medical and statistical reviewers' reports from the FDA and one that we have done ourselves. I can show you but I just want to be clear that the primary endpoint, of course, counted the first event. For the second and component endpoints we counted the first event of that type without regard to whether the patients had had a prior event of a different type, as I described. So, this is really just an accounting and we have done it.

DR. PICKERING: Could you show us the numbers?

DR. EDELMANN: Yes. Let me just get the slide up, but I think what we have is a comparison; I think it is a side by side presentation.

DR. BORER: While you are pulling up those numbers, John, you had a question to ask?

DR. NEYLAN: A couple. The first question I would like to ask is for perhaps a bit more detail regarding the study's conduct and interaction with the investigators as they monitored the degree of blood pressure control in these two treatment arms. Looking at the overall result at the end of the five-year period, the

degree of blood pressure control is roughly in the ball park of what might be expected for general clinical practice, but could you speak a little bit more as to what procedures you had in place to try to improve upon that kind of baseline?

DR. EDELMANN: Yes, sure. This was something that was, as you mentioned, carefully monitored, and there were regular reviews conducted between the monitoring personnel and the investigator about the level of blood pressure control for each individual patient and the dose level of blinded study therapy and discussions about appropriate up-titrating or adjusting therapy to achieve blood pressure control.

This was an active campaign, if you will, that the steering committee orchestrated to ensure that, as much as possible, therapy was applied to attain control in as many patients as possible. You can see that it was a lot more effective at the diastolic level than it was at the systolic level, but it was an organized effort that continued through pretty much the whole study.

DR. PICKERING: And a follow-up to that, if, indeed, this attempt was applied universally were there any distinguishing characteristics to

the institutions or the subsets of patients to which this application of increased effort was successful or not?

DR. EDELMANN: No, it was equally successful, to the degree that it was, pretty much across the different centers in the study, including across countries, in terms of getting additional patients to goal who weren't there to begin with.

DR. BORER: Do you have the numbers in response to Tom's question yet?

DR. EDELMANN: Yes. Could I see slide 382? What we have on the left is using the intention-to-treat approach that I presented counting the number of patients who experienced the event. This is the way the Merck analysis was done. Both Merck and FDA agree this is the appropriate way of doing the analysis of each of the components.

There are 204 patients who had a cardiovascular death, irrespective of whether they had an MI and survived or stroke that they survived prior to that, in the losartan group and 234 in the atenolol group. You can just read the numbers across for stroke and MI.

Looking just at the primary composite endpoint, that is, the first event of any type, the numbers break down in this fashion so you can see that there were fewer cardiovascular deaths, 137 versus 154, a difference of 3.0 and 3.4 percent for the losartan group. There were many fewer strokes as a first event, 197 versus 266, and slightly more MIs in the losartan group than the atenolol. If you add these up, these will come out to 508 and 588 because that is the number of patients that experienced a primary endpoint in the losartan and atenolol groups. This may be instructive but it is not the kind of thing that we have done any inferences on.

DR. BORER: Bob?

DR. TEMPLE: It is just worth noting that cardiovascular deaths, which you did break down in your background, are a mixture of things that look cardiac and things that look cerebral. In fact, most of them are cerebral.

DR. EDELMANN: Yes.

DR. TEMPLE: So, most of that 30 patient difference is due to what looked like cerebral deaths. There is overlap. There are deaths in all three groups.

DR. EDELMANN: Yes, that is definitely true in this analysis, that there are deaths in all three groups.

DR. BORER: Do you have more questions?

DR. PICKERING: Yes, I have a question regarding the isolated systolic hypertension subgroup. In the publication it looks as though only about one or two percent were on just a single drug. There were more withdrawals in the atenolol group than the losartan group. Was that significant, do you know, this 169 versus 216?

DR. EDELMANN: Yes, I am not positive about the level of significance. Let me just make sure that I understand your question. You are referring just to the isolated systolic hypertension in the paper?

DR. PICKERING: Yes.

DR. EDELMANN: And you want to know whether the difference between those who were on monotherapy for the entire trial was different?

DR. PICKERING: No, because that was just one and two percent in the two groups, but discontinued therapy appears to be quite a lot higher in the atenolol group.

DR. EDELMANN: Yes, it is something that

we can look at. The ones who discontinued therapy in the overall population were higher in the atenolol group compared to the losartan group, as I showed you earlier. I don't know what the p value is. The pattern is similar.

DR. BORER: Any other issues, Tom?

DR. PICKERING: No.

DR. NISSEN: On your slide 79 you gave us the patients with diabetes. I would be interested in a similar Kaplan-Meier sort of analysis with the non-diabetics.

DR. EDELMANN: Right. Well, I don't have a Kaplan-Meier but I can go back to, I think, just one slide before this. You can see the risk reduction in the non-diabetic population. It is just slightly less than that for the overall population.

DR. NISSEN: Right, but again not statistically different from atenolol.

DR. EDELMANN: Yes, again, this is an opportunity to provide the way in which we looked at subgroups. In this case we are talking about the subgroup of diabetic versus non-diabetic. We have taken, as I think has the FDA, a cautious approach in evaluating subgroups in wanting not to

over-interpret them. We looked to see whether or not the difference between the subgroups varies to a greater degree than might be expected at random, and we do that with this test for interaction. In this case, with the diabetic patients there is no significant test for interaction, which suggests that the best treatment effect is that of the entire population irrespective of whether patients had diabetes or not; the same for isolated systolic hypertension.

DR. NISSEN: We still don't have those p values. The reason I keep coming back to this combination therapy is because it is a paradox for me which I don't understand. If you could put up slide 48, I think Tom was trying to get at the same question. Let me see if I can state the paradox for you and why I think it would be helpful to the committee to answer it.

Basically, what we see is that more patients on atenolol were off study drug and more patients on losartan were on combination therapy. Now, since losartan lowered blood pressure nominally more than atenolol, what I don't understand then is why should there be more combination therapy use. You would expect if

atenolol were a less effective antihypertensive that there would be much more combination therapy with atenolol. It is exactly the opposite of what one would expect knowing the blood pressure data. My p values here, and I will be interested if you can confirm these, for the off-study drug is 0.001 for the differences, and for the combination therapy it is also 0.001. So, statistically significantly more patients on losartan got combination therapy even though their blood pressures were lower, and I don't understand why that happened.

DR. EDELMANN: First, let me just refer to this slide. This represents an accounting of patients at a particular time point, that is, at the end of follow-up for patients who did not have an event and just at the last available point prior to an event for those who did. Right there is a basis for understanding some of the differences because there are more events in the atenolol patients and they happened earlier in the trial so there is more of an opportunity for a difference there.

Also, it is very difficult to tease out of this kind of data reported as a single point in

time for why things happened because patients are being treated continuously through the trial. So, another way of thinking about this is to look at the proportion of time rather than the proportion of patients. It is something that we are going to provide for you because I think it is very useful. We are working on it and as soon as we have it, I think it will be helpful to make the distinction that although the differences might appear to be big when you take any one point in time, if you look over the entire time of follow-up, which is probably a better reflection of what happens in the trial, the differences are not as big as you might think. I will show you that as soon as I get it.

DR. BORER: As part of answer to Steve's question, do you believe there may be some contribution of incomplete blinding to the selection of adjunctive therapy here? You know, there was a significant difference in heart rate, as you would expect and maybe there is no way to avoid this, in fact, I am sure there is no way to avoid it, but to what extent might the therapy and adjunctive therapy specifically have been a response to the perception of investigators that patients were on one drug or another?

DR. EDELMANN: First of all, as you said, the study was a blinded trial and it followed all GCPs so there wasn't any unblinding per se. I presume you are talking about educated guesses.

DR. BORER: Yes, exactly.

DR. EDELMANN: We did look at this a little bit. Of course, anything I say is speculation about what happened but we did look to see how well an investigator could guess what treatment a person was on, on the basis of heart rate reduction. What we observed was that heart rate reductions although on average were greater with atenolol than losartan, were present nonetheless in both treatment groups. So, every time an investigator saw a reduction in heart rate and guessed that a patient was on atenolol, they would have been wrong more than a third of the time. So, we think that it is unlikely to have had a substantial contribution to their decisions.

DR. BORER: Just for the record, I agree completely with what you say. I don't think that it is possible with any certainty to guess what drug people are on by just looking for the presence or absence of a heart rate reduction. I would expect that most people on average would have some

heart rate reduction. The issue, I would think, might be with people who have rather marked reductions in whom a better educated guess might be made, and that might affect the way other therapy was given. I don't know if it did. I have no reason to suggest that it did but I just raise it as a question. Steve, you had other points I think?

DR. NISSEN: Actually, that was the end of my questions.

DR. GOLDMAN: Dr. Bonnie Goldman, from regulatory from Merck. I just wanted to answer Steve. As Jonathan said, that is a particular time point. Importantly, if you look at how many patients in either treatment group are on any diuretic, and as we said this is over time, it was pretty evenly balanced. Any of the ways you look at this, obviously there is a disproportion because more patients stayed on losartan longer. That is why we wanted to give it to you looking at the percentage over time.

In addition, we did look at this using HCTZ as a covariate--I am sorry, this is any diuretic, not just HCTZ. As you can see, it really had minimal effect.

DR. NISSEN: Let me see if I can help you see where I am going because I am struggling with this a little bit. You know, we know more now than we knew a month ago, and one of the things we have, of course, is the ALLHAT database and what we saw in ALLHAT was that drugs mediated through the renin angiotensin system or a drug like lisinopril was the least effective at stroke reduction compared to diuretics and amlodipine which were more effective at stroke reduction than a drug with similar mechanism of action.

So, what I was trying to understand here is if a lot more patients on the losartan arm got concomitant therapy with other agents that are more effective at stroke reduction, that could have really a pretty substantial effect on the endpoint. When I looked at the data, what I saw were what looked to me to be highly statistically significant differences in the number of patients getting combination therapy, at least in slide 48 that you showed. I know you are making some other calculations but, to me, that is an important consideration because it appears from ALLHAT that drugs that work through the renin angiotensin system are not particularly effective at stroke

reduction.

DR. EDELMANN: Let me just respond again about the difference in counts of patients at any one point in time which I think can mislead you into believing that there were substantial differences in treatment, rather than looking at the time course. What we are pulling together for you is combination therapy, not just diuretics, but I think you can see that the differences are not large between the treatments over the course of the study even though the differences were larger at the time that--

DR. NISSEN: The time was at the end of the study though where there is more opportunity to add concomitant therapy, so you would expect the effect to get bigger over time.

DR. EDELMANN: I don't want to speculate but if we could put back up the diuretic over time I think this pattern is what we are going to see. That is slide 1026. As you would expect in this trial based on the design which was to achieve goal blood pressure within the first six months by adjusting therapy, the addition, in this case of a diuretic but it would be similar with concomitant therapy I am sure; maybe a little bit delayed, is

pretty prompt and then thereafter is fairly stable through the course of the trial. As I said, if you pick a single point in time based on the occurrence of an event or an endpoint it varies. For patients who have an event you are picking a level of concomitant use at any point just prior to when they had an event, whereas patients who go to the end of the trial, you are picking the last time point. I think this is the basis for why you can see a difference in the accounting. I think this is probably a better reflection of whether or not there were differences between the treatment groups. Then the question becomes is this magnitude of difference observed over the course of the treatment important in explaining the outcome advantage of losartan over atenolol?

For diuretics, let me just reiterated it if I can just show the time-varying covariates slide again, one of the approaches we have taken, imperfect as it is, is to account for, as a time-varying covariate, things changing during the course of the trial. In this case it is the time-varying use of a diuretic up to the point where an endpoint occurs. What you see on this slide for the primary endpoint is the unadjusted

result, so that is the hazard ratio of 0.85 and a 15 percent risk reduction. Now, taking into account that slight difference that you saw over the course of the trial by adjusting what happens to the hazard ratio it goes to 0.87 or it changes by two percentage points.

So, there are all kinds of limitations to this in terms of interpretation but it certainly suggests that this magnitude of difference observed over the entire course of the trial in concomitant diuretic use does not explain the advantage of losartan over atenolol for the majority.

DR. BORER: Bob, then Tom and Beverly.

DR. TEMPLE: Two observations. One is that the ALLHAT data on lisinopril are very race dependent. In the white population, it didn't look to me like there was really any difference.

The other observation is that there is a difference between a study in which people are randomized to a treatment and everybody gets a diuretic, and one in which where there is a two percent difference in concomitant diuretic. I mean, one of them is where 100 percent of the people are on a drug; the other is a small difference. It is not easy to think how a small

differences of that size would account for the differences seen here.

DR. KEANE: I am sorry, I was just going to follow-up on Dr. Temple's comment because it gets back to ALLHAT a little bit. I think it is important for us to recognize that the ALLHAT diuretic arm was an arm that actually employed a beta-blocker very, very frequently. You know, 28 percent of the patients started off in that trial on a beta-blocker and some 60-plus percent actually were titrated on a beta-blocker as well.

So, when we are thinking of regimens and comparing, even though these are very different trials, what we have and what the ALLHAT did I think it is very important for us to recognize that there were a lot of regimens there. The same is true for lisinopril. The lisinopril arm in their secondary analysis, as you know, where the issues came out, again was a very different regimen because they excluded diuretics as the agent because that was their primary comparator; the chlorthalidone was their primary comparator in that arm. So, they went to other non-diuretic-based regimens. So, it distinctly separates some aspects of what this trial did versus the ALLHAT trial. I

wanted to make that clear. I will be back up in a few moments to actually talk a little bit about these issues.

DR. BORER: Before you go away, can you say your name into the microphone?

DR. KEANE: I am sorry, I did forget. I apologize. I am Dr. Bill Keane.

DR. BORER: Thank you, Dr. Keane. Can I suggest though that we try to avoid intensive reference to the ALLHAT trial for the simple reason that we have not been given the database to review. All of us have seen only the publication whereas here we have a complete dossier. Tom?

DR. PICKERING: Yes, I am a little confused. You showed a slide showing that about 70 percent in both groups had been treated with diuretics at one time and, yet, there is a table that shows that at the end of the trial 26 percent of losartan patients were on diuretics and 22 percent of the atenolol group. Could you reconcile those two?

DR. EDELMANN: I think 48 is the table you are referring to.

DR. PICKERING: Well, I am looking at the FDA.

DR. EDELMANN: This is the accounting for the proportion of patients at the time point which represents the occurrence of an endpoint or the end of follow-up for patients who did not have a primary endpoint. You have to sum a couple of different lines in order to get it, but 14 percent in both groups with 50 mg plus diuretic; another two and four percent with other drugs plus diuretic; and then of those on 100 mg, you see 18 and 16 and addition of 26 and 22.

This slide, 29, shows this which is a reflection not of patients but of time, proportion of time, to account for the fact that all of those different groupings were possible for all patients throughout the trial. It is impossible in one number to summarize that in a meaningful way looking at counts of patients, but it is possible to account for the amount of time and that is what this does. This difference of 72 and 70 percent is a reflection of the graph that I showed. Maybe I could throw that up again, 1026. That is the use of diuretic over the time of the trial. So, this 72 and 70 percent represents the amount of time that this proportion of patients, which is increasing rapidly and then is pretty much stable,

were on diuretics. The 72 percent of the time in yellow and 70 percent in blue reflects the difference in the two treatment groups. Does that clarify it for you?

DR. PICKERING: Well, that is just the patients who got diuretics. Is that right? Not the whole population?

DR. EDELMANN: That is correct. This is the proportion of the whole population who received a diuretic at any time, and time is on the horizontal axis. So, it is accounting for the entire study group by treatment group and what fraction of them at any moment were on a diuretic as concomitant therapy--actually on diuretic.

DR. BORER: Beverly and then Alan?

DR. LORELL: Thank you very much. I think maybe another way of thinking about this issue of whether these seemingly small perturbations in extra drug use or diuretic use were meaningful is asking the question as to whether or not there is a difference in the proportion of patients who had endpoints who had severely poor blood pressure control. I think one of the things that the committee is wrestling with is whether the differences that are seen are drug specific or

relate more generally to the issue of hypertension control.

I would welcome your comments. I hope you have had a chance to see this. The FDA review Table 36, page 63, indicates that rates of extreme poor blood pressure control, systolic blood pressure greater than 160 or diastolic blood pressure greater than 100, were more prevalent for every endpoint among the atenolol receiving group as opposed to the group randomized to losartan. So, in some ways this raises the question as to whether, for whatever reason, the net effect of these perturbations in other drug use or slight differences over time in diuretic use translated into the variable of very poor blood pressure control being a variable that contributed to the outcome. Maybe you could comment.

DR. EDELMANN: Sure. This is an important issue and in Dr. Keane's presentation he is going to go over this. But let me just give you our general response about this. As with the discussion about use of concomitant therapy, blood pressure control is something that varied over the course of the study and at the beginning of the study naturally was low because patients were just

beginning therapy, and improved over the course of the trial. The table you are referring to in the medical reviewer's document picks a single time point again and accounts for patients at that time point who did and did not achieve that level of poor blood pressure control. It is limited in the same ways as the concomitant therapy is. It is a non-random comparison. It is not protected by randomization anymore because the decision about titration and, therefore, the level of blood pressure response is something that is influenced by actions within the trial after randomization.

Nonetheless, it is still possible to do the same kind of analysis to account for all of the time and to look at the level of blood pressure goal between the treatment groups, not just poor blood pressure response but devise a method of accounting for level of blood pressure control that includes the entire population and divide the patients into losartan and atenolol groups into those control groups, good control, moderate, poor and so on, and then see to what extent the difference in that categorization explains the treatment advantage of losartan over atenolol. It is much the same as looking at individual blood

pressure values, systolic blood pressure level and diastolic blood pressure level, and to what extent do the differences explain the treatment benefit.

We have done that using the same time-varying covariate approach. It explains a very small proportion. I think it is less than one percentage point of the treatment benefit that is explained that way. Although if you look at a specific time point, one time point for the proportion of patients at poor control and then go back and say how many of those patients had events you can get the mistaken impression that that explains the whole difference.

The findings we observe in the LIFE study are exactly what you would expect, that is, the occurrence of an event is more likely among patients whose blood pressure is less well controlled. If you are looking at event numbers, you know there are more patients that had events on atenolol and you are undoubtedly going to see more patients who are at poorer control in the atenolol group just because of the numbers.

DR. BORER: Before we go on to Alan, Paul and back to our rotation here, I am going to make a statement that I hope will be helpful in the

committee's thinking about this very important issue that Beverly is raising. There are two separate issues that might be considered with this supplemental NDA, only one of which is highlighted by the sponsor and that is really the one we have to focus on. That is, does their regimen, their product and regimen, reduce cardiovascular endpoint risk as opposed to just reducing blood pressure? That is number one. In that regard, the comparator is just a comparator. Either the proposed regimen is better, not better or the same.

The second issue is whether the proposed regimen is actually superior to some other regimen. That is not what the sponsor is asking about and our response to that might be different than the response to does this regimen work. That will come up again in the questions but I think we have to keep that in mind as we look at this. It may not be so critically important that one regimen may have been a little less effective in lowering blood pressure. The question is does the other regimen reduce cardiovascular event risks. So, just with that thought in mind. Bob?

DR. TEMPLE: If I can, I would like to dilate slightly on that question. There is some

discussion of comparisons in the ICH document called E10. If you want to say that something is better than something else it is crucial that the comparison be fair in every way, that each drug was used optimally, etc., etc., etc. If you merely want to show that your drug works you don't have to use the comparator regimen optimally. In fact, you could use a placebo to show that your drug works but no one will let you do that in hypertension.

So, it is a fundamentally different question and even if there are imbalances in this and imbalances in that which disfavored one of the treatments, you might still reach the conclusion that the drug was shown to be effective.

I just want to make one other point about that. The most tempting thing to think about here is, obviously, if you have learned something about how best to treat people with hypertension, and it is reasonable to consider that and the questions go to that. There is another important factor that needs to be weighed here, which is that current labeling for antihypertensives uniformly fails to include any outcome data and what Merck is doing here--I don't know if they intended it but they are really performing a very valuable service--they are

provoking the question of whether it is time to start to put outcome data into any hypertensive labeling.

We have been thinking about this in a somewhat desultory way for at least six years and we will eventually propose language to the committee on how to do that but they are forcing the question because they are saying, "hey, we've shown something; you owe us reference to that in labeling." So, it is a very interesting thing to think about but, of course, that question doesn't require that it be better than atenolol. It just requires that it be better than nothing, which is the exact point you made. So, there are two very different kinds of questions for us. Then, how you say it and what you say, and all those things, are obviously crucial in labeling too. But from a regulator's narrow point of view it is sort of forcing the issue of outcome data in labeling for clinical trials which, as I said, we don't have. Some people think we do in the form of ramipril but we didn't think that was a hypertension claim. Steve may be right; it maybe was but we didn't think it was. We thought it was something else.

DR. FLEMING: Jeff, can I comment on the

last two points? Beverly was referring to data from the FDA document and Dr. Edelmann was responding about a time-varying covariate analysis. I just wanted to close the loop on that. It is Table 30 I think in the FDA briefing document, page 61 that I think Dr. Edelmann is referring to. If you look at any point in time of systolic blood pressure as a time-varying covariate and look at differences between the two regimens in being able to maintain systolic blood pressure, does that explain the treatment effect? It would suggest, as he said, that it explains very little. Now, it may be the wrong surrogate. It may be pulse rate, pulse pressure or other markers that should have been used in there, but if you just use systolic blood pressure it explains very little.

I wanted to return to Bob Temple's point because this is a refinement of what we talked about this morning. What is the question? We are going to be asked a number of questions about the experimental regimen here with losartan and what is the role of losartan, and we are looking at is losartan against atenolol in the presence of diuretics. A comment that I had made earlier today is if you look at the comparator regimen, diuretics

plus atenolol, there is considerable evidence, as we were discussing this morning, that that regimen has a considerable influence on outcome. So, now if you look at the regimen of losartan plus diuretics one question is, is that regimen going to be effective?

I think a very relevant and much more difficult question is what is the role of atenolol in those regimens? The LIFE study is going to be able to tell us what is the comparison of losartan versus atenolol in this LVH population in the presence of diuretics. Is losartan effective there? And, one question that is relevant is, is atenolol effective? So, specifically, what is the effect of atenolol in the combination with diuretics in this LVH population?

At some point I would like to return--I don't know if you want to return to it now or later--at some point I would like to have a clear indication of the exact data that are relevant to that question.

DR. BORER: Maybe we can hold that for a little bit later because that is going to be an important point of deliberation. Just to come back to the point that Bob was discussing though, it may

not be necessary to know exactly how effective atenolol is or isn't. It may be important to know that there is a reasonable basis for concluding that it is not harmful. We will come back to that but let's hold that.

DR. TEMPLE: Jeff, can I just add one thing? There is some reason to think that it matters whether it is known to be effective, and that goes to strength of evidence. It is remarkable how similar this is; this is exactly like our considerations of clopidogrel at the time when we were considering the CAPRE study. I don't know if you remember, but it sort of beat aspirin with a p of 0.052 or something like that, not a very strong finding. However, everybody believed that aspirin itself was far, far better than placebo so when you did a putative placebo or whatever kind of analysis you wanted to do, the strength of the evidence that clopidogrel was effective--which is all its labeling says; it doesn't say it is better--was very, very strong.

So, if you believe that there is some effect of an atenolol regimen, if you don't know exactly what that is, that makes this single study, with a p of about 0.02 or 0.03, much stronger than

it would otherwise be. So, it is relevant how much you believe in the control regimen.

DR. FLEMING: I am jumping ahead but that is exactly the issue. That is exactly why this question is important. We are jumping ahead, but if we believe LIFE nails adequately on the strength of evidence of however many trials you think we need of losartan versus atenolol, we don't need to know any more than that atenolol isn't harmful. But if we think the evidence is suggestive but not compelling, then it becomes very important to understand how effective atenolol is in the context of administration with diuretics in the LVH population.

DR. BORER: Alan and then Paul?

DR. HIRSCH: Well, I am going to take us back to something more mundane and we will come back to the philosophical argument about atenolol's effect in a minute. I want to follow-up a little bit on a point that both Steve made and that Bev made and make sure that we are understanding what caused the endpoint of stroke reduction.

I think we are all impressed and happy, as Bob said, that we actually have a hypertension trial where we actually have a hard clinical

endpoint that changes. So, for stroke I just want to make certain that there isn't any other concomitant or confounding variable that was not accounted for and I couldn't quite pull it out of the packet you provided or the FDA packet.

For the use of aspirin, clopidogrel, other antithrombotic drugs at any time point during the study, one of the packets showed that it was a low use and equal at least at one time point. But I would think it important for the committee to be sure there are no other stroke-preventing therapies that are not imbalanced between the two groups. So, I am wondering, just as you showed us the diuretic usage across time, do you have other antithrombotic usage over time?

DR. EDELMANN: We have looked at that and I mentioned this point a little earlier. There was balance at baseline in the use of concomitant aspirin, for example, and increase in the use of aspirin during the trial as I guess you would expect when these patients are followed regularly, but no imbalance between the treatment groups. So, we have looked and haven't found that.

DR. HIRSCH: Again, you don't have any graph of that over time?

DR. EDELMANN: Not over time, no. I can give you concomitant--

DR. HIRSCH: I do worry a bit. I always like to see data.

DR. EDELMANN: Well, I can tell you that 35 percent--you can see this is the concomitant co-administration of study drug with aspirin between the treatment groups.

DR. HIRSCH: I am sorry, this is?

DR. EDELMANN: This is aspirin.

DR. HIRSCH: At what time point?

DR. EDELMANN: It is the proportion of patients who received concomitant aspirin with study drug between the treatment groups. It is 35 percent. At baseline it was lower than that but also equal.

DR. HIRSCH: That is not quite how I would like to see it. For warfarin?

DR. EDELMANN: I don't know if I have warfarin on a slide. It was smaller in number and, again, comparable between the two. I guess maybe in the same category you might consider statin therapy and, again, it was the same pattern. It was 19.8 and 21.1 percent for HMD reductase drugs.

DR. BORER: Doug?

DR. THROCKMORTON: I was just going to give you those numbers, but they did.

DR. ARMSTRONG: I am still trying to understand the role of myocardial infarction in the composite and its play-out in the mortality. As you pointed out in slide 62, stroke certainly comprises the majority of the endpoints, but in slide 68 it is clear that whereas it comprises the majority of the endpoints, it comprises less than a quarter of the mortality, and myocardial infarction presumably is grouped within the CHD and accounts for more than half the mortality. So, again, I would like to understand what is the mortality rate of myocardial infarction.

DR. EDELMANN: Unfortunately, I am not able to give you an explicit answer to that question based on the way the endpoint committee classified the events. An event was determined to be a myocardial infarction, and you saw those results, irrespective of whether it was fatal or not. When there was a fatality, if it was determined to be related to coronary heart disease or a fatal MI as you would say in clinical practice, the endpoint committee called it coronary heart disease death and categorized the time

between the onset of symptoms and the death into less than an hour, an hour, one hour to 24 hours or more than 24 hours, but didn't specifically call it fatal myocardial infarction.

DR. TEMPLE: There is a table. Why don't you show the table? It is not what you are asking but it is as close as you are going to get.

DR. ARMSTRONG: You make the point that--

DR. TEMPLE: It is in the briefing book so it must exist.

DR. ARMSTRONG: You make the point that the mortality rate of stroke accentuates the overall effect on stroke. So, you have very clear data on mortality from stroke and unclear data on myocardial infarction, which is the other part of your composite, and I am unclear why you would have better data on one component and not on the other.

DR. EDELMANN: There was a lengthy discussion on the steering committee about how to do this and one of the concerns was the ability to actually determine whether or not someone had a fatal MI. In deference to the debate, and there was debate about it, the decision was made, rather than make that determination, MI or not MI, to call it a coronary heart disease event and anchor it in

terms of time between the onset of symptoms and the occurrence of death. So, within the coronary heart disease deaths are the kinds of things that you would think of as associated with that--fatal MI, sudden death.

This was part of the debate and I can recreate a little bit of it for you, if a patient presents with an MI and presents with symptoms of chest pain and an arrhythmia and dies, is that a fatal MI or is that sudden death if it all happens within an hour or if it happens within 24 hours? So, rather than try to make an arbitrary decision and distinction among those otherwise potentially overlapping clinical conditions, this was the way in which the endpoint committee classified things.

DR. ARMSTRONG: Can you tell us what proportion of those were hospitalized deaths versus non-hospitalized deaths?

DR. EDELMANN: Well, I am not sure that I have the figures right at the tip of my fingertips but the overwhelming majority, vast majority of all endpoints were hospital-based. There were some deaths that occurred outside of hospital, sudden deaths, and it is something I can probably get for you. But the vast, vast majority of endpoints,

fatal endpoints included, occurred in hospital.

DR. ARMSTRONG: The second point was just to return to this composite. We had tabled the issue of statistical heterogeneity and I don't know whether this is the time but it seems to me we do need to address the occurrence of the heterogeneity and its impact on our acceptance or non-acceptance or better understanding of the primary composite, Mr. Chairman. I would welcome Tom's view and the response of the sponsor.

DR. EDELMANN: If I might, this is an issue which we know is important to the discussion and Dr. Keane will present our perspective on it. So, if you wouldn't mind holding just a little bit more.

DR. BORER: JoAnn and then Susanna?

DR. LINDENFELD: I have two slightly different issues. The baseline ECG that was used for evaluation of LVH, was that done at entry into the study or was that a screening ECG?

DR. EDELMANN: There was an ECG by which patients qualified for entry into the trial. That was read by the core center and given a thumbs up or a thumbs down. Separate from that, there was an ECG on the day or near to the day of randomization

which we called the baseline ECG and that was the ECG that served as the ECG for baseline measures and adjustments for the covariate, and so on.

DR. LINDENFELD: And can you tell me, and I am sorry for asking this question but I just don't know the answer, if acutely lowering the heart rate changes the ECG criteria of LVH?

DR. EDELMANN: I am not sufficiently expert to tell you the answer to that. I don't know if one of our consultants--no. No, so says Dr. Devereux.

DR. LINDENFELD: Okay. Then, my next question is, again, a little bit different. We haven't discussed at all the urinary albumin-creatinine ratio in this study. I guess I would expect that there might be a subgroup which would have a fairly larger effect of losartan than atenolol. I wondered if you could show us the endpoints by the group with an abnormal urinary albumin-creatinine ratio and those without. We already know that is a subgroup that has a particular effect of this type of drug and it seems to me, if we are really going to get at who is benefiting we have to know that data.

DR. EDELMANN: This is using

microalbuminuria, the presence of microalbuminuria as a place of dichotomization for subgroup with and without. Here is the treatment effect. So, those with microalbuminuria and those without, and it is a relatively small fraction who had reported microalbuminuria. Again, our thinking on this is that the best way to interpret it is in terms of the degree to which these vary from one another as reflected in the test for interaction. So, the interaction test is not significant.

DR. LINDENFELD: I believe data from this study has reported that the effect of microalbuminuria is related to LVH perhaps more significantly than the blood pressure effect. Is that a correct statement?

DR. EDELMANN: I am not sure--

DR. LINDENFELD: I didn't say that very well. In other words, isn't there data from the LIFE trial published that suggest that there is an independent effect of drug treatment on microalbuminuria and the decrease in LVH separate from the blood pressure effect?

DR. EDELMANN: I don't believe there are any publications yet relating to treatment and their relationship, but it is baseline levels--

DR. LINDENFELD: Baseline, I am sorry, yes.

DR. EDELMANN: So, it is in pooled groups.

DR. LINDENFELD: Right.

DR. EDELMANN: Let me refer to Dr. Devereux.

DR. DEVEREUX: Hi, Dr. Richard Devereux, from Cornell. We haven't yet done the analyses you suggested to evaluate the association between changes in albuminuria and changes in LVH and outcome as a three-way association. We have shown very strong cross-sectional associations between albuminuria and LVH at baseline that are independent of blood pressure level. We intend to do those analyses. We have about 40 papers we plan to write.

DR. LINDENFELD: You may be collecting this data. I just wanted to come back to this issue of the individual centers that requested the use of a 25 mg dose of both drugs, could you just show us, in those centers, how often each of the groups were decreased to 25 mg?

DR. EDELMANN: Well, I don't have a slide but I have the numbers now. As I mentioned, it was an option available on a center by center basis and

it was used relatively infrequently. Less than one percent of patients in both treatment groups; 78 atenolol patients total went to the 25 mg dose and 32 losartan patients went to the 25 mg dose.

DR. LINDENFELD: Could you just give me a rough idea of how many patients were in centers that could have reduced the dose?

DR. EDELMANN: Well, it was an option that was available to all centers. In other words, if the center felt that a lower dose was necessary we instituted the paperwork, the protocol amendment and so on to make it possible but it was available at all centers; it just wasn't used very frequently.

DR. LINDENFELD: Right, but I guess what I am getting is that twice as many patients had the atenolol dose reduced as losartan. Again, I think this is a bit of an issue because in this older patient population 25 mg of atenolol could be effective therapy. I am not too concerned about this but I worry a little bit because it was an amendment made well into the study I think in 1998, and I worry that some of the withdrawal may have been because the option wasn't there to reduce the dose in those older patients. I think that is an

issue in these older patients.

DR. BORER: Susanna?

DR. CUNNINGHAM: Yes, I was curious about the left ventricular hypertrophy. You chose your population because age increases risk of morbidity and mortality so I was wondering what your data shows that happens to morbidity and mortality with a reduction in LVH since that would be something of interest. Sort of the implied assumption I think is that if you did reduce LVH it would reduce morbidity and mortality.

DR. EDELMANN: Right, well, this is another example of things changing in the protocol during the course of the study simultaneously so we have used the same kind of approach here. LVH, as you saw, was reduced over time. There were fewer endpoints. To what extent does the change in LVH explain the benefit? And, we used the same time-varying covariate method. Again, I will remind you this is a method for adjustment that starts with the unadjusted result of the 14.6 percent risk reduction and then accounts for differences between the treatment groups in left ventricular hypertrophy and looks at the relative risk.

What you see is that the risk reduction goes from 14 percent to a little under 10 percent. So, this is almost a five percent endpoint change. This is a more substantial magnitude of change being accounted for by differences in left ventricular hypertrophy and probably consistent with what you would expect if left ventricular hypertrophy is actually having some effect given the limits of the analysis and the methods. LVH was measured only once a year. It was measured on the electrocardiogram which has its own imperfections in accuracy of measurement. So, for all these reasons it is not a precise or exact thing but it shows an association of some of the benefit of losartan over atenolol associated with left ventricular hypertrophy.

DR. FLEMING: Before leaving this point, does this explain at all the interaction by race, blacks/whites, if you did a similar type of analysis?

DR. EDELMANN: No, it does not.

DR. HIRSCH: That same analysis for stroke alone?

DR. EDELMANN: For stroke alone for LVH reduction? I can show you that. Essentially, when

we did the time-varying covariate on the primary composite and then looked at the secondary component endpoint we saw roughly the same thing, that is, an effect of about four percentage points, just focusing on the change here--about four percentage points to be explained or associated with accounting for the left ventricular hypertrophy change. I think this makes sense. Left ventricular hypertrophy is certainly not causing stroke but is associated with stroke, as I reviewed in the beginning part of my talk, because it is a surrogate and a marker for other processes that are occurring outside of the heart but in response to the same things, like blood pressure and angiotensin II, and when you take into account the change in left ventricular hypertrophy you see some effect.

DR. BORER: Susanna, did you have some other points?

DR. CUNNINGHAM: No.

DR. BORER: Mike?

DR. ARTMAN: Along those lines, sticking with LVH, the ECG criteria and the question I think Tom raised about does this explain the ethnic differences that were seen, in the black

population, by the Sokolow-Lyon criteria they had greater LVH and by the Cornell time product less LVH. I am wondering, in that subset analysis about ten percent of patients had ECHOs and there was a predominance of black patients in that. If you look at that subset of patients that had ECO assessment of LV mass, which I think is a little more reliable, does that provide us any insight?

DR. EDELMANN: Unfortunately, it doesn't. As you pointed out, it is a subset of a subset so we had only about ten percent of the overall patients in the LIFE study who were in the ECHO substudy to begin with and only a fraction of those were black. We are talking about 64 losartan patients and 65 atenolol patients. When you look at the LV mass change there, there is no difference between the treatment groups. Both treatments regress left ventricular mass but there is no difference between the two. Numerically, I think it is a little bit in favor of atenolol but there is not anywhere near the kind of power that you need to draw any conclusions.

DR. BORER: Tom?

DR. FLEMING: You have talked about the subgroups and the need for caution in interpreting

those subgroups. I have a couple of quick specific questions. If you don't know the answer, you can provide it to us at the break. You have indicated that when you look at the diabetic subgroups, yes versus no, and look at the primary endpoint the test for interaction is 0.17. Basically you are seeing a bigger difference in effect in the diabetics, 24 percent reduction rather than 11 percent reduction. Mortality breaks out a bit more strikingly though, all of the mortality differences in the diabetics. Could you at some point give us the test for interaction p value for that?

DR. EDELMANN: Yes, we have done that. For total mortality you are asking?

DR. FLEMING: Yes.

DR. EDELMANN: I don't know if I can give you the p value but the magnitude of difference is significant.

DR. FLEMING: Maybe you could get that for us later. Let me move on. When we look at race, you have indicated a 0.005 significance level for the test for interaction for the primary endpoint. Stroke shows a very similar interaction. If we could get that significance level, just looking at the stroke component, that would be helpful.

DR. EDELMANN: Okay.

DR. FLEMING: Then my other question is we are looking at the LIFE study as the primary source of evidence here for losartan or more generally ARBs in the presence of diuretics. If you are going to come back to this later on just let me know, but is there any additional evidence that you think we should be considering when you are looking at the effects of ARBs in the presence of diuretics on this composite endpoint of death, MI and stroke in hypertensive patients with LVH?

DR. EDELMANN: I don't know that there is specific evidence about the addition of a diuretic to an angiotensin receptor antagonist, but I am sure you are aware that the blood pressure lowering effects are well studied when a diuretic is added to an angiotensin receptor antagonist and augment the benefit in terms of blood pressure. I think that is probably the most relevant bit of information. That is to say, the combination of an angiotensin receptor antagonist and a diuretic has a substantial benefit on blood pressure which is contributing in some fashion to the benefit that you see in absolute terms. The contribution of the relative difference between losartan and atenolol

on diuretic I think is probably best addressed by the in-trial accounting for the use of diuretics that we have been over and doesn't really seem to explain very much the treatment advantage.

DR. BORER: Steve and then JoAnn?

DR. NISSEN: Because it appears that more atenolol patients were withdrawn from therapy than losartan patients I would be very interested in seeing the pro-protocol analysis. Now, I recognize that the intent-to-treat analysis is the preferred one but when you see these kind of differences in withdrawal of therapy it is helpful to me to look at a pro-protocol analysis. I am sure you have slides for that.

DR. EDELMANN: I can show you that, sure. As you said, pro-protocol has the disadvantage of eliminating information because patients who are no longer on therapy are not considered for future events; they are censored.

DR. NISSEN: Yes.

DR. EDELMANN: So not surprisingly, the number of endpoints in the pro-protocol analysis is a lot less because you have censored out a lot of the patients, but you can see that the hazard ratio and confidence intervals are really pretty similar.

DR. NISSEN: In the FDA's analysis though the p value is non-significant for the pro-protocol.

DR. EDELMANN: Yes, as it is here. I think it is just barely above 0.05. Maybe it is because of the dashed line, but you can see that the confidence bound is just barely approaching the unity line. So, it is 0.05 and another digit, not significant.

DR. BORER: JoAnn?

DR. LINDENFELD: Just a quick question. I notice that the losartan blood levels are twice as high in women as men in this study. The metabolite levels aren't different. Then, also, the sensitivity, the ECG for LVH is half that for women that it is for men. I wondered if you could show us the difference by sex in this study.

DR. EDELMANN: Sure.

DR. LINDENFELD: And maybe if you have the blood pressure differences. In other words, did the blood pressure drop equally in men and women?

DR. EDELMANN: Well, let me start with the first one. I can show you the primary endpoint by gender as a subgroup. You can see, again, looking at the interaction p value for a method for

interpreting this that there is no interaction. So, we assess this to say that the best treatment effect in men and women is reflected by the overall.

In terms of blood pressure response by gender, that is not something that I have off the top of my head but I know it is something we have looked at so I may be able to get that information to you.

DR. BORER: If there are no other clarifications of the efficacy data--Mike?

DR. ARTMAN: I just have one more question. I realize we have talked about subgroups, and when you tested for interaction among the different countries there was no overall interaction, yet, the only country where there is no overlap of 1 for the confidence intervals for the primary endpoint was Norway. Norwegians also have lower baseline stroke rates. I just wonder if I am reading too much into that or is it better to be in Norway?

DR. EDELMANN: I have been in Norway; it is a nice place! As I said now several times and I will repeat it again, we have been very conservative in our view of how to interpret

subgroups because there are all kinds of pitfalls in over-interpreting. Our conclusion is that it is essentially the same story; there is no evidence of a treatment by country interaction, and our interpretation for the primary endpoint is that the best estimate of the treatment benefit is for the overall population. Yes, there is a variation that you describe but it is not more than would be expected to occur at random with this distribution of patients among countries.

DR. BORER: Let's see if we can go on to the safety assessment.

DR. EDELMANN: Next I am going to review the results of adverse event reporting and other safety parameters that were evaluated in the LIFE study.

This table summarizes the overall adverse event reporting in the LIFE study. Not surprisingly, in a study of this duration almost all patients in both treatment groups experienced at lease one adverse event. However, patients treated with losartan experienced significantly fewer drug-related adverse events compared to those treated with atenolol and discontinued due to adverse events with lower frequency compared to

those patients treated with atenolol.

At the outset of the trial the steering committee defined nine adverse events of special interest. Chosen based on the comparator agents in the trial, these adverse events are shown on this slide. AEs of special interest that occurred with higher frequency in the losartan group are shown on the top half of the slide and those occurring more frequently in the atenolol group are shown on the bottom half of the slide. On both halves the AEs are listed in decreasing order of frequency for losartan.

Most of the AEs occurred with equal likelihood between the treatment groups. Hypotension was more likely to occur in the losartan group whereas bradycardia, cold extremities and sexual dysfunction were more likely to occur with atenolol.

Other adverse events occurring with a frequency of at least five percent in either treatment group but differing between the treatment groups by at least one percent are depicted on this slide, again in order of decreasing frequency in the losartan group. This is a complete list of such adverse events. The differences between the

treatment groups are not of clinical significance.

Laboratory values, including serum electrolytes, hematologic and metabolic parameters, as well as urinary albumin and creatinine were measured in the LIFE study. There were no important differences between the treatment groups in these parameters whether measured by absolute value or predefined limits of change from baseline.

The occurrence of new diabetes was prespecified by the steering committee to be of interest and was diagnosed by the investigator according to an algorithm based on WHO guidelines. The diagnosis of diabetes required documentation of at least two fasting blood glucose values above 140 mg/dl or a positive oral glucose tolerance test. Patients treated with losartan were significantly less likely to develop new diabetes, representing a 25 percent risk reduction compared to atenolol.

To summarize the safety findings of the LIFE study, losartan was well tolerated and associated with fewer drug-related adverse events and fewer discontinuations due to adverse events than atenolol. New diabetes was more likely to occur in patients treated with atenolol.

The observed AE profile for losartan in

the LIFE study was consistent with the profile observed in the general hypertensive population as reflected in our current product circular.

Depicted here again are the results of the primary endpoint and secondary component endpoints as a summary of the major findings of the study. The important reductions in these cardiovascular morbidity and mortality endpoints with losartan, coupled with the excellent tolerability which was observed, lead us to a favorable benefit to risk assessment for the use of losartan in these patients.

I will now turn the podium over to Dr. William Keane who will conclude our presentation by reviewing the evidence within an external study that supports our application for a new indication.

DR. BORER: Thank you, Dr. Edelmann. Does anybody have any questions specifically about the safety data? If not, let's move right on.

Review of Evidence and Conclusions

DR. KEANE: Thank you, Dr. Edelmann. Dr. Borer, members of the advisory committee, ladies and gentlemen, my name is Bill Keane and I am vice president for clinical development at U.S. Human Health at Merck and Company. I joined Merck about

a year ago, just as the LIFE study was concluding. Prior to that I was in the academic practice of nephrology at the University or Minnesota for 28 years, and for the last ten of these years I was chairman of the Department of Medicine at Hennepin County Medical Center, University of Minnesota Medical School.

The purpose of my presentation is to describe why we believe the LIFE study is sufficiently strong as a single trial to support our request for a new indication. As Dr. Tucker pointed out during his initial presentation, there is an FDA document which provides guidance on making regulatory decisions based on a single study that I will use to help frame my discussions.

As I go through my presentation I will specifically try to provide our perspective on some of the questions that the committee has been asked to address. First of all, the ability to consider a single study for an effectiveness claim is generally limited to situations such as the LIFE study where there is a clinically meaningful benefit on irreversible outcomes and it is unethical or impractical to repeat the study. The additional characteristics of the LIFE study that

support the proposed claim include the study design, the consistency of the results in multiple subsets of the population, the demonstrated effects on additional endpoint and the consistency of the study findings with data from the scientific literature.

Let me discuss each of these points with a bit more detail. First of all, the characteristics of the design and execution of the LIFE study provide support for the strength of the results. LIFE was a large multicenter, multinational, double-blind study conducted according to good clinical practice standards. The study enrolled over 9100 patients and followed them for an average of 4.8 years at 945 centers in seven countries. More than 1000 patients reported at least one primary endpoint and complete endpoint adjudication was reported for approximately 99 percent of potential patient days of follow-up.

An independent blinded endpoint committee adjudicated cardiovascular morbidity and mortality endpoints. The LIFE study focused on hypertensive patients with left ventricular hypertrophy, a group at particularly high risk for cardiovascular events. Importantly, the control group of the LIFE

study received an atenolol-based antihypertensive regimen that has established benefits in the reduction of cardiovascular morbidity and mortality.

One question that this committee will be asked to comment on is what is known about the effects of antihypertensive therapy with beta-blockers and angiotensin receptor antagonists in patients like those in the LIFE study. The LIFE study is the first to exclusively target hypertensive patients with LVH. However, none of the studies that established the cardiovascular benefit of treating high blood pressure excluded patients with LVH. As you know, one reason hypertensive patients with LVH were included in the LIFE study is because they are at high risk of experiencing cardiovascular outcomes.

Blood pressure reduction is a well accepted surrogate for benefit on cardiovascular outcomes and there is no reason to expect that blood pressure lowering in patients with LVH would result in less benefit than in patients without LVH. The prevalence of LVH increases with age and elderly patients, like younger individuals, experience significant benefit on cardiovascular

outcomes with blood pressure lowering.

This slide, which you have already seen, and the next several slides show meta-analyses of hypertension treatment trials looking at the impact of treatment on all cardiovascular events. As was discussed in Dr. Edelmann's presentation, this first slide shows the results of our meta-analysis of five hypertension trials comparing a beta-blocker-anchored regimen to either placebo or no treatment.

Again, the red diamond shows the odds ratio and 95 percent confidence intervals for the pooled data for the occurrence of all cardiovascular events, and the individual studies are shown below in green. These historical data indicate that blood pressure lowering with beta-blocker-based regimens is associated with a significant reduction in cardiovascular morbidity and mortality.

This slide shows the results of a meta-analysis of nine hypertension studies performed by Staessen and colleagues comparing regimens based on either calcium channel blockers or ACE inhibitors to regimens that used diuretic and/or beta-blocker therapy.

This plot shows the number of events, number of patients and the odds ratio for all cardiovascular events for both comparisons. The CCB- and ACE inhibitor-based regimens showed similar rates of total cardiovascular events compared to diuretic/beta-blocker-based therapy.

As you are all undoubtedly aware, most recently the ALLHAT study confirmed the effectiveness of conventional therapy based on diuretic with added beta-blocker treatment in the reduction of cardiovascular morbidity and mortality. Considering this established benefit of beta-blocker-based therapy in reducing cardiovascular morbidity and mortality in hypertensive patients, I would now like to provide an overview of the findings from the LIFE study.

Losartan, as you have already seen today, was associated with a 13 percent reduction in the risk of the primary endpoint, a composite of cardiovascular death, stroke and MI after adjusting for the baseline level of the Framingham risk score and the degree of left ventricular hypertrophy.

As I mentioned, this is a particularly important result when one considers that this finding was achieved by the losartan-based regimen

compared to an established and active antihypertensive regimen in the face of comparable blood pressure levels in each of the treatment groups.

Another question that the committee will be asked to address is whether the treatment benefits of losartan on cardiovascular morbidity and mortality could be explained by differences in blood pressure control between the treatment groups. I would like to briefly discuss several observations that lead us to conclude that these small differences are unlikely to explain the benefit of losartan in the LIFE study.

First, as was summarized by Dr. Edelmann, there was a small, albeit significant, difference in systolic pressure of l.2 mm Hg between the groups in favor of losartan, and a small non-significant difference in the diastolic blood pressure in favor of atenolol. The proportion of patients reaching the protocol-specified target blood pressure of 140/90 was similar between the groups, as was the number of patients with poor blood pressure control, that is, 160/100 or above.

One obvious concern in terms of blood pressure measurements is whether the trough blood

pressure measured in the clinic accurately reflects the true blood pressure effects of the treatments during the course of the day. Very recently we were able to obtain data from a LIFE substudy conducted at four Danish centers that measured ambulatory blood pressure at baseline and at one year. These data have been submitted to and reviewed by the agency, but they were not available in time to be included in the briefing documents you received.

This slide shows the baseline and year one systolic blood pressure measurement over 24 hours for 110 patients, 57 in the losartan group, shown in yellow, and 53 in the atenolol group, shown in blue. The horizontal axis shows the time of the day over the 24-hour period, starting from 10:00 a.m. The vertical axis shows the systolic blood pressure level.

You can see the usual shape of the 24-hour blood pressure curve with the overnight dip in pressure and the rise towards the early morning hours. There was a significant decrease in systolic blood pressure after one year in both treatment groups. The box on the right of the slide shows the 24-hour mean systolic pressure

readings at one year. You can see that the 24-hour curves are slightly lower in the atenolol-treated patients throughout the day. This translates into a mean 24-hour systolic blood pressure difference of 1.4 mm Hg in favor of atenolol. A similar result in favor of atenolol was seen for diastolic pressure measurements. The ABBM data observed in this substudy are consistent with the trough blood pressure measurements obtained at all sites, and corroborate the finding of comparable blood pressure reductions in both treatment groups in the LIFE study.

We next evaluated this 1.2 mm difference in trough systolic blood pressure by two different approaches. The first uses a time-varying covariate method to look at the impact of the small observed differences in blood pressure treatments based on LIFE data. The second uses historical study data to estimate the benefit of an outcome of the observed 1.2 mm difference in systolic blood pressure.

This slide depicts our time-varying covariate analysis of the impact of blood pressure differences on the primary endpoint. Although there are limitations to this methodology, this

statistical approach provides one way of adjusting for small in-trial blood pressure differences. The slide shows what happens to the primary endpoint result when such adjustments are made.

The first line of this table shows the unadjusted result for the primary endpoint in the LIFE study, that is, a 14.6 risk reduction with losartan. The subsequent lines in this table show the effect of adjusting for in-trial levels of systolic or diastolic blood pressure for the category of blood pressure control. You can see that when the adjustment is made using small blood pressure level or response category as a time-varying covariate there is a very small change in the primary endpoint result.

Within the limitations of these analyses, these findings suggest that the vast majority of the benefit of losartan on the primary endpoint is due to factors other than the small differences in blood pressure between the treatment groups.

The next several slides illustrate how historical study data can be used to estimate the expected benefit on cardiovascular outcomes of the observed 1.2 mm Hg reduction in blood pressure using stroke as an example.

This is a graph that shows the relationships between the level of blood pressure lowering, which is shown on the horizontal axis, and the percent risk reduction in the outcomes of stroke, which is shown on the vertical axis. Here are the point estimates from three different meta-analyses of clinical trials in hypertension, one by Staessen and colleagues, on the left; one by He and colleagues, in the middle; and one by MacMahon and Rodgers, on the right.

The dots represent the percent risk reduction for the specified differences in systolic blood pressure. The lines show the 95 percent confidence intervals around the estimate of risk reduction. These meta-analyses were chosen since they represent studies of over 38,000 patients with hypertension and provide estimates on the occurrence of stroke.

As you can see by the highlighted bars on each axis, for a difference of between 10-15 mm Hg in systolic blood pressure there is an expected 30-40 percent risk reduction in the occurrence of stroke. Assuming a linear best-fit line going through zero, this slide shows the relationship between systolic blood pressure and the risk of

stroke.

The arrow shows that in the LIFE study there was a 1.2 mm Hg difference in systolic blood pressure which, as you can see, would correspond with a less than five percent risk reduction in stroke, as indicated by the solid white lines.

In contrast, and as you heard this morning, we observed a 25 percent risk reduction for stroke in the LIFE study, as is shown here by the yellow dot. Therefore, based on both the time-varying adjustments for blood pressure level or the achieved blood pressure control category using LIFE data only, as well as a secondary method using external reference data, it is unlikely that the benefit of losartan can be explained by this level of systolic blood pressure difference.

Returning to our considerations of the characteristics of a single study to support an effectiveness claim, another characteristic is the presence of consistent results in important subsets of patients. In the prespecified analyses of subgroups in the LIFE study there were no significant interactions with treatment. In the two special interest population of patients of high risk categories, patients with diabetes and

patients with isolated systolic hypertension, a consistent benefit was observed for the primary endpoint.

In the analyses of the 23 baseline demographic disease history and clinical characteristics subgroups consistent benefit of losartan on the primary endpoint was observed. These findings indicate that the benefits of losartan in the LIFE study are applicable to patients with varying clinical and demographic characteristics.

However, there was a suggestion of an interaction between ethnic group and treatment. In post hoc analysis dichotomizing the population into black and non-black patients, black patients treated with the atenolol-based regimen appeared to have a greater reduction in the risk of the primary endpoint compared to those treated with losartan.

As presented in detail by Dr. Edelmann, further exploration failed to reveal any basis for the apparent qualitative difference in response in the black patients. As he showed, blood pressure reduction, LVH regression and heart rate responses were similar in the black population compared to the overall population. Thus, we were unable to

find a clinical explanation for this finding. These observations, together with our entire clinical database for losartan, lead us to be confident that black patients receiving losartan are not being harmed by treatment. Still, we believe it is important that the information from the LIFE study about black patients be available to physicians as they make their treatment decisions and, thus, believe a description of this finding should be included in the clinical study sections of the label.

Another consideration for a single trial is the presence of benefit in endpoints involving different events. In the LIFE study we observed a substantial and meaningful 25 percent reduction in the risk of the secondary endpoint of stroke with a losartan-based regimen. The reduction in cardiovascular deaths seen with losartan, although not significant, was consistent with the primary endpoint, largely due to a significant 35 percent reduction in the risk of fatal stroke with losartan. Importantly, there was no significant difference in the rate of fatal and non-fatal myocardial infarctions between the treatment groups.

Consistent with our hypothesis, there was also a significant reduction in the endpoint of LVH with losartan compared to atenolol. There were several other observations in the LIFE study which may have contributed to the observed benefit of losartan on stroke that I would like to mention briefly.

One is its effect on the carotid artery wall thickness, which was measured in a LIFE substudy, and the other is its effect on the occurrence of atrial fibrillation which we evaluated after discussion with the FDA reviewer. In a small substudy of patients in LIFE, called ICARUS, there was evidence for a greater benefit of losartan than atenolol on the carotid artery. As you are aware, increased carotid artery wall thickness correlates with the risk of stroke. Ultrasound of the carotid was conducted at baseline and yearly for three years in 57 patients. As depicted on this slide, for the 39 patients with data at year three, losartan reduced the intima-media cross-sectional area while atenolol had little effect. These data support the presence of a structural benefit to the carotid artery of losartan, independent of blood pressure reduction,

which may have contributed to its beneficial effect on stroke.

Another question that this committee is asked to address concerns the relationship between atrial fibrillation and the occurrence of stroke. It is well-known that atrial fibrillation is associated with a two- to a five-fold increase in the risk of stroke. Data from the LIFE study confirm this finding.

The diagnosis of atrial fibrillation in the LIFE study was made in two ways. First, investigators reported a. fib. as an adverse event or as part of an endpoint narrative. The second way that a. fib. was diagnosed was based on ECGs as determined by the core reading center. By either method, the presence of atrial fib. at baseline was associated with a 3.5-fold increased risk of stroke when the data were pooled across treatment arms. Again, as detected by either method during the trial, the development of new a. fib. was associated with a five-fold increase in the risk of stroke when the data were pooled across treatment arms.

As was pointed out in the FDA briefing document, losartan was associated with a lower

incidence of a. fib. in the LIFE study. This conclusion was based on investigator reports of atrial fibrillation as adverse events. After discussions with the FDA reviewer, we performed several post hoc analyses that were based on information about atrial fibrillation that was contained in the ECG database as well.

We looked at the occurrence of new a. fib. during the trial, as described on this slide. Patients with a. fib. at baseline, determined either by investigator report or ECG codes, were excluded from this analysis. Of the remaining patients, those who experienced a. fib. during the trial, based either on the investigator report or the presence of a. fib. on the ECG or both, were evaluated using the same statistical methodology as for other endpoints.

Among those patients without a. fib. at baseline, this plot shows the hazard ratio for developing a. fib. during the trial. The first line shows the hazard ratio for a. fib. determined by the investigator. The second line shows the hazard ratio for a. fib. determined by the ECG core lab only. The third line shows the hazard ratio for a. fib. determined by either method. To the

left of each point is the number of patients with a. fib. in each treatment group as determined by the method indicated. You can see that there were some 762 cases of new atrial fibrillation during the LIFE study. Regardless of the diagnostic method, losartan was associated with fewer cases of a. fib. than atenolol. Consistent with the FDA reviewer's assessment, the finding of less a. fib. with losartan may have contributed to the observed 25 percent reduction in the risk of stroke with losartan.

Another aspect of the benefit on multiple endpoints involving different events is the effect of treatment on the components of the composite endpoints. As noted during our presentation, there was variability in the results among the secondary component endpoints in the LIFE study, with no evidence of difference in the risk of MI and a greater reduction in the risk of stroke with losartan.

Although consistency in the treatment effect of secondary component endpoints is often supportive, the presence of heterogeneity in these components in the LIFE study does not diminish our confidence in the results. In trials in which

different active treatment regimens are being compared, differences in outcomes may be less than those observed in studies comparing active therapy with placebo. Thus, the finding of no difference between losartan and atenolol in the risk of MI is understandable given the known cardioprotective benefit of beta-blockers and the benefit of losartan on LVH.

In contrast, the statistically persuasive benefit of losartan on stroke is consistent with the known biological actions of angiotensin receptor blockade with losartan such as the reduction in arterial wall thickness. In addition, the benefits of losartan on atrial fibrillation may have contributed to its benefit on stroke.

Data external to the LIFE study are important when considering the use of this single study to support the proposed new claim. While LIFE is the first trial to evaluate cardiovascular outcomes with an angiotensin receptor antagonist in hypertensive patients with LVH, there are additional published data that are consistent with the findings of the LIFE study.

Preclinical models of hypertension have shown a particular benefit on stroke with AT I

receptor blockade independent of blood pressure level. Myocardial hypertrophy and fibrosis have been reduced by treatment with losartan. In clinical trials, interruption of the angiotensin II axis with ACE inhibitors and AT I receptor blockers has been shown to reduce LVH to a greater degree than with other blood pressure lowering agents. Structural and functional benefit of losartan on the vasculature has also been demonstrated in human peripheral arteries.

Let me summarize these findings in light of the considerations for an effectiveness claim based on a single study. First of all, the LIFE study showed that losartan provided a clinically meaningful reduction in irreversible cardiovascular morbidity and mortality compared to the active antihypertensive agent atenolol. This result was achieved with substantial and comparable reductions in blood pressure. Given these findings, it is impractical to repeat this trial.

LIFE was a large, multicenter study that followed a rigorous design according to good clinical practice standards. Consistent reductions in the primary endpoint with losartan were observed in the subsets of the population that were

assessed, including those at high risk of cardiovascular events like diabetic patients.

In the LIFE study there were additional benefits of losartan on multiple events, including a significant 25 percent reduction in the risk of stroke and a greater reduction in LVH, consistent with the study hypothesis. There were also findings of benefit on carotid artery wall thickness and a lower incidence of atrial fibrillation with losartan. Both of these latter effects may have contributed to the benefit on stroke.

Finally, the study findings of losartan's benefit on stroke, LVH and vascular structure are consistent with data external to the study showing a similar benefit with angiotensin receptor blockade in preclinical models and in humans.

In addition to the significant benefits of losartan therapy on cardiovascular morbidity and mortality, losartan was well tolerated in the study. Losartan was better tolerated than atenolol, with an adverse experience profile consistent with its current prescribing information. There was also a lower incidence of new onset diabetes in patients treated with

losartan in comparison to atenolol. In total, these findings lead to a favorable benefit to risk assessment. Thus, we believe that the LIFE study is sufficient to support our request for a new claim for losartan.

In conclusion, based on the rigorous design as well as results that are clinically important, internally consistent and supported by external scientific data, the results of the LIFE study provide strong support for the proposed new indication. Cozaar is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy. Thank you for your attention.

DR. BORER: Thank you very much, Dr. Keane. Before we raise any further questions for you and for your colleagues prior to our discussion of the FDA questions, since it is 12:15 we will take a one-hour lunch break, so that I don't get lynched, until 1:15. But I am going to just ask you, during that lunch break after you have your lunch, if you could pull together the data that

would allow us to look at the event rates--I don't need statistics; I just need event rates--for the subgroups on monotherapy, on the primary therapy plus diuretics alone and for the primary therapy plus diuretics plus anything else. I understand the company's aversion to providing these analyses earlier but I would like to see them anyway.

With that having been said, let's break and we will come back here at 1:15.

[Whereupon, at 12:15 p.m., the proceedings were recessed, to resume at 1:21]

A F T E R N O O N P R O C E E D I N G S

DR. BORER: We are six minutes behind schedule and that is really completely unacceptable for a government organization! So, we are going to begin.

I would like to take a minute to frame the issues, as I see them, that we need to discuss before we move on to the questions which frames everything more precisely. We will have an FDA presentation but we will have that after the sponsor finishes its grilling, and my comments are really specifically related to how the sponsor is going to answer what we ask it. Through the morning several issues have surfaced and I would like to state them so that they are out in front as we continue this discussion, and then get the FDA presentation and any public statements that need to be made.

The first, of course, is whether the data here show that one regimen is better than another regimen. Let's say that it is, then we have to know how much better to determine what we can conclude from that and that requires that we have some idea whether the comparator regimen truly is effective or questionably effective. It has never

been labeled or reviewed for this, for effectiveness for event reduction and, as a corollary, how much each component of the comparator regimen contributes to whatever the effectiveness of the comparator regimen is, and that will be important in our determining whether a single trial is adequate to draw any conclusions if one regimen is better than another.

Assuming we get through all that, we have to know what the regimen is that the sponsor is proposing. The stated requested labeling says that it is losartan but we have to be sure that it really is that rather than a regimen that contains losartan 80 percent of the time and has a lot of other stuff too.

Finally, if we get through that we have to know whether that regimen can be accepted as effective for all patients, the way the requested indication would seem to suggest, or whether that needs to be circumscribed with regard to descriptive factors that might exclude part of the population, like age, race or LVH or EF.

So, I think those are the key issues that we have to be thinking about as we are asking questions and as you are giving responses. With

that in mind, shall we ask for public comments now? Let me momentarily please open the hearing for public comment if there is any. Is there any member of the public that wants to make a comment? If not, then we will move on with the questions to the sponsor.

One that I had asked that is specifically relevant to the issue of what regimen we are talking about is the one I asked about the rates of events for the various subgroups. Ray Bain gave me a chart here. You may have some way of putting it up for everybody so that we can see what happened to people who were on monotherapy, monotherapy plus hydrochlorothiazide, monotherapy plus whatever else, and whatever else without the monotherapy. Maybe you can go through this for us.

DR. SNAPINN: Steve Snapinn, from Merck. Let me just run through the tables. There are two separate tables here, one describing crude event rates, numbers of events divided by the numbers of patients, and another table giving event rates per 1000 patient years of follow-up. In each of these two tables the results are broken into four columns, the columns representing four cohorts of patients. Just as a reminder, these are cohorts of

patients defined by the therapies they were taking at the end of the study. That is, they are not randomized cohorts of patients and, as such, these results need to be interpreted with caution because of the potential for bias here.

But the four cohorts represent first patients who were taking blinded study drug only, that is, without additional hydrochlorothiazide or other antihypertensives; patients who were taking blinded study drug along with hydrochlorothiazide as study therapy but no other antihypertensives; patients who were taking blinded study drug and other antihypertensives in addition to hydrochlorothiazide; and patients who at the end of the trial were no longer taking blinded study medication.

In this table there are four rows representing the composite endpoint and the three components of the composite, cardiovascular death, stroke and myocardial infarction. That is orientation to the table.

In terms of running through the results, we are only beginning to absorb the results ourselves and I am not sure how much I can say about them, but you do see little difference here

in the first column between the two treatment groups for those patients on blinded medication only; a benefit for losartan in the second cohort with hydrochlorothiazide; no difference for those with other antihypertensives; and a benefit for those who are off study medication.

DR. BORER: Does anybody want to question these data further or just try to digest them and include them?

DR. LINDENFELD: Would it be possible for us to get a copy?

DR. BORER: Could everybody get a copy? Can we get copies of this chart for everybody, please?

DR. SNAPINN: Yes, we will do that.

DR. FLEMING: There is a lot to absorb here but, as Steve points out, one needs to be careful since these aren't randomly configured, what we call proper subgroups. Looking at stroke, which is where the signal seems to be in these data, the stroke differences are of different magnitude but in the same direction in all of these four subgroups, improper subgroups.

DR. BORER: We will get copies of these. Everybody can look at them. Maybe we will ask you

some questions about them later but thank you for providing this information.

I am sorry, I should have done this earlier but before we continue our grilling of you, Dr. Keane, and your colleagues, because the information that he will present is undoubtedly relevant to the questions we are going to ask, I would like to ask Dr. John Lawrence, who is the mathematical statistician for the FDA, to present the ethnic subgroup analysis that he did. Then we can move on to ask you more about that.

FDA Presentation

Ethnic Subgroup Analysis from the LIFE Study

DR. LAWRENCE: Good afternoon. My name is John Lawrence. I am a statistician with the FDA.

First, the outline of my presentation, I will start with some general issues about subgroup analysis and talk a little bit about some other studies, and then talk about the LIFE study subgroup analysis, and then a summary.

In a clinical trial we are trying to make an inference about the overall effectiveness in a population and the trial is designed to answer that single question. The effectiveness is not uniform across individuals or across subgroups. For

example, if a drug lowers diastolic blood pressure by 8 mm you know that every single patient is not going to get exactly an 8 mm reduction so you have to increase the dose or add different drugs. There are many possible explanations for this, including pharmacokinetic variability, genetic or environmental differences and differences in the disease pathogenesis.

A successful clinical trial shows that as a group a large number of patients treated with the test drug will be better off, and it does not show that every individual will be better off by taking the test drug. Subgroups can be surrogate markers for genetic or other factors that affect individual responses to a drug. So, you might think that individuals within a subgroup would be more like each other than they would be to the other members of the population.

In general, we use confidence intervals for treatment effects within subgroups to describe what was observed in the trial, and we expect to see differences in the point estimates. Generally we don't do any formal test of hypotheses for subgroups because there are small sample sizes and there is low power to do any of these tests. The

analysis is usually post hoc and there are different ways of testing for interactions.

In general, a subgroup analysis is intended to explore the uniformity of the overall effect and it is usually informative only when there is a significant overall effect. If there is no overall effect, then there is a relatively high chance of finding false-positive effects in subgroups. If there is an overall effect, there is a relatively high chance of finding false negatives, at least in terms of point estimates going in the opposite direction.

Interactions can be separated into two different types. A quantitative interaction is when the treatment effect varies in magnitude by the subgroup but it is in the same direction. This is the kind of interaction that we expect to see and it doesn't worry us too much.

A qualitative interaction is a more serious kind of interaction. This is when the direction of the treatment effect varies by subgroups, in some cases positive and in other cases negative.

This is a picture to show the different kinds of interactions. This line, here, shows that

two drugs would be equal. On this side it would favor the test drug; on this side it favors the control. This is exaggerated. We usually don't have this level of precision in subgroups in a clinical trial, but just to make the point here, in a quantitative interaction, in both subgroups it is on the same side so it is in favor of the test drug. But these are clearly of different magnitude. For a qualitative interaction they are on different sides of the line. So, here it is pretty clear that for this subgroup the test drug is worse than the control, and here the test drug is better than the control. With this type of interaction it is not so serious because although the subgroup doesn't appear to have the same magnitude as this one, it is still in favor of the test drug.

Usually the first level of screening is to just look for the quantitative interaction as the first level of screening. If a quantitative interaction is found, then you can go further and look for a qualitative interaction. There is a test that can be used to test for that. It is a likelihood ratio test. It tests the null hypothesis that the treatment effect in all

subgroups is in the same direction, and the test is defined by calculating the probability of the data under the null hypothesis and the probability of the data under the alternative hypothesis and looking at that ratio. If that ratio is large, that would indicate that one of the hypotheses is more likely to produce the data than the other one.

There is a more intuitive way of thinking about this test. If the point estimate of the hazard ratio in both subgroups is on the same side of 1, then there doesn't appear to be any evidence of a qualitative interaction and you could define the test statistic to be zero. If the point estimates are on opposite sides of 1, then the further they are from 1 gives you more evidence of a qualitative interaction. So, you could standardize each of the point estimates by the standard error and take the one which is smaller in magnitude. That is the level of evidence of a qualitative interaction. These are definitions of the Gail-Simon test.

So, the summary of the general approach to subgroup analysis is that it is generally an exploratory exercise. There are different types of interactions and, because it is normally post hoc

and hypothesis generating, if you find something there to really find out whether it is real or not you tend to look for biological plausibility or evidence from other studies to confirm what was observed.

Now I will move on to some evidence that is external to the LIFE study. From hypertension studies there are sometimes differences in effects by racial subgroup. In the losartan label it says that Cozaar was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients. So, this is an example again of a qualitative interaction. Similar statements can also be found on labels for beta-blockers.

I don't want to make too much out of the other studies because some of this data has not been reviewed by the FDA, but I just want to report what the authors said. For the SOLVD trial the authors reported that a significant reduction in the risk of hospitalization was found among white patients but not in blacks.

For V-Heft II the authors reported a reduction in mortality was observed in whites but not in blacks. Those authors also point out that

these conclusions must be viewed as hypothesis generating and that a prospective trial in black patients would be needed to test this hypothesis.

In the LIFE study, you have already see some of this already, approximately 9000 patients were randomized and about 500 were blacks and nearly all the blacks were from the United States.

The subgroups we generally tend to focus most on are the United States region, gender, race and age. So, when you look at the subgroups this way these are the confidence intervals that you see. Again, for most of them you see quantitative interactions, differences in the point estimates but on the same side of 1. But here you see a difference kind of interaction.

Since most of the patients in the study were white, these two survival curves for white patients alone look similar to the overall results. The way that you have seen the curves before was upside down. I am showing the event-free rates so to start out nobody has any events and at five years 90 percent still do not have an event, or 10 percent do have an event. So, this is in favor of losartan.

In the black patients it is in the

opposite direction. The survival curves are in favor of atenolol. Nominally, this is a significant p value here.

A different way of looking at the same information is to look at the hazard rates. The survival curves accumulate over time, whereas the hazard rate shows the risk only during that time. For example, during the first year there were approximately 30 events per 1000 patient years in the atenolol group and approximately 25 in the losartan group during the first year for white patients. This hazard stays fairly constant during the whole six years of the study and it is nearly uniformly in favor of the losartan group. The vertical lines here show the confidence intervals.

When you look at the black patients, the confidence intervals are going to be much wider because of fewer patients. Nonetheless, it looks like during each of the years the difference is in favor of atenolol having a smaller risk each year.

Now I am going to show the three components of the primary endpoint by race. For CV mortality in white patients, it is in favor of losartan. In black patients it starts out in favor of losartan but at about year two the curves cross

over and there appears to be an advantage to atenolol. These p values are not significant. I am just showing whatever the data there is.

For MIs there is no difference in white patients. There appears to be an advantage to atenolol for black patients, with a non-significant p value again.

For stroke, a very significant advantage for the losartan group in whites and a nominally significant advantage for atenolol in blacks.

To try to look for internal consistency of the result I looked at the demographic subgroups within the black subgroup. In the top row here is the overall comparison for all blacks. This is the number of events and the total number of patients in the losartan group and the number of events in the atenolol group. For all blacks the hazard ratio is 1.67. If I look at black females alone the point estimate is about 3. For black males the point estimate is about 1.2. For blacks under 65 the point estimate is 2.5 and for blacks over 65 it is 1.31. Two of these p values are nominally significant but the point here is that they all point in the same direction.

If I apply the Gail-Simon test that I

talked about earlier for a qualitative interaction, the p value is 0.016. However, you have to be cautious in interpreting this p value because there were many different subgroups that I could have looked at and it is impossible to correctly adjust this p value for the multiple comparisons.

There were three subgroups prespecified in the statistical analysis plan as being of special importance, U.S. region, diabetics and patients with isolated systolic hypertension. The black subgroup was not one of those subgroups. A formal analysis plan would list all the important groups and specify a method to correctly adjust for the number of tests.

Nonetheless, it still is a pretty rare finding that a confidence interval for a subgroup would go in the opposite direction than the overall effect. So, to get some idea of how unlikely this is you can do these following calculations. If I assume that the true hazard ratio in all subgroups is 0.869--that was the point estimate for the overall effect--the probability that the point estimate for the black subgroup would go in the opposite direction is 28 percent, and the probability that the point estimate for any of

those subgroups listed would go in the opposite direction is 37 percent. So, it is not very unusual to see one of the point estimates in the wrong direction.

However, it is very rare to see the entire confidence interval go in the wrong direction. The probability that the black subgroup would be in the opposite direction, the whole confidence interval, is 0.003. The probability that any of those subgroups would have a confidence interval in the wrong direction is 0.005. That means that another way of looking at this is that you could look at a thousand different clinical trials and in only five of them would you see one of the confidence interval, out of those demographic subgroups, go in the wrong direction. So, it is very rare to see it.

There are other approaches. For example, in those calculations I just showed you I assumed that the overall treatment effect, 0.869, applies equally to all the subgroups. You can instead assume that the treatment effect varies by subgroup and the effects come from some distribution. However, to do this you need to make some assumptions about this distribution that the

effects come from. For example, what is the variability and do they have a common mean, or would you expect one of the subgroups to have a larger effect? Without a consensus in the scientific community about these assumptions, you cannot make any strong conclusion.

In summary, it is not rare for a subgroup to have a point estimate in the wrong direction, but it is rare to have a confidence interval in the wrong direction. Exactly how rare is impossible to determine from a post hoc analysis. In general, post hoc analyses are hypothesis generating.

Although the p value from the test for qualitative interaction is significant nominally, there are many factors that can mitigate that value. Some factors that may decrease the strength of evidence are that there were multiple subgroups and, therefore, many chances to find something unusual, and there was no prespecified analysis to control for multiplicity.

There are factors that may increase the strength of evidence. There may be racial differences that were observed in other related studies. There appears to be a consistency of the effect within black subgroups. There appears to be

a consistency in the three components of the primary endpoint, and there was a consistency across different analysis methods. That is it.

DR. BORER: Thank you, Dr. Lawrence. Are there any questions from the committee about Dr. Lawrence's presentation? Tom?

DR. PICKERING: You showed, and didn't comment on it, a similar analysis with age which looked as though the younger and older groups were on the opposite side of the null point but there wasn't a genuine qualitative difference. Is that correct? Could you show that slide again?

DR. LAWRENCE: It certainly appears that this is a difference in magnitude at least because the confidence intervals appear not to overlap. It is hard to say whether this is a genuine qualitative interaction or not. My memory is that the sponsor did this. I don't know if they did it exactly by categorizing age in this way so I am not sure.

DR. BORER: Yes, the FDA medical review showed a progression of benefit as patients got older, so consistent with this. Any other issues that we want to raise with Dr. Lawrence now? We can always ask him more questions as we go along.

No? If not, thank you very much. That was a very illuminating presentation. Now, Dr. Keane, if you want to come back we will move ahead. John?

DR. NEYLAN: Thank you. Bill, let me see if I can develop a line of thought with you and perhaps you can then clear up some holes in my understanding. To start, and I wish I had a visual aid here but to start, the primary endpoint is in large measure driven by the difference in the rates of stroke. In the agency's analysis there is a very strong interaction between the occurrence of CVA and atrial fibrillation. The appearance of atrial fibrillation appears to peak bimodally, that is very early, first quarter and then at the end of the study, fifth year. My question is, it is a bit counter-intuitive to me why the atenolol-treated group should have a higher rate of atrial fibrillation, and I am wondering if there may be a methodologic issue that plays into that, namely, the possibility that we are witnessing a rebound effect with the withdrawal of beta-blockers from the group randomized to receive the atenolol.

With that hypothesis, you might then expect that there would be a higher rate of atrial fibrillation in patients who were withdrawn from

beta-blockers and that, in turn, might predispose them to the risk of CVA. So, I am wondering if you have any data that begins to address this issue with on-therapy analyses, the occurrence of atrial fibrillation, its relationship to the occurrence of stroke and, again, the occurrence of atrial fibrillation in the presence or absence of the assigned treatment regimen.

DR. KEANE: Thanks, John. Yes, there are a number of data analyses that we can look at and we have looked at atrial fibrillation in a number of different ways. Probably the most effective way of looking at this is with a time-varying covariate analysis that we had. Clearly, it had an impact upon it. We have additional data that we would like to share with you but I just wonder if I could just make a couple of comments before we get into the question.

Doug and I chatted a little bit before the meeting, and I guess I may have mis-spoken about the ambulatory blood pressure monitoring data. Just so that we are absolutely clear about it, we have submitted the data to the agency. The agency has the data and they are in the process of reviewing it, and I think that covers what Doug

wanted me to say. So, we have actually been in communication with them and they know what we are doing so we are both on target with that, but just to clarify the record.

I might just make one other comment too about the presentation on the black subgroups. In a sense, we actually agree with much that has been presented today by the FDA, and in fact we don't really see very much of a difference. I just would also like to underscore the fact that in the black population, which represented only 550 patients, the event rate was also very low. We saw less than 50 in each of the arms. So, as you are thinking about these things, I think it is important to recognize that it is a small group with a small event rate and, yet, we did see this important qualitative interaction. That qualitative interaction was really the only one that we were able to observe here, and we felt very strongly that we should bring it forth as an issue that we have uncovered during the analysis. So, I think that would set this straight.

Now let's get back to a. fib., John. I think we have some data that we can present here, which I have already alluded to, John, in terms of

the atrial fibrillation data that provides the time-varying covariate analysis of atrial fibrillation.

John, just to be clear, we felt that probably the most reasonable way to look at something that was not measured consistently on a daily basis or even on a monthly visit--probably the best way to do this, and there were three different approaches that we used, we had it as an AE event that was reported. We had it in the narrative that the investigators provided to us. And, we had it at the ECG level and this is new onset atrial fibrillation looking at our event rate.

As you can see, the hazard ratios are approximately the same, 0.85, and when we adjust for this it is 0.87. So, there really isn't very much of an impact of atrial fibrillation in terms of the occurrence of this during in-trial. So, I think that was one of your questions that you had.

I think the other question--John, was there something else that you brought up?

DR. NEYLAN: Yes. First, let me harken back to what you just showed there. If you look not at the composite but at the relation of atrial

fibrillation and the occurrence of CVA, is there significance seen there? In the agency's document it appears to be so.

DR. KEANE: Yes, and if you look at what the agency has done, it is all a. fib. in whatever proximity to the event. So, it is anybody who may have had a dose adjustment in their atenolol and whether or not that was associated with the onset of new a. fib. I think, you know, from a clinical perspective one has to sort of at least raise the question whether or not that is a completely fair analysis because stopping or changing a dose months or years out of sync with an event might provide some question.

I think, nonetheless, what we did see is that both in the atenolol group and in the losartan group there were approximately the same numbers of events in terms of changes of occurrence of atrial fibrillation when one looked at dosage change. Again, we didn't have it in immediate proximity. The closest we could look at was about 14 days. Within that, with any dosage adjustment it was about the same percentage. Within that context, losartan consistently had an effect that seemed to have a lower outcome result in terms of the

outcomes that we saw associated with atrial fibrillation.

DR. NEYLAN: Could I ask a few follow-ons? I am wondering if you have any data that look at the possibility that the new onset of atrial fibrillation may have any relationship to the withdrawal of atenolol as possibly a consequence of a rebound phenomenon?

DR. EDELMANN: A couple of things in regard to that. First of all, I just want to go back to one thing that Dr. Keane presented in his main presentation and just confirm this, atrial fibrillation that developed during he course of the trial was associated with a significant increase in risk, a five-fold increase risk of an event of any type irrespective of treatment. So, the develop of a. fib. was a harbinger of events no matter what therapy patients were on.

With regard to the occurrence of events, particularly stroke, in relation to dose change mediated through atrial fibrillation, that is something that we looked at in detail and I want to respond about that. We looked at this in a couple of ways. The first was to look at the consequence of dose change on the risk of an event. We did in

the pooled treatment groups and then by individual treatment groups.

I think it is not a surprise that when we look at dose change the event rate is extremely high in the following period. We believe that this is a consequence of the fact that the reason for dose change and the reason for the event are often one and the same, rather than that the dose change leads to the event. So a patient, for example, is hospitalized. Their drug is stopped and then they die of some cardiovascular cause. So, it is the same thing that is causing the event is causing the dosage change. Therefore, when you look at it you see a high rate of events associated with dosage change not just in the atenolol group but in the losartan group as well. They are really quite high depending upon which event you are looking at, extremely high for example for cardiovascular death. But, again, I think this is a function of the way we collect data and the inability to separate cause and effect.

In terms of the relationship between atrial fibrillation and stroke, another thing you asked particularly about, again, the medical reviewer for the FDA, if I have understood it

right, has done the analysis on the basis of adverse events reported by investigators of atrial fibrillation. We have supplemented that with the ECG information so we have a couple of ways of diagnosing atrial fibrillation.

What I can show you, similar to the analysis that Dr. Keane put up, is a presentation of impact the impact of accounting for the difference in the new occurrence of atrial fibrillation during the trial. It is patients who didn't have a. fib. at baseline and then did go on to develop a. fib. during the trial, accounting for that, what happens to the outcome on stroke.

If I could have slide 998? Just to be clear, this one is not new onset but all a. fib. so all patients are included here, including those who might have had atrial fibrillation at baseline. You see when you account for the endpoint of stroke for the hazard ratio, changing from 0.74 or 26 percent risk reduction; when you adjust for the occurrence of atrial fibrillation during the trial it goes to 24 percent.

So, it is not a big effect. But if you look just at the new onset, slide 1001, now just by eliminating the patients who had atrial

fibrillation at baseline and looking only at the new occurrence of atrial fibrillation during the trial--this is for the primary endpoint, you see there is a bigger effect here.

Within the limits of this kind of an approach, and again I remind you atrial fibrillation was measured by investigator report whenever it happened and/or as detected on the annual ECG at the ECG core center so it is an imperfectly measured thing and not 100 percent measured in connection with the event, there does appear to be some magnitude of benefit on the primary endpoint.

DR. TEMPLE: Can you show us this for stroke?

DR. EDELMANN: For stroke, yes. It is the same thing for stroke. This is again among the cohort of patients who started out without baseline atrial fibrillation, the consequence of adjusting for new atrial fibrillation on stroke. It is a similar magnitude of effect. So, the hazard ratio goes from 0.74 to 0.8 or 26 percent risk reduction to 20 percent risk reduction. So, it does suggest that there is some association within the limits of such an analysis.

DR. NEYLAN: Then, could I ask even though this is a population at risk for new onset development of atrial fibrillation, I would expect that it would be fairly evenly distributed between these two treatment groups. The possibility of a withdrawal syndrome as a result of removal of a beta-blocker might potentially increase the risk in that population of patients. Do you have any data that looks at the incidence of new onset atrial fibrillation development in those patients in whom atenolol was withdrawn, and is there any data also looking at the time course between that development and the withdrawal of the drug?

DR. EDELMANN: You are talking specifically about the development of atrial fibrillation so what I mentioned before is the development of endpoints that we measured as part of our primary composite of the secondary component endpoint. As I said, there is a strong connection between the risk of an event and dosage change, including largely discontinuations.

This is discontinuation and a. fib. Let's see this one. The same kind of thing is seen. This is the relative risk increase, so the hazard ratio for the occurrence of atrial fibrillation

when there is a discontinuation of drug. You asked about atenolol. That is over here. It is almost a 13-fold increase in risk but it is not specific to atenolol. It is associated with losartan to the same degree, which leads us to think this is not unique to beta-blocker withdrawal but, again, there is cause and effect mixed up here. The reason for discontinuing the study drug and the reason for the development of atrial fibrillation may be one and the same so they appear to be highly associated like this.

DR. BORER: Does that answer the question, John?

DR. NEYLAN: I will accept that.

DR. BORER: JoAnn?

DR. LINDENFELD: Just a follow-up on this atrial fibrillation issue. Amniodarone is used much more commonly in Europe than it is here for atrial fibrillation. I wonder if you can tell us what the use of amniodarone was at baseline and maybe at one year? I guess what I am getting is was amniodarone withdrawn more commonly in the beta-blocker group because of bradycardia? Is that the explanation for this?

DR. EDELMANN: Right, it is not data that

I have at my fingertips. We can look to see what the use of amniodarone particularly was at baseline and then in concomitant therapy and see if I can come back to you with those numbers.

DR. KOWEY: Jon, can I make a comment? Peter Kowey, consultant for Merck. The atrial fibrillation data I think is extremely important; obviously very, very important. But just so that the committee understands that this was not a study that was really out to look at atrial fibrillation as an endpoint, there were very infrequent samplings of echocardiograms throughout the course of the study. It wasn't systematically looked at. The analysis that you saw was a post hoc analysis. So, I really think that it is extremely hazardous to get too involved in a discussion of atrial fibrillation.

Having said that, there is certainly biological plausibility that a drug such as losartan could have an effect on atrial fibrillation, given what we have seen recently with this whole class of compounds and drugs in general which have an effect on the angiotensin system in terms of fibrosis and also in terms of the changes in left ventricular hypertrophy.

In addition, I would not be one bit surprised if a large proportion of the contribution to the stroke reduction that was seen in the study had something to do with AF. It is certainly plausible. But I think to try to drill down any further on that, either from the point of view of concomitant antiarrhythmic therapy or beta-blocker use or withdrawal, is just probably stretching it a little bit further than you can do it. It is very interesting though, I must say.

DR. KEANE: Dr. Borer, I wonder if I could respond actually to some of the questions that were raised this morning, to go through some of the discussion points that came up and we can get some further discussion on that. Is that okay with you?

DR. BORER: It is but can you begin with the questions that came up about the effectiveness of the comparator?

DR. KEANE: We can.

DR. BORER: Can you provide us the evidence that, a) the comparator regimen is effective and, b) that atenolol is important in that effectiveness?

DR. KEANE: Well, I think what we have already discussed and presented this morning was in

a part of my presentation and also some of the data from our meta-analysis looking at a number of different trials. So, let me just re-review that with you, if that is of help.

DR. BORER: Yes, I think we are going to need a little more detail. We saw your meta-analysis but you heard the questions about it. Tom?

DR. FLEMING: Yes, Dr. Keane, the meta-analysis was certainly very helpful. Rather than revisiting that entire meta-analysis, the aspect that at least I would like to better understand is what the historical data would tell us what is known in this setting about the effect of atenolol in the presence of a diuretic's regimen. So, what I would really like to see is comparative data that looks at diuretics and atenolol against diuretics so that we can get a sense of what atenolol is adding in the presence of diuretics ideally in an LVH population.

DR. KEANE: I think one of the problems that you are having and we had with this data is that when you look at what has actually been published, most of the studies either had diuretics added to beta-blockers or beta-blockers added to

diuretics. It is very difficult, and it has been very difficult for us to tease out, if you will, the difference of beta-blocker effects specifically or beta-blocker/diuretic effects specifically within any of the clinical trials that have been done. Lots of patients clearly have been treated with the combination, and we have seen some of those data this morning. Both Dr. Edelmann and I have presented them and if you don't wish, we don't have to go through them.

I think one of the things that we should recognize is that at least in the populations with hypertension that we are talking about, you know, most of the studies that have been done haven't specifically addressed the patient population that we have, i.e., with left ventricular hypertrophy. But as I alluded to in my presentation, it doesn't mean that they weren't included. They were not excluded from these trials.

If you look at epidemiologic data and what-have-you the association of hypertension with left ventricular hypertrophy, particularly in this patient population, is some 20 percent. So, that is why we pooled all of these studies in a meta-analysis to try and come up with the best

estimate for the beneficial effect that we are seeing.

The other reason, of course, that we used left ventricular hypertrophy is because I think it is clearly a marker of risk in those patients that have left ventricular hypertrophy. Based on a variety of different epidemiologic-based data, they are clearly at increased risk for cardiovascular events. So, that is really what I have in terms of information to shed some light on this particular complicated issue.

DR. PICKERING: I would like to have further discussion about the meta-analysis. Could you show slide 23 again, please? If you look at the JNC VI recommendations, they actually quote a meta-analysis done by Bruce Psaty where he had 18 randomized studies with beta-blockers and diuretics. They concluded that beta-blockers protect against strokes and congestive heart failure, whereas diuretics not only protect against them but also MI and total mortality.

If you look at your meta-analysis, I think the only two studies where there was a randomized comparison between a beta-blocker, a diuretic and a placebo were the two MRC trials. I think those

results are largely driven by MRC where there are 13,000 patients. These were younger patients. I think the average age was 55 whereas the average age in LIFE was 67, and that is closer to the MRCII where the average age was 70 and where there was no hint of any benefit from beta-blockers.

Certainly in my practice I would not use a beta-blocker as a first-line drug in patients over the age of 60 or 65. The analysis that we just saw suggests that there was, again, no suggestion of any benefit. If anything, it was going the other way in patients under the age of 65. So, how did you select these particular studies for your meta-analysis?

DR. EDELMANN: As I alluded to before, the Psaty meta-analysis is one that we are familiar with but it did not include, I think, the UKPDS study for whatever reason; I think it probably wasn't out at the time. What we did, we looked at all the antihypertensive treatment trials and selected, in this grouping of five, those trials that had at least a beta-blocker-anchored regimen as one of the options, if not the only option. So, that was our criterion. There were a couple of other things. There had to be a sufficient

exposure in terms of patient years and there had to be information on endpoints reported in the papers that would permit us to provide the cardiovascular event analysis.

We went to this step because we felt that we could focus on any one individual trial but that the best estimate for the effect of atenolol as represented by beta-blockers is from all of the data, not just any one individual study. For example, the MRCII trial, which you said is the likeliest similar population in age, is a trial that had a tremendous amount dropouts and lost follow-ups. So there are limitations to the strength of the conclusion from that trial just on the basis of how it was done.

So, rather than rely on that kind of picking and choosing, we had a more general approach, looking only at the studies that involved beta-blocker-anchored therapy to start with. Then we supplemented that--and maybe I can just show it again--with the other direction, the diuretic plus beta-blocker studies and that added an additional three. That just strengthens the evidence that this approach, a regimen of diuretic and beta-blocker, is effective in reducing outcomes

including coronary heart disease outcomes in hypertensive patients.

So, it is our view that the best estimate of the data, not exactly perfectly applicable to the LIFE study population but a pretty good assessment, supports the notion that this treatment approach is effective. The ALLHAT trial confirms that. A diuretic regimen with a large proportion of patients having beta-blocker added on is quite effective in preventing outcomes in hypertensive patients.

DR. BORER: I think one of the issues here that everyone is trying to grapple with is what is the contribution of the beta-blocker to this regimen. The reason for that may be that there will be a question about the strength of the excess benefit of your regimen versus the comparator regimen. Some idea about the contribution of the components of the comparator to the overall effect of the comparator might be helpful in giving us some sense of the strength of evidence that we are going to be judging. You know, that is sort of what we are looking for. It sounds like you don't really have much information.

DR. EDELMANN: I think it is an excellent

point and it is exactly the issue, but there are two ways of looking at this. The perfect study that you are referring to would be one in which there was only a beta-blocker compared to no treatment or there was a beta-blocker added on to an equal background of treatment, and that information is just not available, or at least to our understanding it is not available in the literature.

The one place where there is evidence of a comparison of a beta-blocker/atenolol with an equal concomitant medication applied where you could tease out the difference in the impact of the beta-blocker is the LIFE study which shows the benefit of losartan. Not wanting to get into a circular argument, I think if we relied on the external historical data to establish a beta-blocker-including regimen as being effective, the LIFE study then serves as evidence of the contribution of losartan over atenolol on that similar background. Maybe that is helpful.

DR. BORER: Just for argument's sake before we get to all the other comments, did you look at the hypertensive subgroups of any of the post myocardial infarction studies?

DR. EDELMANN: Well, we looked at this but they are not well reported and we felt that the post MI studies randomized patients only after the occurrence of myocardial infarction, which represents a different kind of patients. Rather, in our assessment we focused on the hypertension trials because we thought that was the most relevant.

DR. BORER: Bob and then Tom?

DR. TEMPLE: Actually, Jeff, this is for you. The multiple drugs in hypertension regimens are used to get the pressure down to some goal. Are you expressing doubt as to whether lowering the blood pressure 6 mm or 7 mm more with, say, a beta-blocker has some role in improving outcome compared to using a diuretic alone?

DR. BORER: Certainly not, Bob. I would never suggest such a thing.

DR. TEMPLE: Well, the difficulty with all these things is that what I understand them to be trying to do is to show that regimens based predominantly on having a beta-blocker in one group and not having a beta-blocker and accepting whatever you accept, and the other to show some expected benefit on outcomes. It is hard nowadays

to test that prospect any further because no one will allow you to leave a patient incompletely controlled, and that has been a problem actually for many years. What the old data show is that even if you add it to a diuretic or have it alone you have sort of the predicted, expected every drug has this favorable effect on outcome from a beta-blocker.

DR. KEANE: Dr. Borer, I want to reemphasize what Dr. Temple has said. I mean, it is very clear that in the practice of medicine in today's world you are looking at how to get the blood pressure down to a specific target. Therefore, the issue that we are all confronted with is, in fact, getting the blood pressure down. Dr. Neaton is our statistical consult and I am just wondering if he could actually make some comments about these issues.

DR. NEATON: Yes, I was going to respond to two points. I am Jim Neaton, from the University of Minnesota. First, Tom, in response to one of your earlier questions, there are actually four trials that have been head-to-head comparisons between diuretic and beta-blocker. Those are the two MRC trials, IPPPSH and HAPPHY.

The point estimate for the odds ratio which favors the diuretic is by seven percent, and it is not statistically significant. The bounds are minus 18 to 5 percent favoring the diuretic.

If you go back I guess almost ten years now to one of the original overviews by Collins, and I don't think the story has changed that much, they actually reviewed the beta-blocker trials, the diuretic trials, as well as the head-to-head comparisons and concluded that there really isn't sufficient data to argue that one is superior to the other. I believe that was Psaty's kind of conclusion as well in 1997 or 1998 in which he looked at these trials minus the diabetic trial in the U.K.

Concerning Bob's last point, just listening to some of the questions this morning, two about sorting out the types of therapy, I don't think you can have it both ways. If you are going to do a trial to test the paradigm that really equivalent blood pressure lowering with different regimens gives rise to differential clinical events, strokes and heart attacks, then I think you have to accept the fact that to control blood pressure many treatments have to be used. To sort

them out I think really is a very hard thing to do in a trial like this.

So, I think what you have here is a very well done trial with a regimen which is predominantly losartan and one that is predominantly atenolol that you can kind of compare. Actually, it has the merit compared to some other trials, in which the regimens which are being used where the comparator is one which is used an awful lot in the real world.

DR. BORER: Can I just clarify one thing? I don't disagree with anything that you said. I think you are absolutely right and I think this was a superb trial and on, and on, and on. That is not the question I am asking. I am asking to what extent I can infer from the comparator data that this trial has shown an important difference from what we could see with the comparator or with nothing.

DR. NEATON: I think the response earlier was that there are no trials, there is no big set of data that you can go to among people with LVH. Unfortunately, even the trials that have been done have not published those subgroups to look at. However, as the discussion earlier alluded to on

subgroup analyses, I think it is very unusual to see the kind of differences in response in those with LVH compared to other subgroups. So, I think it is a very reasonable inference to assume that the effects you see in the diuretic/beta-blocker trials apply here to this population.

DR. FLEMING: Jeff, can I follow-up?

DR. BORER: Yes, please.

DR. FLEMING: Jim, just to have you kind of respond to this as well I think just to try again to at least phrase the question as I see it, suppose one looked at the LIFE trial and says, all right, we have a comparison of two regimens and we have losartan with diuretics and we have atenolol with diuretics. Suppose you look at these data and you say I am not fully persuaded here that even though there are suggestions of differences, particularly in stroke--I am not fully persuaded by the standard of strength of evidence of two positive trials that we have shown superiority of losartan to atenolol. If, in fact, you did I would have much less concern about the next issue.

But if you are not fully persuaded, then one is left with trying to see what supportive evidence there is that is relevant here. I am

persuaded by the historical data that had been presented, the meta-analyses, that diuretics and atenolol as a therapeutic strategy is effective. It is not clear to me, however, what atenolol is providing in that therapeutic strategy.

So if, in fact, I am looking now at diuretics plus losartan against diuretics plus atenolol, if I know that atenolol itself is very influential in that combination, in the active comparator, then I am reinforcing the strength of evidence that I have that losartan is truly contributing meaningfully to the beneficial effects in the outcome.

What you have said is that diuretics as compared to atenolol--you are talking about those differences and atenolol may, in fact, be effective but is it additively effective in the presence of diuretics? And, we can't entirely rely on blood pressure because the whole argument that the sponsor is giving here is that there is a lot more to effects on clinical endpoints than blood pressure. In fact, LIFE is attempting to tell us that even though we see minimal differences at least in systolic blood pressure, we are seeing substantial differences in stroke.

So, if we are left with some uncertainties. I mean, the bottom line, the negative side of this would be to say, sure, atenolol is important but in the presence of diuretics it doesn't add a lot. If, in fact, it doesn't add a lot how do I know for sure that in our regimen with losartan it is not mostly the diuretics? So, it becomes very important to try to understand historically how much does atenolol add to the diuretics.

DR. NEATON: Well, I think some of the trials that Bill showed earlier that used both contributed to that. Plus, most of the old trials that looked at diuretics, atenolol or beta-blocker was a second-line agent. That is the way the trials were done because there blood pressure wasn't controlled to the same level that we try to control it these days but additional drugs were added.

DR. FLEMING: But what I am hearing, just in closing, is that at least you are not able at this point to put forward randomized comparative strategies that look fairly clearly at what addition of atenolol to diuretics would provide.

DR. NEATON: I think the best data to

address that question are the four trials that have a head-to-head comparison of a diuretic versus a beta-blocker. There at least you have good evidence that they are pretty comparable.

DR. FLEMING: But that doesn't tell us that when you then add in the beta-blocker to the diuretic you get something even better than the diuretic-based regimen would provide.

DR. KEANE: Except for blood pressure control. I think that is an important factor to remember here.

DR. FLEMING: Well, can you show us that?

DR. KEANE: The blood pressure control? Sure, we can go back over that. In fact, that was in Dr. Edelmann's presentation. Do you have the blood pressure slides? I am sorry, I maybe misunderstood what you were saying. You were looking for the blood pressure in the historical trials or in our trial?

DR. FLEMING: No, I am looking for the meta-analysis historical evidence to try to provide a clear understanding of what atenolol is adding to the regimen based on diuretics to basically refute an argument that would say once you got diuretics you get a favorable result and the addition of

atenolol, or losartan for that matter, doesn't meaningfully influence outcome.

DR. ZEGER: I am Scott Zeger, from Johns Hopkins. I just wanted to say if this trial gives evidence, strong evidence that losartan plus concomitant therapies is better than atenolol which is useless, let's suppose, and concomitant therapies, if you believe those concomitant therapies are effective, then you have the added strength of evidence I think you are asking for.

DR. BORER: That would be true if the benefit of the combined losartan plus whatever clearly is strongly compellingly better than the comparator. I think the question that Tom is raising here is what is the strength of evidence that the losartan-based regimen actually is better than the atenolol-based regimen. It is one trial with a p value that is not as strong as we would usually see for one trial.

DR. ZEGER: I understand your question but I think Tom's point, if I understand it correctly, is if this were 0.02 and 0.01 on stroke against something that was useless you might have some reservation. But if it is something that has been demonstrated to be effective, whether that effect

is the result of the atenolol or the diuretics, what is the difference?

DR. BORER: Tom?

DR. PICKERING: Yes, I would like to get back to the age issue. You raised two other studies, IPPPSH and HAPPHY. IPPPSH was stated to be a comparison of beta-blockers and non-beta-blockers versus diuretics but in both IPPPSH and HAPPHY the average age was 52 so they are comparable to the MRC mild hypertension trial but not to the LIFE population where, again, the average age was 67. If you look at the data on the handouts, there is no suggestion of any benefit from losartan in the blinded only group or really in the blinded plus other group. It is all in the blinded plus hydrochlorothiazide group where it was 17.6 per 1000 patient years in the losartan group and 26.1 in the atenolol group.

DR. EDELMANN: I am not sure if there was a question there but if the implication of the statement is that the difference in diuretic use between the treatment groups is where the benefit is, we don't think that explanation follows based on not just accounting for those non-random groups but accounting for the entire time for diuretic use

and then adjusting for it. This is something I went through before. That is to say, about 70 percent of the time patients were on concomitant diuretics. When we accounted for that in a time-varying covariate adjustment it didn't really make much of a difference in explaining the treatment benefit.

So, that leads us to conclude that, although diuretics may have added to the level of benefit, they don't contribute to the difference in benefit observed in the LIFE study. It is like if you take an analogy of being in a high-rise building and being in an elevator, and the higher up you go the greater the benefit. Where you are off the ground in terms of absolute benefit is something that may be impossible to determine and what got you there, atenolol or diuretic or both. But relative to one another, losartan is at a higher level of benefit than atenolol and both are likely to be off the ground, in other words not no benefit, based on the evidence from the regimen trials where you can't dissect out whether it is the diuretic or a beta-blocker that is getting you up the elevator, if you follow my analogy.

DR. BORER: Beverly and then Steve?

DR. LORELL: Well, I would enjoy hearing you respond a little bit more in depth to Dr. Pickering's comment that I think raised some concern. This is a highly specific and somewhat narrow hypertension population. As has been measured earlier, it is skewed toward the older patient. It applies to the 20 percent of patients who have ECG evidence of hypertrophy and I am concerned about his comment that among prior comparator studies the one that is, in fact, relevant or most relevant to this group is MRCII in which an older population was looked at and his comment that no benefit appeared to have been seen, at least as illustrated in slide number 23.

DR. JULIUS: I am Steva Julius, from the University of Michigan and I was the U.S. coordinator of the LIFE study. You know about MRCII. Fifty percent were lost up front. At the end, only 32 percent were on beta-blocker. So, it is a large trial in the beginning and it is a small trial at the end, and it doesn't affect my thinking as to how useful beta-blockers are.

DR. LORELL: Part two of that question then might be phrased a little bit differently, can you help us with a population from studies done in

the elderly, forgetting about the LVH--we appreciate that the data just isn't there, but in a population that is skewed toward this much more older group of people who are at higher risk of stroke than, obviously, a 55-year old person is?

DR. KEANE: Right, there are a couple of data sets we can show from the literature, and one that has been commented upon is the Psaty database. Maybe we ought to show the meta-analysis from Psaty from a number of years ago so that you can actually appreciate it.

I will mention again, as we have said earlier in the presentation, you know, when we did look at age as a subgroup and we looked at treatment by subgroup interactions there was no interaction term that we could define within the different age groups of individuals within the LIFE study. Nonetheless, we could show this data. Jon, do you want to run through this?

DR. EDELMANN: Yes. Before reviewing those data I just want to go back to a point that I made before which I think is so important I want to reemphasize it. It is possible to draw lots of different conclusions depending upon which study you choose to believe is the right study. So, if

you look at the MRCII trial and say that is the truth, then that tells you one thing about the effect of beta-blocker- or atenolol-based regimens. But we think that it makes more sense to consider all of the data, and in terms of the representativeness of the populations, studies even in younger hypertensive patients and the benefits that are seen in younger hypertensives, we think that it makes sense to apply those data to assessing the benefit of a beta-blocker-based regimen as it does in applying the benefit of the losartan-based regimen based on the LIFE study.

I didn't show you but I mentioned a comparison of the LIFE population to a reference population in the U.S., that is, patients who were eligible for the LIFE study inclusion from the NHANES database. So, that is older patients with hypertension and LVH and very similar characteristics. But I can show you, and I would like to show you if I have the overhead, the same comparison. Now, this is a reference population in the U.S., but not limited to the older group. This is hypertensives who are above the age of 40, I think it is. So, above the age of 40, and then do they have left ventricular hypertrophy? In other

words, they have hypertension with left ventricular hypertrophy but they are not limited to being 55 and above.

If I can find that, what you will see is that the baseline characteristics are very similar between U.S. patients in the LIFE study and this reference population. So, I think based on the characteristics of the patients we enrolled it is not necessary to constrict the applicability of this trial to only older patients and, for the reasons I said before, doesn't make sense to only focus on one trial, particularly MRC II, because of the issues of its conduct and how much you can believe the result. Rather, to look at all of the data for beta-blocker including from the younger hypertensive patients and make an assessment of the relative benefit of a beta-blocker regimen in providing benefit.

DR. BLACK: My name is Tom Black and I am from Merck. The idea is that we are discussing here where there is blood pressure lowering in both groups and there is more blood pressure lowering, and part of that blood pressure reduction is attributable to both the atenolol and to the diuretic, attributable to the losartan and the

diuretic. So, the assumption is that the diuretic is providing all the endpoint benefit, whereas we know from many studies that the further you reduce down in blood pressure, like in HOT, the further reduction in endpoints.

The FDA and medical practice accepts that the more you reduce blood pressure, the better effect you are going to have on reducing endpoints. So, the implied assumption here is that even if atenolol is reducing blood pressure more it is not affecting the endpoints at all and, therefore, sort of how do you know that you are getting any benefit.

DR. FLEMING: I am not assuming that. My questions, which still aren't answered but it may be because there are no data to answer them--just to reiterate, if we go through the progression of controls here you are looking at losartan in addition to a diuretic against atenolol in addition to a diuretic, and ultimately to know what losartan is doing against placebo the comparator is the diuretic. If you are saying the diuretic is not capable of achieving the blood pressure lowering that you saw in your control regimen here, okay, show me that and that is relevant to me but show me

that.

DR. EDELMANN: I think you are right to say the data you are asking for aren't available, and that is because blood pressure treatment trials--this is what Jim Neaton was saying before--have taken the approach of controlling blood pressure by adding therapy as needed. Trials to look at the efficacy in blood pressure, just on blood pressure, have done what you are asking about but trials that have looked at outcomes have not done that. they have added therapy as needed, just like ALLHAT. So, I mean, if that is the evidence you are looking for, it is certainly not there.

But I think it is reasonable to look at the blood pressure lowering data with the knowledge that lowering blood pressure is beneficial from all of these outcome trials to look at the incremental benefit of adding a diuretic to a beta-blocker or a beta-blocker to a diuretic and showing that, when you do that, you see an effective blood pressure effect of one and an incremental effect to that blood pressure lowering when you add a diuretic to a beta-blocker for example.

DR. TEMPLE: Can I just mention something?

DR. BORER: Yes, please do.

DR. TEMPLE: There are hundreds of studies of combination products containing a diuretic with whatever that show that the effects of the two components are roughly additive. That is really not in question. It is true that all the outcome studies we know of take a baseline and then add something to it, leaving unanswered the question of suppose you didn't have the baseline therapy. You never get a specific answer because nobody ever does a factorial outcome study, or hardly ever. But on the mere question of blood pressure, that is really not debatable.

DR. LORELL: But I don't think that was quite what we are trying to get at.

DR. TEMPLE: No, I know that.

DR. LORELL: I think we would all agree with that a hundred percent. I think the concern that was raised in my mind earlier by Dr. Fleming's comment really goes back to the issue that we are here today to look at labeling for an outcome measure, and that is predicated on a comparator being superior to a placebo since placebo was not tested, for good reasons, in this study.

So, the question that was raised earlier was, whether a diuretic or beta-blocker was added

first or second, whether the combination therapy of a beta-blocker and a diuretic is, in fact, superior in an older population to placebo. That was the concern that Dr. Fleming's comment raised and why I was interested not so much in the age 40-year old patient but what can you tell us about this combination relative to placebo in a much older population?

DR. EDELMANN: And that is one of the reasons why in my talk I showed Rodgers and MacMahon. That was an assemblage of data on older hypertensive patients and those were all trials that were based either on a beta-blocker regimen or a diuretic regimen, and in most cases if it was one, then the other was added.

Let me put that up again. This is not in the form of whisker plots but what you can see is the reduction in the odds down here for stroke, coronary heart disease and vascular deaths. So, these are five trials in elderly hypertensives. This is Coope and Warrender, SHEP, MRCII. There are two more that over age, SYSTUR and STOP. So, they are all beta-blocker and/or diuretic-based regimens and they show, in what we thought was a relevant population, the benefit of lowering blood

pressure with a regimen approach to attaining blood pressure control. You can see the magnitude of benefit there. Does that help?

DR. LORELL: It may be that the data that we are trying to tease out specifically about the combination is not quite there to be pulled out from this.

DR. BORER: Steve?

DR. NISSEN: First of all, I don't think we have actually said this well enough, but let me say that I really want to compliment the sponsor and the investigators for doing this study in the first place. I think it is to the credit of the company and of the investigators. This is an important study and, you know, obviously we are drilling down to some very narrow details here but it doesn't take away from the fact that you all invested a lot of time and energy in doing this.

Having said that, I want you to put up slide 109, if you would, and I want to narrow down a question just to make sure I understand what you are asking us. You know, Jon Staessen and others have convinced a lot of people, I guess me included, that in the wisdom of Bob Temple, "it's the blood pressure, stupid." He said that once in

this committee and I happen to think it was rather relevant.

What you see here is that basically it doesn't seem to matter how you lower blood pressure, based upon tens of thousands of patients. I know we haven't seen ALLHAT but, you know, ALLHAT seemed to show the same thing. I mean, those ratios were 1.0, 0.99 and 0.98 for three different regimens. So, we have this history, this incredible body of data that says "it's the blood pressure, stupid."

Is what you are asking us to say here no, that is not right? If you lower the blood pressure with losartan you get more bang for the buck than you do with an alternative regimen. Is that really what you are asking us to do? Then, the question we have to ask ourselves is, given this body of evidence, what will it take to convince us that you are the first folks in history to prove beyond a shadow of a doubt that a specific regimen for lowering the blood pressure, for a comparable degree of lowering, is better than another regimen? Is that what you are asking us to do?

DR. KEANE: I think we are looking at understanding the effects of losartan in this

trial, and I think that is the question you are sort of looking at yourself. I think there are, as I have tried to present, some biologically plausible explanations as to why the observed effects may, in fact, be true. We looked at left ventricular hypertrophy regression. We looked at a carotid artery ultrasound study that showed regression. It is biologically plausible from existing data and a whole host of preclinical data and stroke prone SHR rats. There are data in a variety of different preclinical studies that would support this. We have data from Schiffrin which again shows that independent of blood effects there may be some biological effect on the arteries that is different from what we have seen in atenolol. So, you have a number of things out there that are beginning to coalesce and merge into exactly what I think you are saying, that there is a difference and it matters how you actually lower blood pressure.

DR. NISSEN: The ALLHAT investigators had the same hypothesis and they didn't prove it.

DR. TEMPLE: I appreciate the quote and slightly regret being the wise guy. I think the evidence is overwhelming that lowering blood

pressure is good for you and it doesn't matter how you do it, but that doesn't mean that drugs can't be distinguished. For example, without judging it at all, it doesn't surprise me entirely that treating the heart failure before it occurs in a hypertension population leaves you less likely to see manifestations of heart failure later, which could be what ALLHAT proved. We don't know.

DR. NISSEN: We will see.

DR. TEMPLE: So, there could be differences even though probably all drugs are good for you to some degree.

DR. NISSEN: But you understand what I am getting at?

DR. TEMPLE: Can I ask one thing that I didn't understand? I thought the meta-analyses that you showed were all situations in which atenolol or sometimes atenolol and other beta-blockers were better than nothing. In some cases this was when they were added to a diuretic; in some cases when they were not. So, I want to go back to the question that has been raised. The fact that something is better than nothing when used alone doesn't absolutely tell you that it is better than nothing when you add it to a diuretic.

That is specifically the question. There is evidence that in the absence of a diuretic this has an independent effect on these outcomes. So, the question is only whether it still works.

So, that is like the question we ask in heart failure: you have a diuretic; you add this; you add this and you don't really know you need the diuretic anymore and no one is willing to find out as a general matter because you would have to leave out a drug that everybody thinks saves life. So, you have the same situation here. In hypertension nobody is going to go back and leave people inadequately controlled by taking the diuretic away anymore.

That is the question. It seems to me the thing one has to think about is if you have persuasive--and I don't know whether you think it is persuasive or not--evidence that atenolol by itself, in the absence of a diuretic, has a favorable effect on cardiovascular outcomes what, if anything, does that tell you about an effect of lowering blood pressure in the presence of a diuretic on similar outcomes?

DR. BORER: I think you are starting to go down a path where you may not mean to go down. You

know, it doesn't seem as if you are actually asking us to support the concept that losartan plus whatever is really better than some specific alternative regimen but, rather, that losartan plus or minus anything works; that it reduces cardiovascular events. It is in that context that these questions that we are trying to articulate in a more and more focused way are emanating from.

If you have evidence that a diuretic works you don't know if the atenolol is adding anything or not but the regimen that has the atenolol works, and you are not sure exactly how well it works. Now we have a data set that says a diuretic plus something else works better but not overwhelmingly statistically significantly better. Can you conclude that the new regimen, because of its new component, actually is better than just giving the diuretic alone, which we all accept works?

I don't know if I have made what I am mean clear enough so that you can respond to that, but that seems to be the issue that we are grappling with, not so much is there a biologically plausible basis for assuming that one drug is better than another drug for treating people with hypertension. Maybe it is; maybe it isn't. I think it is

plausible enough. The question is have you actually shown in a statistically reliable way that you have a regimen that works and that is what we are sort of trying to grapple with by looking at the strength of evidence that the comparator works.

DR. GOLDMAN: Bonnie Goldman, regulatory. If you look at the way we did our claim structure, it is not a superiority claim structure so you are correct.

DR. BORER: Steve and then Paul?

DR. NISSEN: I want to continue along those lines. There is one other thing I really think I have to help clarify here, and that is slide 118, if you could put that up. I think there obviously are some differences in blood pressure and one has to do some thinking about this. You might argue that it doesn't matter; that it doesn't matter how you got there but I do think this has to be discussed.

If you look at Staessen's meta-analysis and, by the way, I reviewed it in great detail before this meeting because I wanted to be comfortable about it, he shows very strikingly a non-linear model. I don't know if you have his meta-analysis that you can put up there but I

certainly have it here. What he shows is that the first few millimeters of difference account for the vast majority of the differences in the stroke events. In other words, a little bit of blood pressure difference on the stroke endpoint goes a long way. Another example of that would be a trial I am not particularly fond of, the HOPE trial where they had a 3 mm difference reported and a 25 percent difference in stroke. It is a 0.75 risk ratio.

You know, I guess the problem with what you did here is you drew a straight line and we know the straight line is not the right relationship. In fact, we know it is curvolinear.

DR. EDELMANN: If I could just respond to that, the Staessen meta-analysis that you are referring to accounts for the individual trials, including the ones with active comparators against one another. So, the first thing to say is that when you plot this point on that curve the finding of losartan's benefit over atenolol is even outside the 95 percent confidence interval that Staessen draws around the curve. So, I think it is still consistent. But the reason we chose--

DR. FLEMING: And so is HOPE actually. I

mean, when you look at his curve, it is a trial that shows more effect on outcome than you would expect just by blood pressure alone, as obviously with LIFE in that curve.

DR. EDELMANN: Just to reiterate, even if you take that as the proper model as reflected in that publication, this is still outside of the 95 percent bounds. The reason that we chose to draw this as linear is because these are data taken from the meta-analysis only looking at the no treatment trials. In other words, this is the "pure" effect of blood pressure and not the concomitant effects that the active drugs have on outcome, which would then be an inevitable confounder and might serve to make the line curve.

I mean, I take your point. I am not sure this is right but that is the reason we did it. Even if we looked at it straight out of the Staessen paper the point is still the same. Blood pressure doesn't seem to explain the benefit.

DR. NISSEN: Just to conclude though, one conclusion that someone might draw is that blood pressure accounts for a much larger proportion of a difference between two regimens than would be accounted for by this. That was my only point.

Whether it accounts for all of it or not, we can argue about it and we probably will, but in point of fact--and keep in mind this is based upon systolic pressure and pulse pressure--the differences were somewhat larger. So, again, we are looking at issues as they relate to strength of evidence. It suggests that a drug has effects that are independent of its blood pressure lowering effects; that it has some special magical properties that are going to reduce events. To do that, I want to know for a given degree of blood pressure reduction what the reduction in events would be because we treat patients to goal.

I think one has to argue here that you have taken a best-case scenario for losartan and I can think of a number of intermediate scenarios and even a worst-case scenario that, in terms of how one regulates, one has to think about when one does this analysis.

DR. EDELMANN: Just to respond to the issue about pulse pressure and, in fact, blood pressure in general, we have taken this in a very detailed way and looked with the available data in the literature for what is reported as the external source for reference here, but we have also done

the internal analyses which are easier to do because it is completely internal to the LIFE study database. When we adjust for the differences in systolic blood pressure, diastolic blood pressure, systolic and diastolic simultaneously, pulse pressure, mean pressure, it doesn't make much of a difference. It matters one percentage point on the hazard ratio.

I think we are asking more of the data than is reasonable to expect to be able to parse it to say how much of the benefit you could attribute to blood pressure. What we can say is that it is pretty likely, in fact very likely, that the benefit of losartan over atenolol in the LIFE study is not explained by blood pressure, certainly not to any large degree.

DR. BORER: Paul and then Tom, and then we are going to take a break.

DR. ARMSTRONG: I am remaining optimistic that Tom, as the primary reviewer, is going to come back to the question on statistical heterogeneity so I will pass on that, Mr. Chairman. But as I reflected on the discussion over the last hour and a half, I feel that the atenolol has been wrestled to the ground as almost a neutral component of the

comparator arm. Before accepting that and reflecting on stroke as the dominant feature of the composite, and reflecting on the discussion that the beta-blocker in fact could be a progenitor of the atrial fibrillation which is strongly associated with stroke, I suppose one should at least raise, if only to dismiss, the rather outlandish proposition that there could be a negative interaction between atenolol and the thiazide diuretic in the comparator arm such that it would appear less good than it might if it was thiazide alone. I will just put that on the table to chew on.

DR. BORER: Does anyone want to respond to that?

DR. KEANE: Just to make it clear, the use of the diuretic in both of the treatment arms was the same.

DR. BORER: Tom?

DR. PICKERING: I have two questions. One is have you done the same analysis looking at the composite endpoint, which is what you are requesting rather than stroke? The other has to do with the 24-hour blood pressures.

DR. EDELMANN: Sure, yes. Using the same

assumption of a linear model, we are limited by the data as they were reported. There is only one trial that reports all cardiovascular events. But the same finding is true. Slide 217.

It is the same pattern of developing the evidence. The only difference is we have only one published meta-analysis to estimate here. So, this is risk of the cardiovascular event difference based on blood pressure, constraining the point through zero, and here is the primary endpoint for LIFE with the magnitude of blood pressure difference. So, it is the same point with less precise ability to estimate best fit because we have only one point here.

DR. PICKERING: Thank you. The other question had to do with slide 112, the 24-hour blood pressure. What this shows to me is that the effects of losartan tend to wear off at the end of the 24-hour period, which I think has been documented in other studies. If you look at the early morning period, which is the time of highest risk, the effects of atenolol appear to be much greater. My question is that about 50 percent of the patients were on 100 mg of losartan and were they taking it twice a day or once a day, because

that could make a difference?

DR. EDELMANN: A couple of points about this. First, the answer to your last question is that losartan was once a day throughout the trial. The second thing has to do with the data at the end of the 24-hour and the beginning of the 24-hour period. There are fewer data points that comprise this because not every tape ran to fully 10:00 a.m. While I agree with your observation about the results, there is more variability at the very ends of both of these curves, just inherent in the fact that not everybody's tapes were started and ended at exactly the same time.

DR. BORER: Dr. Keane and Dr. Edelmann, I think we have grilled you sufficiently, which is our traditional manner of operation. So, we are going to stop now. It is 3:04. At 3:19 we will reconvene and we will begin with a formal discussion around the questions.

DR. KEANE: Dr. Borer, we still have some responses to questions that were raised this morning that we haven't had a chance to get through. So, if we have some time, maybe after the break, we will be more than happy to go through those.

DR. BORER: Okay, if there are questions that people on the committee think haven't been answered sufficiently. We will take some time after the break.

[Brief recess]

DR. BORER: Dr. Keane, you wanted to respond to some specific questions that had been raised before that we haven't yet discussed. Why don't you go ahead and do that? We will try to take no more than ten minutes to go through these, and then we will begin a discussion focused around the structured questions.

DR. KEANE: Thank you, Dr. Borer. I think one of the first things that I would like to start out with is really to review an important point about blood pressure lowering and the efficacy of blood pressure lowering with the beta-blocker and the diuretics.

One of the key trials that has been performed in the last decade has been the STOP trial. Dr. Bjorn Dahlof, one of the principal investigators, has asked to make a comment on that to underscore the importance of how these regimens, which is a beta-blocker or a diuretic regimen, influences blood pressure and influences outcomes.

DR. DAHLOF: I was also the principal investigator of the STOP trial. I just want to emphasize that I think that study is one of the few studies that actually can bring more light to the discussion than we maybe think because three-quarters of the patients in this elderly population, 72 to 84 years of age or on average 75 years, were starting on a beta-blocker and they had added diuretic in the majority to control blood pressure. The outcome versus placebo was about 40 percent for stroke; 50 percent for total cardiovascular and also an effect on all-cause mortality. It was a very, very effective treatment and it was based on beta-blockers. We also looked at LVH afterwards with the LIFE criteria and about 30 percent of the patients had LVH, and the event rate on average was the same as in the beta-blocker/diuretic arm in the LIFE trial. So, I think it is one of the best trials. I am biased, of course, since I did the trial but I still think so. Thank you.

DR. KEANE: Thanks, Bjorn. There was another question that came up this morning about male/female differences in achieved blood pressure during the trial, those in losartan or the atenolol

group. Making a long story short, and we can certainly provide the data for that, the females in the atenolol group compared to the females in the losartan group had basically a very similar antihypertensive response, about 29 mm Hg systolic and 17 mm diastolic in the atenolol arm, while the females in the losartan arm had about a 30 mm systolic decline and a 17 mm diastolic decline. So, they were very similar.

I think one of the points I did want to make is that when there was a discussion about our achievement of control, we did achieve an effective level of control in some 50 percent of the patients. That is quite different than what is going on in the community. I think if you use the NHANES data to look at effectiveness of control, it is still down below 25 percent. So, I think it is important to recognize that this was a very well conducted and solid trial from the perspective of actually trying to achieve blood pressure.

The other points that I would like to address that came up this morning in terms of questions, we have already heard the overall prevalence of left ventricular hypertrophy in the populations, particularly that are of our age

group. They fall in the range of approximately 20-25 percent of the older population. It is clear that those patients with left ventricular hypertrophy are at increased risk for a cardiovascular event. It is about twice as great as one might anticipate. So, when we look at this, the important point of recognizing this risk associated with left ventricular hypertrophy when we looked at our treatment effect of losartan, the benefit occurred across the entire range of tertiles of left ventricular hypertrophy. So, we saw the lowest tertile, the middle tertile and the upper tertile both in men and women in terms of the beneficial effect of losartan. So, it occurred across all levels of left ventricular hypertrophy.

I think if you look at some of the other trials that have actually been discussed today, in many ways it doesn't make a heck of a lot of sense to say that all of the risk is actually associated with just left ventricular hypertrophy because to see the beneficial effects, if one extrapolates a 20 percent prevalence of left ventricular hypertrophy to the beta-blocker and diuretic studies only to that subpopulation which represented no more than 20 percent, the other part

of that population would have actually had no benefit whatsoever. So, I think it is an important thing.

There are a couple of other questions that came up, and I think they came up with regard to the type of medications that people were on. One of them was focused around concomitant use of warfarin. There was about 4.9 percent in the losartan group and 5.9 percent in the atenolol group. That was statistically significant, with a p of 0.03.

With regard to amniodarone usage in these patients, from the perspective of prior use of therapy there were only two patients that were on this medication in the losartan group and five in the atenolol group, and it increased slightly in losartan to 17 and increased to 16 in the atenolol group, and there was no difference between the two groups.

I think one of the last sets of issues that came up, and I think we have discussed many of the other questions but there was some question about the p value for test of interaction for all-cause mortality in the diabetic patient population. That achieved a p value of 0.006, a

highly significant event.

Finally, I just wanted to mention a little bit about heterogeneity. Clearly, I think this was mentioned by the FDA and I mentioned this in my presentation. The finding of heterogeneity within the context of an active comparator trial does not really invalidate the conclusions. We found that there was a significant difference in the different effects, particularly as it pertains to stroke. Stroke had a p value of 0.001 in this clinical trial so it was a very robust observation and it was a very important observation.

This heterogeneity issue that has been discussed and been talked about within the clinical trial, as the FDA reviewer has underscored and pointed out, to achieve a p value of 0.02 on our composite means that at least one of the components in our composite has to be robustly statistically significant. Again, that appears to be related very specifically to stroke where we, again, found this very robust p value of 0.001.

I think I have touched upon all of the outstanding questions and issues that were raised this morning and this afternoon. We have a couple more data points that I can provide to you. The p

value for interaction for blacks for stroke was another question that we didn't have a specific p value to provide this morning. That had a p value of 0.004, again, a highly statistically significant observation.

The percent of time on combination, let me get you that information as well. The percent of time that patients were on combination therapy, the diuretic, was between 65 and 74 percent and between 62 and 73 percent, the former being the losartan and the latter being the atenolol arm. Is that right?

DR. SNAPINN: Steve Snapinn. Can I clarify? Let me just clarify that. There was a question about how much time patients were on combination therapy. We looked at the number of days the patients were taking blinded study drug along with another antihypertensive and calculated that as a percentage of two different things, as a percentage of total study follow-up and as a percentage of the time when they were on blinded therapy at all.

As a percentage of total study follow-up, it was 65.5 percent of the time with losartan versus 62.4 percent of the time with atenolol, a

difference of three percentage points. However, as a percentage of time on blinded study drug, it was 73.9 percent with losartan versus 73.1 percent with atenolol, very similar numbers.

DR. KEANE: I think that actually covers all the additional questions that came up. If there are no further questions, I think we will leave the podium.

DR. BORER: That is fine. Thank you very much, Dr. Keane and everyone else from Merck. That was really a very informative presentation. As Steve pointed out earlier, we are all very impressed with the study and with the analyses, etc., etc. However, it is our job to make you feel bad when you are standing there.

[Laughter]

Committee Discussion of FDA Questions

We will move on to a discussion of the questions and if we have any other clarifications we need, we will ask for them in that context.

The Cardiorenal Advisory Committee is asked to provide an opinion on the relative effects of an antihypertensive regimen containing losartan compared with a regimen containing atenolol, both administered once per day. Specific guidance is

sought on the adequacy of the current program to support a claim of superior efficacy for losartan at reducing the incidence of the combined endpoints of cardiovascular mortality, MI and stroke, as well as guidance on how to describe any relevant differences in labeling. That sounds a little confusing. You are not really asking primarily whether the regimen is superior but whether it works, I think. Right?

DR. THROCKMORTON: Well, I think while the sponsor is not interested in that, as we will come to when we come to the questions, there is at least some interest in that.

DR. BORER: Yes, there are questions that deal with that. All right.

DR. NISSEN: I am not sure though I understand the question.

DR. BORER: Well, this is the preamble. The questions divide the issue into does it work and is it superior so maybe we can sort of gloss over that one.

Specific guidance is sought on the adequacy of the current program to support a claim of superior efficacy for losartan at reducing the incidence of the combined endpoints of

cardiovascular mortality, MI and stroke, as well as guidance on how to describe any relevant differences in labeling. Additionally, guidance is sought regarding the relevance and appropriate description for an observed qualitative interaction between race and the effects of the two study drugs.

In the past, the agency has told sponsors that a robust demonstration of a clinically relevant difference between the two drugs, if done fairly, would be appropriate for inclusion in labeling. There are few examples of such trials being presented to the agency and being incorporated into labeling, such that the current trial has some value as precedent.

So, with that as a preamble, the first question, the LIFE trial compares the effects of losartan and atenolol on cardiovascular outcomes. For a population like that studied in LIFE, what is known from external sources about the effects of beta-blockers, including atenolol, and angiotensin receptor blockers, including losartan, on the incidence of death, MI or stroke? Describe the basis for your opinion.

We have some options here: 1.1, cannot be

determined; 1.2, both are superior to placebo and equivalent to each other; 1.3, one or both are superior to placebo, but not equivalent to each other; 1.4 both are equivalent to placebo.

The committee reviewer is Tom Fleming. Tom, do you want to take the lead in that discussion and we will see if there are any other comments?

DR. FLEMING: Sure. Let me just begin the discussion and I will focus my comments as it relates to the atenolol part of the question.

We have been provided a very informative meta-analysis by the sponsor that provides a lot of insight about regimens that are diuretics, diuretics plus atenolol, atenolol-based regimens, and where one is using titration strategies in helping to achieve targeted blood pressure levels. It seems that there is considerable evidence to indicate that those strategies, in fact, do have a very favorable impact on the composite clinical endpoint of death, MI and stroke.

But an additional element of this question that is really important is that the question is specifically in part asking what is atenolol's influence. I think this is really critical in an

active comparator trial. Ultimately, we are looking at understanding the influence of losartan. If one simply looks at the regimen and concludes, as I have, that the atenolol plus a diuretics regimen is effective, then there is, with the addition of the LIFE data, considerable evidence that the losartan/diuretics regimen, in fact, is also effective.

But what is much more difficult to understand is, is losartan integral to that benefit. Working backwards, where we have in the LIFE study evidence of a direct comparison of diuretics and losartan versus diuretics and atenolol, it would be extremely important with diuretics and atenolol now as the active comparator to understand whether atenolol is, in fact, also positively influential in that combination. This is an issue we have been struggling with now for a considerable amount of time in our questions. It is unclear to me at this point whether a strategy that is based on diuretics, titrating to an achieved or targeted blood pressure, would yield a different outcome in the clinical endpoints than a strategy that is based on diuretics plus atenolol.

Essentially, I am giving two different

answers to this. If one is simply asking whether the entire regimen of atenolol plus diuretics influences these clinical outcomes, I believe there is considerable evidence that it does, and that is relevant because that provides further reinforcement when we look at whether the regimen of losartan plus diuretics influences the composite clinical endpoint.

However, if we are also required to go beyond that and say we all accept that this class of agents that involves diuretics or beta-blockers are capable of influencing clinical endpoints, mediated in large part through effects on blood pressure, now the question is what is the integral role of atenolol in that strategy so that ultimately when we ask what the integral role of losartan is we can then determine whether or not the evidence of losartan's superiority to placebo is more than what its superiority is against atenolol.

This is my own reason for interest in understanding what the effect of atenolol is. I am coming to the conclusion, based on evidence and perspectives that I am hearing from the committee, that a strategy that would titrate to a targeted

blood pressure based on diuretics or a strategy based on diuretics plus atenolol probably would yield comparable effects on clinical endpoints. As a result, if we are going to conclude that losartan provides even more influence or more benefit on these clinical endpoints, one is going to have to show superiority in the LIFE study.

DR. BORER: Let me raise one additional point and maybe, Tom, you can respond to this--Tom Pickering. I don't think anybody would have any other opinion than the one you just stated, Tom, but in terms of the combination, in all fairness, versus diuretics alone, my understanding is that one of the reasons that we combine these drugs is that the effort to achieve blood pressure control with diuretics alone leads to the use of doses of diuretics that have harm associated with them, and that is one of the bases for putting together the combination to control blood pressure. That might influence our concern about the independent contribution of atenolol to the atenolol plus diuretic combination. Tom, can you discuss that?

DR. PICKERING: Well, I think one issue is that the question addresses two specific drugs and a lot of what we are talking about with

beta-blockers is general, and the question is whether you can generalize from atenolol to all the others. In the post MI trials, we know that you can't because the ones with intrinsic sympatomimatic activity didn't confer protection but the others did.

Again harping back to the MRCII trial, this was about the only trial where there was a direct comparison between atenolol, a diuretic and placebo. I accept that it was a flawed study but that is the closest that we can get. Again, I think the age factor is an issue here. Most of the beta-blocker trials, not necessarily with atenolol, that showed a positive effect were in younger patients. I acknowledge the STOP trial but, again, I would interpret that as a combination of a beta-blocker and diuretic trial which certainly was superior to placebo, and I don't think any of us would question that. So, I think the age and the drug are potentially important questions.

DR. BORER: Yes, again, a little information might be helpful about the possibility of achieving the blood pressure control, which was the target in the trials of atenolol where diuretics were used versus using diuretics alone.

My understanding is that one of the reasons that one would not do that, and the algorithms have been developed, is that driving the dose of diuretics high enough to control blood pressure has potentially deleterious effects if the dose is pushed beyond 50 mg a day of hydrochlorothiazide for example. I don't know about chlorthalidone.

DR. PICKERING: Yes, I think that was in the HAPPHY study where sudden death was much lower with the beta-blockers, and one issue was that a lot of the patients were on a very big dose of diuretics and there was a lot of hypokalemia and there was a question of whether that was an issue. But, again, in practice all these trials are going to need combination therapy to achieve the blood pressure control, particularly in people of this age group.

DR. BORER: Yes, that was the point. Tom was raising the issue of did atenolol really add anything compared with just treating with diuretics alone, and the practical matter is that one might not be able to do that if you are treating to a blood pressure endpoint.

Tom, do you want to respond to the specific questions 1.1, 1.2, 1.3 and 1.4 or do we

not need to do that?

DR. TEMPLE: I just want to ask Tom a little bit about what he said because some of the words being said would have a lot of implications. Since Tom is sort of "Mr. Surrogate" let me put it this way, we start out with a strong bias that blood pressure has something to do with outcome. We have a lot of epidemiology and also a lot of clinical trials of various drugs.

But it is still relevant to ask for any particular drug whether lowering blood pressure with it has the expected favorable effect on outcome. So, the meta-analysis presented to us, while not in most cases on top of the diuretic, is an attempt to show that lowering blood pressure with atenolol has a favorable effect on outcome, just like the epidemiology would suggest it does. That doesn't mean some other drug isn't better or anything like that.

What I hear coming from you is the question of whether that remains true when there is a background of diuretic. That is an interesting question but it poses major problems. For example, we have no doubt that chlorthalidone, SHEP, has a major effect on outcomes. Does that mean that if

somebody started out those people on an ACE inhibitor and added a diuretic to get control we now would be dubious as to whether that was still true? My answer would be no, we would not because we have concluded from SHEP that lowering blood pressure with this diuretic, or a diuretic, perhaps has the expected, based on epidemiologic considerations, effect on outcome just like you would have predicted.

So, I guess my question is if you believe the meta-analysis--I make no judgment on that--wouldn't that apply to lowering the blood pressure with atenolol whether or not the person was already on a diuretic, already on--I don't know, something else? How reasonable is it to make a distinction there? In other words, does the meta-analysis tell you that blood pressure lowering with atenolol is good for you or does it only tell you that it is good for you when used alone and you are completely at sea about the question whether it is still good for you when you add it to a diuretic or you add it to, you know, anything else?

DR. FLEMING: Let me try to begin answering that by putting us in a different context, which doesn't apply here but it is an

easier one to think through. That is, suppose you had a control regimen of diuretics and then you had an alternative regimen of diuretics and atenolol and a third regimen of diuretics and losartan--I will call them D, D plus A and D plus L. Suppose that these were fixed dose regimens. What ultimately I think, in my view, we would want to be able to show is that D plus L is more effective than D to conclude that L is, in fact, favorably influential in achieving benefit.

DR. TEMPLE: But you are going to lower the blood pressure more. Two drugs lower the blood pressure more.

DR. FLEMING: You are ahead of me.

DR. TEMPLE: All right.

DR. FLEMING: So, in this line of reasoning it is not necessary to show that D plus L is superior to D plus A if, in fact, D plus A is better than D. If you knew how much D plus A was better than D, you are now in a non-inferiority situation, and if you have marginal evidence, strength of one study evidence to show that D plus L is better than D plus A and D plus A is better than D at some level, you may well be able to conclude superiority.

DR. TEMPLE: We all know the best non-inferiority study is where you win.

DR. FLEMING: Well, if in fact the judgment--

DR. TEMPLE: And that is the question here.

DR. FLEMING: If the judgment here is D plus L is better than D plus A at the strength of evidence necessary to conclude superiority, unless you think A is harmful I don't have to worry about how much D plus A is better than D.

DR. TEMPLE: This has come up before on the strength of evidence matter. One study at a p of 0.02 as a basis of effectiveness is generally considered sort of marginal. You make what you will of the stronger effect on stroke alone, but leaving that aside, one study at a p of 0.02 against a drug that you are quite sure has some effect has been taken for clopidogrel and something as representing quite a high level of evidence. So, it does matter what you think of the atenolol data.

DR. FLEMING: Yes, you are exactly right. That is my view as well. That is why I believe that the time this committee has spent struggling

with what is ultimately this first question is very important for that very reason.

What I have just described though is not exactly the situation we are in. It is not exactly the situation we are in because when you are comparing D plus A versus D, those aren't the same Ds because what you are going to do with the diuretics without the beta-blocker is that you are likely going to have to achieve higher doses, etc. So, we are really confusing the issue. If ultimately now I believe in surrogates, if I believe in blood pressure and I believe that you could, in fact, effectively titrate to a targeted blood pressure with either D or D plus A, if I believed all of that, then I am saying technically A isn't adding anything over D that I could get unless there are some harmful things happening when I have to titrate to such high doses of the diuretic.

DR. TEMPLE: If in this case D was much greater in one of the groups, then that would be a concern but my recollection is that D was pretty much the same in both groups.

DR. FLEMING: What I am hearing from all of the data is that D plus A and D and A are really

good, even though none of them are labeled for this setting. They are all really good in terms of achieving blood pressure adjustment and in a lot of cases we have data to show that they influence this composite clinical endpoint. Hence, the importance of that conclusion is we now know that our active comparator regimen, D plus A, is very effective and the LIFE study, to my way of thinking, unequivocally is going to show that D plus L as a regimen is having favorable effects on this clinical composite endpoint.

The tougher part if you, in fact, wish to answer this question is, is L integral to that--although we don't have to know the answer to this--partly mediated through mechanisms beyond its effect on blood pressure? Then I circle back to your point. My view of the LIFE study is it is an important step in saying D plus L, hence L, is better than D plus A, hence A, but only at the 0.02 level can I reinforce against placebo.

DR. TEMPLE: It is that last part that confuses me. There isn't any data, I don't think, that D plus L is better than D at lowering blood pressure. I mean, that is hardly news and that shows up all the time. Two drugs are always better

than one. We have a thousand combination studies that show that.

DR. FLEMING: To a point that you would believe that there is adequate evidence to conclude we have affected the clinical endpoints?

DR. TEMPLE: No, no, that is a different question.

DR. FLEMING: That is a relevant question.

DR. TEMPLE: I am going back to my original question. I would have said that the question of blood pressure surrogacy can be answered by a study in which you showed lowering blood pressure with drug X has the expected, the epidemiologically predicted effect on outcome. That then tells you that this drug's blood pressure lowering is a good kind of blood pressure lowering. That is the reasoning I have had. Okay? I would have said that applies whether you use the drug to lower blood pressure from a systolic of 180 to 160 originally or whether you add it to another drug to lower it from 160 to 140 because what you have learned is that lowering blood pressure with this kind of drug is good for you. Everybody feels comfortable with that with chlorthalidone, say, because there is such a lot of recent data.

But that is the general approach that I think we have thought of. Your question gets answered once. Now, maybe that is wrong thinking and maybe you want to challenge that, but that is what I would have thought the idea is. The question is if I lower blood pressure with drug X, does that have the expected, epidemiologically predicted favorable effect on outcome? So, it shouldn't really matter whether you add it to a third drug, a second drug, a first drug if you now have come to believe that you now know that lowering blood pressure with drug X is good for you. So, it shouldn't matter whether it is alone, on top of a diuretic or any of those things unless there is a flaw in the reasoning here. I am laying out the reasoning because that is how we have been thinking about it, and also because I, frankly, don't know what we would do if every conclusion about outcome was based on a specific drug. You would never get anywhere.

DR. FLEMING: I would just ask you though, and it doesn't argue against what you are stating, that lowering blood pressure is a good thing, are you prepared to label every agent now, and there is an array of them in this setting that have been

shown to lower blood pressure--are you prepared to give them a label for effects on this clinical endpoint?

DR. TEMPLE: That may well be, but in this case what Merck is doing is saying something different. They are saying we already know from outcome studies that atenolol blood pressure lowering is good for you. They are saying, okay, in a population where the diuretic treatment is the same not only were we equivalent but, in this study, we were actually better. Ergo, we must be good for outcome too. That is all they are asking. They are not asking for a superiority claim. Whether they should get one is a question you are being asked but they are only saying doesn't the conclusion that you have already reached about atenolol now support, on the basis of a single study with a p of 0.02 or thereabouts, the same conclusion for losartan? I think that is what they are asking.

DR. FLEMING: The easy part to this for me is that the regimen of diuretics and atenolol or the regimen of diuretics and losartan favorably influence the clinical composite endpoint potentially largely, fully--at least largely

mediated probably through some type of blood pressure effect.

The question though, as I see it, that is much more difficult and I would think integral for this committee to answer is how influential is losartan for achieving that effect? Is it contributing to achieve that effect? Ultimately what is making this complicated to answer is that it is being given in combination with diuretics which, obviously, are very influential in both lowering blood pressure and achieving the beneficial clinical endpoint. So, the complications here are that it is not enough just to say we know atenolol or we know diuretics or atenolol and diuretics are all effective. What is important is, if the active comparator, as it is in the LIFE study, is diuretics plus atenolol, is atenolol itself adding to that combination on the clinical endpoint, more so than diuretics?

The reason that is an important answer to get is what you mentioned up front, Bob. That is, if you are looking at the LIFE study and you are saying it is getting a favorable result but the strength of evidence is marginal, if you know that atenolol is integral in adding benefit then you are

in a superiority against placebo, if not superiority against atenolol--

DR. TEMPLE: Right.

DR. FLEMING: --which is essentially the minimum that we want to achieve.

DR. TEMPLE: So, it adds to the strength of the evidence from a single study at a not extreme p value.

DR. FLEMING: Yes.

DR. TEMPLE: Right.

DR. BORER: Steve? While you are making your comment maybe you can take a stab at 1.1, 1.2, 1.3 and 1.4 so that it is on the record.

DR. NISSEN: I will but first let me just say that there is a conundrum here and I want to see if I can state this properly. What the sponsor had to do here, they wanted to do an active control trial, which is always very difficult when event rates are relatively low. So, they studied an enriched population. The way they enriched the population in events was that they went to an elderly population with left ventricular hypertrophy. And, there is one other thing that is a little bit different from, say, our population, it was largely white and we have more African

Americans particularly with hypertension.

So, you asked the question for a population like that studied in LIFE, what do we know? You know, that is the problem here because there is evidence that these drugs have differential effects among younger versus older patients. In fact, you see that in LIFE because what you actually see is that among the younger patients it actually goes in the opposite direction.

So, it makes it much harder for me. I am not saying the sponsor made a mistake or did anything wrong; they had no alternative. If they wanted to have any chance in four or five years to see a difference between the regimens they couldn't have studied a general U.S. hypertension population because they wouldn't have gotten enough events to do that or they would have had a sample size of 40,000. So, they studied a very specific population. Now what you really want to know, Tom, to add to your puzzle here, is for that kind of population what do we know about atenolol? The answer is we know precious little.

So, my answer to the question, to get back to it, is that I don't know what the effect of

either of these agents is from external sources on a largely elderly, LVH--only 20 percent of the population has LVH, largely white population. I am suspicious here that those demographics are what drove all of this and not necessarily the biology. Of course, the label is not going to say, you know, this drug is indicated for elderly, LVH, white people, you know, living in Nebraska. So, you see, we are trapped. There is a trap here and I don't know how you get out of the trap because I don't know very much about atenolol in this population. What I do know suggests that atenolol didn't work very well in that population.

DR. BORER: You know, one way out of this might be to suggest the label say something fairly specific.

DR. NISSEN: So, my answer to 1.1 is "cannot be determined."

DR. BORER: Does anyone have a different opinion? If not, after Doug's comment we will move on.

DR. THROCKMORTON: Steve, I want to pin you down just a little bit. In some places people on the committee have used some demographics like that, or sponsors have used demographics like that,

as you pointed out, to get a high event population. For instance, you might use microalbuminuria as a sort of marker for cardiovascular disease, or something. Under some circumstances the committee sort of treated those as markers of high risk, not as things that necessarily precluded you from generalizing to a population that might not have those things. Here, I am hearing you say, no, that's it. LVH is a thing that sets you into a fairly restricted population. It is a thing that precludes your being able to understand the behavior of these drugs, the comparative behavior of these drugs in a non-LVH population. Am I hearing that right? If so, could you sort of tell me which of the demographics you picked up. I think you said Nebraska. Was that it?

[Laughter]

And LVH and elderly and race.

DR. NISSEN: Well, let me tell you why it is so important. By the way, I forgot one other. The fourth one is people who are at lower risk for myocardial infarction than for stroke because the post MI patients were largely excluded. So, when we look at the general population at risk here with hypertension we have an awful lot of coronary

disease people and a lot of them were pulled out of this trial because they needed a beta-blocker for other reasons. So, that is another cherry-picking--

DR. THROCKMORTON: As were patients with CHF.

DR. NISSEN: Exactly. So, you know, it gets very complicated now. What we have is a very narrow slice and we have pretty good evidence, Doug, that those demographics, in fact, are major drivers. We know, for example, that the elderly respond differently to different drugs. We know, for example, that they don't do particularly well with beta-blockers; they do do particularly well with diuretics. We know that among African Americans, black versus white, drugs that work through the renin angiotensin system tend not to work very well. So, again, if we are going to apply this in the U.S.--

DR. TEMPLE: They don't lower blood pressure very well.

DR. NISSEN: Yes, right.

DR. TEMPLE: That is sort of irrelevant here because everybody's blood pressure got controlled.

DR. NISSEN: Yes, I understand but I am just trying to say that we see evidence here of this kind of thing. If you have a marker which seems to be rather neutral in its effect in predicting the pharmacogenomics of drugs, okay. I mean, for example CRP or whatever. But the point here is that these factors appear to be fairly important in hypertension, and I kind of see that in the LIFE data and that is what makes me uncomfortable because among the younger patients, although the test for heterogeneity doesn't meet your statistical measure, it is on the opposite side of the line if you are under 65 years of age and that makes me think maybe what we are looking at is a population that was not necessarily deliberately selected to look better for losartan that had that effect.

DR. BORER: If I can add to that just a little bit, one of the reasons that I agree with Steve is that these people had LVH and many of them had mild hypertension. A lot of people with mild hypertension don't have LVH. So, it is not "blood pressure alone, stupid." There is some underlying biological difference in this defining its response to blood pressure as compared to another population

with the same blood pressure, it seems. That doesn't mean that you can't extrapolate further; it just means that I feel uncomfortable extrapolating further because I don't understand the importance or basis of those biological differences. Given that, I would tend not to extrapolate widely. I am not suggesting that the LIFE data are in any way invalid or that the sponsor and the investigators haven't proven what they set out to prove. In fact, not to jump ahead, but I think they did. But I would be very concerned about extrapolating widely given the biological variations that I think we can infer in the population that we are talking about here, the hypertensives.

DR. THROCKMORTON: But I really would like to understand what the basis for that concern is, and how you would you like us to do that? When the sponsor came and said we want to do a trial but we are concerned that it is either going to take a million years or the whole, say, State of Nebraska. So, we would like to choose a population that is enriched, let's say, but at the end of the day we would like to be able to understand that in a sort of continuum of disease rather than just your net narrow population.

This sponsor has made one sort of choice. They have chosen a population that has been narrowed or enriched for events, and I am still not sure how narrow but Steve seems to think fairly narrow. Then, at the end of the day, they looked for heterogeneity in that population as an argument to say, look, you can, roughly speaking, understand the effects of these drugs in a larger population than the one we studied by applying largely covariate analyses post study results.

Now, is that convincing to you? Or, am I hearing that that is not a way that you think the sponsor should think about this?

DR. BORER: Beverly?

DR. LORELL: I might answer question one a little bit differently than Dr. Nissen but with many similarities. I would say to this that it is likely that either of these regimens is superior to placebo based on the "blood pressure, stupid." We keep coming back to that because both showed a large magnitude of reduction in blood pressure. But I think for these very issues that Dr. Nissen raised about some of the specifics of this population, the way it was enriched, that one cannot infer, using outside sources, that either

one of them has a superiority over the other because I think his concern is that this an elderly population, is an unusual group, and most of us around the table treating patients would not choose a beta-blocker as the second choice after starting a diuretic if our patients were still not controlled in this age group.

But it is also a little bit unusual in that you pulled out, as he said, the population that is at higher risk for cardiovascular events where a beta-blocker might have been beneficial in those that are having some angina and need beta blockade, or previous infarction. So, it is very complicated but I would say based on the magnitude of blood pressure reduction alone either of these regimens is likely to be better than placebo.

DR. TEMPLE: This may be a regulatory nicety that nobody actually cares about but I will press on it anyway. We all act as if lowering the blood pressure is what counts. Drugs get approved because they lower blood pressure without showing any outcome data. People have criticized that, but that is still what is done.

What is being sought here is not a claim that losartan is better than anything else but that

it has been documented as having an effect on outcome specifically. Even though probably we all would assume it has an effect on outcome because it lowers the blood pressure, they want to write in labeling we have an effect on outcome which, by the way, no other antihypertensive except ramipril, by mistake, has. Steve thinks it is by mistake; we didn't think it was a blood pressure claim.

So, that is the particular importance to us. I should tell you we are busily plotting to include outcome data of some kind in all of these drugs because certainly that is what everybody believes. We certainly haven't done it yet and are not particularly close to doing it.

So, the question that this poses is does a study in which you beat something that probably has a favorable effect or, if you believe in the meta-analysis, definitely has a favorable effect at least in somebody, does this now provide documentation that losartan too has a favorable effect on outcome? It is true it is in a very specific population and you have to deal with that. How generalizable you would find that is something to debate.

On the other hand, they would argue that

in being better than something that has a favorable effect, they have a fairly strong level of evidence at least for this population--and you have to think about whether to generalize it--that they have a favorable effect on outcome. This is probably beyond what anybody really cares about but that is our immediate problem.

DR. BORER: You are the one who is asking for advice so if you care about it, it is important.

DR. NISSEN: May I respond to Doug's question?

DR. BORER: Yes, briefly.

DR. NISSEN: Very briefly, Doug, you asked me a direct question which is, you know, can you do this by going back and looking for heterogeneity. The four things I mentioned, elderly, LVH, race and absence of coronary disease, these are the four things that are here that are very specific, and in the case of the exclusion of patients that have coronary disease you can't go back and look because those patients weren't in the trial so you can't go back retrospectively and figure that out. In the case of race when you go back and look at it, it looks pretty ugly. In the case of LVH you can't go

back and look at what happened to the non-LVH patients because there weren't any non-LVH patients in here. In case of the elderly you can go back and look by age and you see at least a signal there of a difference. So, for all four of the demographic characteristics that I mentioned that were very specific to this group either you don't know or what you do know makes you uncomfortable.

DR. TEMPLE: But in the end what you have to decide is how much of a reservation that is. I mean, you only know about systolic hypertension in chlorthalidone in people over 70. Does that mean you don't treat anybody who is 60? I don't think so. So, somehow in your mind at least you have said it looks like chlorthalidone is a good thing for isolated systolic hypertension, which happens to be a problem more in the elderly than in other people so you tend to believe it.

You are going to be faced with that. How much does the fact that it was done in people with LVH make you not believe that you have learned something about the drug itself but have only learned something very narrow about the population?

DR. BORER: Can I suggest something? Dick, at this point of a meeting we don't entertain

comments. I am sorry, I have left you standing there so long. Can I just suggest so we can move on here that we can say from outside sources that it seems reasonably clear that atenolol is a good thing in terms of these outcome events and we just don't have all that much information about the ARBs? That is not one of your options but that is what I am going to suggest. Unless anybody disagrees with that we will move on to number two. Oh, I am sorry, Tom?

DR. FLEMING: I am not sure if I am disagreeing or not, except to say I think it is more complicated, as I think about it, than to say it is a good thing. Atenolol alone is a good thing. What atenolol is adding to diuretics is still relevant and uncertain in my mind.

DR. BORER: Yes, but that is not what they asked, fortunately. It is just atenolol alone, it sounds like.

Number two, regarding the LIFE trial data in the overall population studied, describe the overall difference between patients receiving the losartan-based regimen and the atenolol-based regimen in the trial.

2.1, was superiority of the losartan-based

regimen demonstrated for the primary endpoint and for each of the three components of the primary endpoint? Tom, why don't you go ahead?

DR. FLEMING: Let me try to initiate discussion on maybe 2.1 and 2.3 initially. Was superiority established? I believe that the LIFE study provides a statistically significant difference on the primary endpoint at a level that I would say is consistent with the strength of evidence of a single positive study. In addition to providing, of course, evidence about the composite endpoint, one of the many strengths of this trial is that it provided a very appropriate continued management and follow-up of these patients beyond the occurrence of the initial primary endpoint, which was an extremely important element of this study in that it allowed us to more clearly understand what were the effects on the components.

There is considerable heterogeneity, as has been pointed out, and the evidence seems fairly strong that there is a superiority, a statistically significant benefit overall in the composite endpoint but seems to be heavily driven by the stroke component. Of the other two components, the

MI and the cardiovascular death, the cardiovascular death that is trending favorably, with a relative risk of 0.89, also seems to be heavily driven by stroke-related death.

So, as I look at this, the overall benefit that has emerged with the significant positive endpoint seems to be fairly strikingly single-dimensional, i.e., we are favorably influencing stroke and stroke-related death; the other elements seem to be neutral. How does one interpret that? How do you address that statistically? You are spending your alpha on the primary composite endpoint and I think that rigorously that is true. They hit the positive primary endpoint. I think good statistics involves good common sense and good common sense here would say that when you look at the totality of these data the essence of the signal is in stroke. So, as I look at this from what I would call a common sense perspective, I think this study has established a favorable result for the combination with losartan over the combination with atenolol on the stroke endpoint.

Where we will come back to this question in numbers 3, 4 and 5 is what is adequate strength

of evidence here. This is a single study. We have often heard the term a single study that is positive where the results are robust or compelling--many of us have said a single study that achieves 0.025 squared, which has a two-sided p value of 0.001, is a trial that contains essentially the equivalent strength of evidence of essentially two positive studies. So, the complication, at least as I look at it here, is that this is a study that is positive. Is it, in fact, a study that is sufficiently positive that it provides robust and compelling evidence?

Let me move on though, having focused on stroke, to 2.3 and question 2.3 says could the observed differences in clinical outcomes be the result of differences in blood pressure control? Let me argue that in a certain sense it is not a fully well-defined question. It is a very relevant question. I say it is not fully well-defined because blood pressure control is a surrogate. It may be a very good surrogate but what do we mean by blood pressure control? There are many ways of characterizing blood pressure control. Is it adequate to talk about the average systolic blood pressure, or diastolic blood pressure, or pulse

pressure, or is it the fraction of people who are below a targeted threshold of 160 systolic blood pressure? There are many variations and it may be that the effect of intervention is substantially mediated through its effect on blood pressure but we can get false-positive or false-negative conclusions if we are not characterizing that exact true functional relationship if we are looking at average blood pressure and, in fact, if we look at average blood pressure there is a one millimeter difference.

The meta-analyses that I have looked at would indicate that if we have a 25 percent reduction in overall stroke rate and there is a difference in the two arms of a 1.2 mm Hg achieved in average systolic blood pressure, it seems that that would account for a three to six percent drop. So, at least by my own crude calculations here, it looks as though changes or differences in the two regimens in systolic blood pressure could be contributing to the difference in stroke, but it seems to me that the difference in stroke is of a magnitude three or four times larger than what would seem fully attributed to that.

On the other hand, maybe it is because the

systolic blood pressure average measure is looking at the wrong way in which the regimens are influencing risk of these clinical endpoints through blood pressure. It could be that it is the difference in the two regimens in the fraction of people who have very high uncontrolled systolic or diastolic blood pressure, in which case, as I said earlier, we may have false-positive or false-negative conclusions.

So, in a certain sense the question is extremely difficult to answer and is, in fact, one of the reasons--coming back to Bob's comment earlier--that I have real concerns about reliance on surrogates if we are trying to draw conclusions about what effects are in clinical endpoints when we are only measuring the effects on the surrogate marker.

In this setting, the sponsor has raised a number of potential mechanisms through which losartan or losartan versus atenolol could be influencing these clinical endpoints. It could be through any one of these arrays of different ways of formulating blood pressure changes. It could be through effects on LVH. It could be through carotid artery wall thickness. It could be through

atrial fibrillation or an array of other yet to be specified effects. In all likelihood, it probably is through a complex combination of a myriad of different effects where blood pressure could be the leading or very significant aspect of it.

If we, however, trivialize this and simply say is this effect of a 25 percent reduction in stroke accounted for by differences in the average systolic blood pressure, at least that is simplifying the question and I am fairly comfortable to say, no, there is more effect than could be accounted for by that. Yet, I realize there may be other ways of characterizing effects on blood pressure that would maybe more fully capture the treatment effect.

DR. BORER: Let's go on to 2.2 because I think we have to answer this in order to be able to answer some of the later questions. Was the comparison between the two regimens a fair one, as discussed in the ICH E10 guidance? For example, were appropriate doses of both medications used? We all received a copy of the ICH E10 guidance and on page six of that guidance is a discussion of the fairness of comparisons specifically related to dose, but the document not withstanding, would

anybody like to offer an opinion about the fairness of the comparison? Tom, do you want to offer an opinion?

DR. FLEMING: I will just be brief and then have others comment. There are two elements of this. One is dose, as you mentioned, and the sponsor indicated that dose was chosen based on label recommendations for treatment of hypertension. My own view about this in terms of a fair comparison is that I would like to see the regimens delivered as good clinical judgment would indicate they would best be delivered to achieve maximal benefit where we achieve levels of adherence that are what I always refer to as the high level of what would be achievable in the real world, whereas in retention I want perfection. I want everybody to be followed for outcome. For adherence to interventions, I would like to know in my clinical trials answers that are relevant to the real world. So, I don't want an extraordinary level of adherence that couldn't be achieved in the real world.

So, in my own view, the essence of the answer to this as it relates to blood pressure because I know there needs to be a lot of

discussion about the fact that only half the patients actually hit a targeted systolic blood pressure and 90 percent diastolic--the essence of this from my perspective is, is that reflective of what we would see in the real world? If not, then that compromises to an extent the relevance of the conclusions.

DR. BORER: Steve?

DR. NISSEN: Yes, one of the problems that I guess I am having, and I might as well put it on the table, is that neither atenolol nor losartan would be the first choice drug in this population. I mean, you asked the question about how do clinicians treat elderly hypertensive patients like this, and the answer is we treat them with diuretics. We go to diuretics; if they don't work, depending on the patient, we add an ACE inhibitor or perhaps amlodipine, as was done in ALLHAT, but neither atenolol nor losartan. So, again, it is difficult to answer that question because I just wouldn't use atenolol in this population as a very common first-choice drug for hypertension. So, it sets up a bit of an artificial construct.

I would be interested in other people's comments. Tom does this for a living and other

people do, but do you all give atenolol to elderly hypertensive patients?

DR. BORER: Beverly?

DR. LORELL: I think your point is a good one, and it is difficult to know how to get around it. I think in an elderly population group--not all, but I think many or most clinicians, unless there were compelling reason because of prior infarct or active poorly controlled angina, would not choose a beta-blocker as the second add-on to a diuretic. It would be extremely rare to start with a beta-blocker or an ARB in that setting.

I think one of the problems in this fairness comparison--and I don't even like using the word "fairness" because it is somewhat pejorative and I don't mean it that way at all--is that, as was raised earlier, you know that when you are going to use a beta-blocker in an elderly population you may have more side effects and you may have more withdrawals from drug. That was, indeed, what was seen in this study and I think would have been predictable in the design. So, is that an issue of fairness as formally defined in this document? Maybe yes.

DR. BORER: Is anybody disturbed at all by

the fact that losartan was given to its maximum labeled dose but atenolol may not have been? Is that an issue here at all for anyone? If not, given the fact that this was the population that was studied, accepting that this was an elderly population and perhaps this regimen wouldn't have been the first choice for this population, within this population was there anything that would preclude us from judging that a fair trial was carried out? It doesn't sound like it. Bob?

DR. TEMPLE: I know I said this before but I want to emphasize it, fairness is critical if you claim you are superior. Fairness is not relevant really if you just want to show you work.

DR. BORER: That is clear. The only reason we have been asked to comment on this is because you do ask about superiority later.

DR. THROCKMORTON: No, there is another reason. There is another reason why you might care about the beta-blocker part of this and that goes to Tom's level of evidence here. If you are using a trivial dose of a beta-blocker that you might imagine, in fact, was roughly placebo, to beat that would be sort of at the one trial level and you would have no additional cushion.

DR. TEMPLE: Right, you are depending in this case for strength of evidence on it working. We had a big argument at the time atenolol was approved. We couldn't see any advantage to 100 over 50 but we left it in the label anyway. Some people think 25 is the right dose so 50 is not too bad.

DR. BORER: On this next question, number three, we need a vote by the committee with a brief reason after you give your vote, if you don't mind, for the record. Number three, are the results of LIFE alone an adequate basis for approval of losartan to reduce the combination of cardiovascular mortality, MI and stroke? Tom, why don't we start with you and then we will go to John at the end of the table and come around?

DR. FLEMING: Well, I have already stated in response to question two that I think the results of LIFE provide the strength of evidence of a single positive study. It is just over the edge of what we would require for statistical significance on the composite primary endpoint.

In terms of whether I would interpret that to be robust and compelling, generally I would have expected we would need stronger evidence. We are

going to talk, in question four, about other data.

I will just mention as an aside at this point that external data certainly does give one some caution in the sense that what we are being asked to consider here in LIFE is that the effects on clinical endpoints are substantially being achieved, when you are at least looking at the comparison against the control arm, in manners other than blood pressure control, at least systolic and diastolic blood pressure control. In that regard, this study is moving us out into new frontiers and is the kind of result that generally you would like to have good reinforcement for from other relevant sources or else you would like to have a particularly strong result in the study.

Now, what gets me in a sense to a stronger result ironically in looking at the elements. When I look at the components, the results on stroke are particularly intriguing with differences at the 0.001 level and, as we noted earlier, the differences we see on cardiovascular death are in a sense giving us a consistent picture because those are substantially driven by the stroke-related death.

So, I struggle a bit as a statistician to

say, all right, you have hit what I referred to earlier when I said 0.001 is the strength of evidence of two positive studies but it wasn't exactly the primary endpoint; it was a component of the primary endpoint. So, I am left very much on the fence here. My more rigorous side of me would say it doesn't hit it. My less rigorous side says that certainly there is considerable evidence as it relates to effects on stroke.

DR. BORER: Can I ask for a clarification here? When I look at number three and number four, the only difference is that number four allows us to consider prior expectations. Do you mean by that that only in number four can we consider the known or reported effects of beta-blockers plus diuretics versus placebo or no?

DR. THROCKMORTON: Yes, you should sort of think of three and four and five as a sort of ladder of--I don't want to use the word claims but sort of descriptions of clinical effect. So, for the first one you could say, you know, this trial in and of itself, without needing to think anything about the comparative effects of the beta-blocker/diuretic regimen versus placebo or diuretics or anything else, is sufficient.

Number four says no, you have to call on the things that I think I understand about the relative contribution that beta-blockers add to diuretics and diuretics add to placebo, however you want to parse that.

Five then sort of takes you to the next level, the level that we have sort of alluded to in the first part, which is to say, well, is this trial, perhaps with other things that you think you understand, in fact sufficient to say that this regimen is, in fact, superior to a regimen based on atenolol? That is a level that the sponsor has proposed. I understand that, but that superiority is possible obviously for the primary endpoint or, as Tom suggests, some component. It may be that you may want to comment on that, that there may be more robust data for one or the other components.

In that latter event, should you choose that in some way some superiority has been demonstrated, what we would need to have from you is a comment on how to describe that in labeling and that is where it would get somewhat more complicated. You can put things in a label in a couple of different places. You can put them in just the clinical trial section describing what you

found, or you can give them a whole new claim. You can say this is something other than just blood pressure; this is a whole new effect of this drug. We would be interested in having some conversation about that as well, should we get to the end of, I guess, that tertiary branching in decisions.

DR. TEMPLE: The immediate need is to distinguish three and four, which are about whether it works compared to nothing, and five, which is whether it is best. I thought what you were answering, Tom, was more related to five or perhaps three without considering whether atenolol works.

DR. FLEMING: Bob, you are making a point here. I have difficulty not answering three, four and five together, not just because it is getting late in the day but because they are, in fact, interrelated. As I view it, three and four say is there adequate evidence to establish that we have efficacy? Whereas, five is saying, in fact, can you also say it is superior to atenolol? I believe my answers to three, four and five are no, yes and no but, in fact, I am not so sure why three is so important. Four seems to be the most important one and my answer yes to four, if it is acceptable to go into that--

DR. TEMPLE: We would agree with that. You should take into account what you know about atenolol.

DR. FLEMING: Essentially, as I am answering four what I am really answering yes to is stroke. I am really moving in the direction of saying when I look at these data, what these data are telling me is that there is efficacy here as it relates to the stroke endpoint and what is reinforcing to me, even though I have expressed all my concerns in question one about how uncertain it is what atenolol's contribution is, when you look at the totality of the data that is provided by the sponsor in their very informative meta-analysis and their Table 2, what comes forward with atenolol pretty consistently is the effect on stroke. Now we are building on that with a result that is at the 0.001 level in the LIFE study on stroke.

So, as I look at these data, on three it is not enough but in four, with that totality of evidence as it relates to stroke, I think there is adequate evidence for a label on stroke as efficacy. But in five I am back to the LIFE study alone and I am not persuaded that there is a superiority to atenolol in the LIFE study even on

stroke.

DR. BORER: Tom Pickering? I am sorry, John, I forgot that you are not voting. Tom Pickering, you can take three alone or, if you want to, three and four.

DR. PICKERING: Again, I guess I don't vote but my answer to three would be yes, but I would be concerned if the labeling actually specifically said MI since somebody looking at it is going to say yes, losartan reduced MI and stroke because that is what the labeling would say and, clearly, it didn't reduce MI. If you look at the safety analysis, they concluded beta-blockers didn't reduce MI in that analysis. So, that would be one qualification. I think I am convinced that it reduced stroke better than atenolol in this population.

My other reservation would be really what Steve has been raising, the issue of how generalizable these results are. Again, I would be concerned if there was just this blanket statement saying it reduces mortality, MI and stroke because I think we should limit it to include the people over the age of 65 and non-blacks. I guess the LVH is already in the proposed indication so that is

not an issue.

DR. BORER: Actually, you do vote, Tom. For the record, are you saying that you would vote yes on number three?

DR. PICKERING: Well, only if it is modified.

DR. BORER: Okay, only if it is modified. Were you answering number four at the same time or do you want to come back to that afterwards?

DR. THROCKMORTON: Is that yes to number four and no to number five but yes for CVA?

DR. PICKERING: Yes, I would accept the stroke.

DR. TEMPLE: Jeff, could I just say I am personally overwhelmingly convinced that all the effect is on stroke-related matters and I can assure everybody that the labeling will convey that.

DR. BORER: Steve?

DR. NISSEN: I am pretty impressed with the stroke results in this very specific population. I think that it is pretty hard to argue with a p value that has a couple of zeroes in front of the one. So, you know, I find it convincing. However, I really do think it has to

be modified by understanding in the label, or putting in the label very clearly the population so that clinicians can, in fact, interpret the data properly.

I don't know if you want this now or later, I actually wrote something, which maybe at some point we can discuss, that I think gets at the heart of this. But the way the thing is written in three I can't vote for. I just simply can't because I don't think that the combination of cardiovascular mortality, MI and stroke was proven. Yes, I know you are going to fix it, but you asked the question that way. So, you know, if I am forced to answer the question that way--now, I can come up with a label that states pretty clearly what I really think.

The thing that actually worries me more is four. Jeff, I recognize that we have not had a chance as a committee to review ALLHAT but there is a signal there that makes me terribly nervous. Here is the signal, that the regimen that did the most poorly on the stroke endpoint was the lisinopril regimen. It was clearly inferior to both diuretic and amlodipine, and we have a drug that works by basically the same mechanism or

extremely similar. Then, in most head-to-head trials, really only two that I know of, the ARBs have not done as well as the ACE inhibitors. So, many of us have suspected that ARBs are less effective agents than ACE inhibitors. In ALLHAT, in a huge population lisinopril was not the drug of choice for stroke prevention.

So, if we do put this in the label, number four is actually much harder for me than number three. LIFE makes the case that compared to atenolol this is a good regimen. The problem is that I don't know whether agents that work through the renin angiotensin system are the best drugs to prevent stroke. So, we may be sending a message to clinicians which is a bad message, which is use ARBs for stroke prevention when, in fact, the best agents for stroke prevention are not ARBs.

DR. FLEMING: Just to probe with Steve a bit, are you unpersuaded that losartan could have alternative mechanisms of action that might be particularly relevant in the LVH population?

DR. NISSEN: You know, it is possible but all I know is that we have two trials where ARBs and ACEs went head-to-head, OPTIMAL and ELITE. In both cases the ARB didn't do as well.

DR. TEMPLE: Low dose, Steve.

DR. NISSEN: Yes, I understand. Bob, I understand all the caveats but I guess what I just trying to help you all understand is suppose that my hunch is right and that, in fact, the bradykinin effect of ACE inhibitors is important, then what has happened is we have now given the first label to reduce these endpoints to a drug which is actually inferior. We have already labeled losartan as inferior to kavisartin in blood pressure reduction.

DR. TEMPLE: Only in once a day dosing.

DR. NISSEN: I understand. So, we have the weakest drug in a class that may be a relatively weak class that happened to beat an even weaker drug, atenolol. So, we are getting onto a slipper slope here.

DR. TEMPLE: Yes, you also don't know all those things. I mean, there are two massive meta-analyses comparing calcium channel blockers and ACE inhibitors and the results depend on who does it.

DR. NISSEN: Yes.

DR. TEMPLE: This is on stroke too. In one stroke looks better on CCBs, in the other it

looks better on the other. All the numbers are very, very close.

DR. NISSEN: In ALLHAT they weren't close.

DR. TEMPLE: In ALLHAT you have to look at race specifically.

DR. NISSEN: All right, all right. I will take a stab at it--

DR. BORER: Can we wait until we go through--

DR. NISSEN: Sure.

DR. BORER: --the discussion of these first few points because the specific labeling we could even deal with later, if we had to.

DR. THROCKMORTON: Yes, I don't have a general labeling question. So, deal with that whenever.

DR. BORER: If I am understanding correctly, Steve, for the record you are voting yes on three and no on four? Is that it?

DR. NISSEN: I am voting no on both because the question is asked regarding the combination and I don't think I can say yes to that.

DR. BORER: And you are not dealing with five yet, which is okay because I think we are

going to have to come back to that.

DR. TEMPLE: Jeff, it is important--we should have done this but we didn't, assume for the moment that what I said is true, which is that if we think there is some claim in there it would be quite specific about what part of the combined endpoint was effective. Assume that and make it a separate question if you want. But I am completely convinced that there is no sign of anything once you leave the stroke area.

DR. NISSEN: Then I would say yes to three but no to four.

DR. BORER: Okay. Alan?

DR. HIRSCH: Would you like me to be succinct or lengthy?

[Laughter]

DR. BORER: Succinct, please.

DR. HIRSCH: I can try that; I have been trying all day. I am going to approach this from the point of view of a strict trialist. I think that LIFE was well designed, performed in a high risk population with appropriate following of a protocol. Within that context in this population, not yet worrying about how we extrapolate; not yet worrying about labeling, I think that the answer to

three is yes, a combined endpoint reached a point of statistical significance for the three combined endpoints. But I am able to say that because Bob got me off the hook earlier.

That means that number four I also think is yes because I think combined with other data we have I am not yet really ready to discard all the other blood pressure surrogate data that demonstrates the efficacy of beta-blockers, atenolol in particular, as being so weak as to have no impact. So, I think we have adequate information there. I will hold on five. I have different opinions.

DR. BORER: Beverly?

DR. LORELL: Your reassurance not withstanding, I do want to clarify that for both three and four I would say yes for the explicit measure of fatal and non-fatal stroke. I do not think the data, as presented, are an adequate basis for approval for the combination, including not only MI but also cardiovascular mortality, since there was not a strong signal of benefit for coronary heart disease and the mortality benefits also seemed to be driven by stroke.

DR. BORER: Interpreting the questions as

I do, I would vote no on three because I don't think without the prior knowledge of the effect of beta-blocker plus diuretic I could conclude that there is sufficient evidence for approvability. But for number four I would vote yes. That is, given what we have been presented and what we know about the effects of beta-blocker plus diuretic, the results of LIFE indicate an adequate basis for approval of losartan to reduce the cerebrovascular event rate and perhaps the associated cardiovascular mortality.

But, certainly, I would concur with everyone else who has said that we need to remove MI from that approval. I would go one step further in that, as Tom suggested, and would only vote for approval for the losartan-based combination in number four if we are relatively strict about the population for whom the combination or the drug is approved. I wouldn't say 65. I think the investigators looked at a population older than age 55. That was the group they looked at. That is where they saw their results and I don't think we should subgroup but I would say over 55 because we have been presented with a great deal of information that suggests that in younger patients

perhaps there would not be a benefit.

In addition to the obvious left ventricular hypertrophy description of the population, I would say that we need to make some statement about race somewhere and we can talk about how we might do that. But with those caveats, I would vote yes on four. JoAnn?

DR. LINDENFELD: Really restating what Jeff said, I would vote no on three but, believing that the active comparator is clearly effective, I would vote yes on four.

With all the caveats you have mentioned, I would have one other. I am uncomfortable saying losartan is better than atenolol. I think this should strongly say in some way losartan included in a regimen use of diuretics because I don't think there is enough evidence here for me to say losartan is better than atenolol. I think we have to in some way phrase it that clearly the majority of the patients were on diuretics. Without that, I wouldn't be comfortable approving losartan alone.

DR. THROCKMORTON: We are mixing things up. I think several of you chose not to answer number five.

DR. BORER: We will get back to that.

DR. THROCKMORTON: That is fine, we will come back to it.

DR. BORER: I want to just amend what I said. I wasn't as clear as I should be. I agree completely with JoAnn. I am referring here to approval of the losartan-based regimen as opposed to losartan alone. Paul?

DR. ARMSTRONG: I agree with JoAnn's caveat to your comments. I have nothing further to add.

DR. BORER: Susanna?

DR. CUNNINGHAM: The same for me.

DR. BORER: So, that is a no on three; a yes on four for Paul and Susanna. Mike?

DR. ARTMAN: I would reiterate everything everyone else has said, but I think I would vote yes on three and yes on four.

DR. BORER: Okay, now we can go on to number five, and we need a vote on the first portion of that which is do you recommend approval of losartan as having demonstrated superior efficacy when compared with atenolol in the population studied in LIFE to reduce the incidence of the combination of cardiovascular mortality, MI and stroke? Forget about the endpoint for the

moment, but Tom, who already voted on this, suggested that while there was enough information here to suggest that the drug works, there isn't enough information to state that the combination including losartan is clearly superior to the combination including atenolol. So, that would be a no on five. Tom?

DR. FLEMING: Just to expand very slightly because I would just like to confirm what I have heard others recently say as well, that is, the refined wording on four that I had voted yes to is a losartan-based regimen involving combination with diuretics in the population, as Steve and others have pointed out, that was specific to the trial in which it was done. Yes, I did say no on five because I believe the evidence doesn't meet what I would consider the standard strength of evidence, even though it is that of a single positive study, to say that superiority has been demonstrated.

DR. TEMPLE: Can I just ask Tom about that? In your first trip through this you were musing about what to make of the rather low p value for the stroke endpoint alone but you came out with not good enough because it wasn't the primary endpoint?

DR. FLEMING: Well, in that regard my answers to three and five are very inter-related. The answers to three and five are based on LIFE alone--

DR. TEMPLE: Right.

DR. FLEMING: --and in LIFE alone we certainly have, as I have said, evidence of a single positive study but if it is going to meet what we call the robustness compelling, at least what I think of in a subjective way, the evidence from one and a half to two positive studies, it doesn't meet that.

DR. TEMPLE: And your stroke endpoint didn't take you over the top.

DR. FLEMING: And here is where my rigorous statistical side comes in, and I don't apologize for it, it wasn't the primary endpoint--

DR. TEMPLE: That is why you are here.

DR. FLEMING: -- and if we had said at the beginning that stroke was the primary endpoint, then I am going to look at that 0.002 or 0.001 p value in a different light. What I did when I took the liberty of saying the primary endpoint was 0.023, this 0.003 only came from an exploratory what I call common sense look at the data to say it

is obviously stroke. But I don't believe any of us can interpret that 0.001 in the same light as if it had been the p value from the primary prespecified analysis. That is my basis.

DR. TEMPLE: I understand. A brief observation, we are telling a lot of people now set your primary endpoint and do a sequential analysis such that you only get to look at your three components at--I don't know, 0.0013 if you win on the first one. Had they done that, they would have had a fairly robust outcome but they didn't do that.

DR. FLEMING: What you are saying, Bob, is very reasonable advice, but that 0.013 I would still interpret as the strength of evidence of a single study. If it is one-sided, what is 0.006 squared times two for the strength of evidence of two studies?

DR. BORER: Tom Pickering?

DR. PICKERING: I would answer yes given the same provisos as in three if it is limited to stroke in the population that we have already discussed.

DR. BORER: Steve?

DR. NISSEN: And since this question does,

in fact, ask about labeling can I make a try at it, Jeff?

DR. BORER: You can if you want to but first why don't we vote whether we agree that it is superior? If the answer would be no, then labeling would not be an issue.

DR. NISSEN: I think on the stroke endpoint it is superior but the devil is in the details on how it is described. You know, I want us to weigh in very carefully what we think ought to be described and you will obviously write it the way you want. But, you know, I would be very, very uncomfortable if this were written excessively broadly.

DR. TEMPLE: But even before we get to that, I mean, Tom looked at the same data and said "close but no cigar" on superiority.

DR. NISSEN: Yes.

DR. TEMPLE: Are you saying it makes it because of the stroke?

DR. NISSEN: I am saying it makes it, and I am saying it makes it in part because I can't explain it all on blood pressure for stroke. You know, you can get some of it. I think atenolol, in fact, is effective. So, I think they beat a

regimen that is effective. It is not the best regimen by any means. So, I feel okay in saying yes to number five but I have very significant concerns about how you say it that would make a big difference on whether I vote yes or no.

DR. THROCKMORTON: Sorry, just to press on that a little bit more, you are voting yes and I guess Tom--Tom Pickering--is voting yes based only on the data from within this trial, or are you drawing on other things that you think you know about the relative efficacy of the two regimens?

DR. PICKERING: This trial.

DR. NISSEN: This trial in this very narrowly defined population.

DR. BORER: Alan?

DR. HIRSCH: It is interesting how we split on this one. I will vote no on this comparison for a series of reasons we have been over. I don't think that we quite have the robustness in the single trial demonstrating superiority. I have some doubt regarding the impact of the atenolol comparator. Back to the fairness doctrine, I am not quite sure that I am comfortable that we have a completely fair comparison across dose range, although on a

real-life level it may not be practical.

DR. BORER: Beverly?

DR. LORELL: For number five I will vote no for the reasons already stated.

DR. BORER: I vote no as well for exactly the reasons that Tom elucidated.

DR. LINDENFELD: No as well for the same reasons.

DR. ARMSTRONG: No.

DR. CUNNINGHAM: No.

DR. ARTMAN: No.

DR. BORER: Given that, I don't think we actually have to go on to 5.1, 5.2. So, let's go to six. The sponsor has presented analyses looking at the comparative effects of the two drugs in a number of demographic subgroups. None of these analyses was allocated alpha as part of the statistical plan. We need to give an opinion on the record for the following portion of this question, do any of these analyses meet the standard for robustness of clinical data sufficient to support the description of the effects of losartan in the population? If so, please identify that population or populations. We need some statement on this. Mike, why don't we start on

your side this time?

DR. ARTMAN: Why don't we start on that side because I am still digesting the question?

DR. BORER: Okay, let's start with Tom who is our committee reviewer?

DR. FLEMING: Well, I assume when we are saying here do any of these meet the standard for robustness of clinical data sufficient to support the description, it really means do we believe that these are sufficiently well established that we need to include in the label an indication that these subgroup effects indicated a level of effect modification that we think is very likely not attributable to chance alone. Is that a fair summary?

That being the case, I am of the perspective that I would say no for all four of these. I would acknowledge what has been said by many thus far, that is, in reality it is probably true that treatment effects do vary by characteristics of participants. The challenge is that we are generally just barely able to understand what the global effect is and unless there are very compelling effect modifications, which is a matter of strength of evidence, external

validation and biological plausibility--it sounds like you wanted to comment.

DR. THROCKMORTON: It is just that I am puzzled. The entire study was done--

DR. LINDENFELD: In LVH.

DR. THROCKMORTON: --in the first population. I guess I thought it likely that that would be one--

DR. LINDENFELD: Number 6.1 is yes.

DR. THROCKMORTON: --given the answers that I heard before I was expecting a yes for. Then, the question would be whether the others came to that same level.

DR. TEMPLE: But perhaps you think it is broadly applicable.

DR. FLEMING: To be frank here, I was really focusing, I apologize, on the second, third and fourth of these. So, indeed, I agree with you.

DR. THROCKMORTON: That was not a trick. I apologize.

DR. FLEMING: I am looking in particular at the gender issue, the age issue and the diabetes issue. In diabetes what certainly in particular did catch my attention was the survival interaction. Of all of these, the one that, in

fact, approached a level of statistical evidence that is not readily attributed to chance alone is the mortality. But unless there is fairly strong biological plausibility for effect modification by diabetes status on mortality, mortality is not a primary endpoint so where I have trouble giving it particular credence is it is a non-specified subgroup. It is not an alpha-spending subgroup and it is not even on the primary endpoint.

But I would think it would certainly be appropriate in the future to be looking for whether there would be other data that could support potential effect modification on the mortality endpoint for 6.4.

DR. BORER: Mike?

DR. ARTMAN: for 6.1 I would say yes, and for 6.2, 6.3 and 6.4 I would say no.

DR. BORER: Susanna?

DR. CUNNINGHAM: I concur.

DR. BORER: Paul?

DR. ARMSTRONG: I agree.

DR. LINDENFELD: Agreed.

DR. BORER: I would vote the same way. Beverly?

DR. LORELL: Agreed.

DR. HIRSCH: Agreed.

DR. NISSEN: Concur.

DR. PICKERING: Again, I think the benefit seemed to be largely confined to the elderly so I was impressed by the isolated systolic hypertension group, which was the same group where there was the reduction of stroke and mortality.

DR. BORER: Do you think that that is sufficient to warrant a description in a label for this combination for this drug?

DR. PICKERING: I guess I would say yes.

DR. BORER: Those are the components of the questions for which we needed individual answers. Let's go on to number seven, the FDA has identified an association between atenolol use, atrial fibrillation and stroke. Does this analysis, combined with other available data, meet the standard for robustness of clinical data sufficient to support a description of these effects? If so, where?

I am going to suggest the answer is no. Does anybody have any disagreement with that? If not, then let's move on. I am sorry, Tom?

DR. FLEMING: I do but, Bob, go ahead.

DR. TEMPLE: I just wanted to compliment

the reviewer, Dr. Marciniak, for noticing it. Even if we ultimately don't conclude that it is real, it just shows the value of a careful review.

DR. BORER: My suggested answer is not meant to indicate that I think it is not real, just that it isn't sufficiently robust for us to warrant a description at this point. That is all.

DR. TEMPLE: I understand.

DR. HIRSCH: I would like to opine on that as well. I think that I would vote no but I think it is worth looking for a future generating hypothesis. It is important.

DR. FLEMING: I actually spent a fair amount of time thinking about this and let me just try to summarize fairly concisely what that thinking is and it largely comes up with the same conclusions others have said.

There are three or four specific issues that are arise here. One, is atrial fibrillation associated with increased risk of stroke? Yes, it is. That is very apparent. It is roughly three-to four-fold higher risk. Hence, it becomes very relevant to ask the question, as the FDA reviewer had asked.

The second question, does treatment induce

a change in atrial fibrillation? Well, there is certainly some evidence that the rate is higher on atenolol. Depending on which definition you are using, it is about an 8 percent versus 6.8 percent rate. Does treatment cause a change in stroke? Yes, it does.

Now, ultimately the question is, is treatment's effect on stroke in part mediated through this differential effect on atrial fibrillation? Essentially, what I had done was to look at Table 48, which is from the FDA reviewer, on page 68. We see some of those things that I had just mentioned. That is, the rate of stroke is much higher in those with atrial fibrillation, but also the higher rate of stroke on atenolol versus losartan is more evident in those with atrial fibrillation.

So, one can essentially try to get some sense of how much of this difference in stroke could be mediated through a differential effect on atrial fibrillation by recognizing that if the increase in stroke rate is about 25 percent going from losartan to atenolol in the non-atrial fibrillation group and about 50 percent in the atrial fibrillation group, then the fraction of

patients who are more likely to have atrial fibrillation will then have an increase that will be induced both by having a larger fraction in the atrial fibrillation group and a larger fraction of stroke rate within the atrial fibrillation group.

Without going through all the calculations, I did a crude approximation that said, under that assumption, about 20 percent to 25 percent of the total effect of losartan over atenolol on stroke could be attributed to atrial fibrillation, but what I would really like to do is see a time-varying covariate analysis, which the sponsor did and came up with almost exactly the same answer in a more sophisticated analysis.

That doesn't mean specifically that a quarter of the overall difference in stroke is specifically mediated through this lower level of atrial fibrillation, but it is suggestive that whatever it is that characterizes patients being different when they have atrial fibrillation that global mechanism could, in fact, be accounting for 25 percent.

So, in a crude way trying to put pieces together here, we see a 25 percent reduction in stroke on losartan versus atenolol. Of that 25

percent reduction, maybe a quarter of it seems to be attributable to a difference in blood pressure. Maybe a quarter of it seems to be attributable to this difference in atrial fibrillation and the other half of it we still haven't figured out. And, all of those are still very crude calculations.

The bottom line, having said all that, is in any way this isn't proof that these are the mechanisms by which these differences have occurred. So, I would agree that there wouldn't need to be any specific indication of this.

DR. BORER: Alan, did you have a comment?

DR. HIRSCH: This harkens back to the first part of the discussion when we asked was blood pressure really the key here. I think we have to circle back before we write a label, which is to say that if we are looking at an endpoint as important as stroke reduction and we are impugning that this is an aid to an ARB-mediated effect by blocking angiotensin effects, we will all go down the pathway of assuming there is some biologic effect on blood vessels unless we design trials to look at the multiplicity of mechanisms that create stroke. So, though we cannot answer the question

from this single trial alone, I think it has real ramifications for future trials that I am sure we are going to see of this design to look at head-to-head comparisons. So, this is I think potentially a major point for future trial design.

DR. BORER: Paul?

DR. ARMSTRONG: Well, because it may be helpful to the agency, for the record I think the issues around withdrawal of therapy and the run-in period, which I tried to get at this morning which we really can't get at, are critical in terms of the potential first component of the bimodal distribution of atrial fib., with the second component being in the termination and the strategy with which withdrawal was accomplished I think is important if one is going to go after that.

The second issue I think is that much of the atrial fib. was investigator determined, which is probably patient driven, which is probably, in the absence of beta-blocker, patient perception of atrial fibrillation, and we are uncertain about the role of perception versus reality with and without beta-blockers. So, there are several issues here of potential important for future study, just to put on the record.

DR. BORER: Let's move on to the final question--

DR. THROCKMORTON: Sorry, Jeff, if we are done voting on this one I wanted to pick up on something Paul just said where you could give a little bit more help to us. This did have a run-in period and then a long-term comparison of two regimens. I wonder if anyone wanted to comment on whether that run-in period--how critical was it to have that run-in period? How critical, in fact, was it to demonstrate that people had some level of hypertension over whatever period of time that was prior to randomization? Or, if this trial, like ALLHAT for instance which had no run-in period and patients were randomized directly, as I recall--would that affect your interpretation of these results in a substantive way?

DR. BORER: In terms of the atrial fibrillation issue?

DR. THROCKMORTON: No, in terms of overall trial design.

DR. BORER: Well, I will give you my opinion and everybody else can chime in. You know, it seems to me that if you are going to be treating people for high blood pressure, to reduce their

blood pressure from a hypertensive level you have to have some evidence they were hypertensive in the first place. While there may have been superb documentation that that was true in many of these patients, I can't believe it was true in all 10,000 or perhaps even in a large portion of them.

DR. THROCKMORTON: I think we had information that the sponsor presented that it was true in--I don't know--1000 out of 10,000 that had blood pressures going too high or too low.

DR. BORER: No, no that is not what I meant. What I meant was that before the drugs were taken away the only way you knew that the people were hypertensive was that they had a history of hypertension. There was no clear documentation, nor was there documentation of the severity which was, of course, an exclusion and inclusion factor. So, you know, I think it is important to document what it is you are giving drugs for before you give the drugs in a trial. Paul?

DR. ARMSTRONG: I think it gives you insight into the heterogeneity of the population that was under study. There 1500 patients that didn't make it to the starting gate but were potentially screened and in the run-in period.

Just as you have said, although we don't yet have the details and, it would be helpful if they are available, to get them, how many, in fact, had blood pressures that were too high? How many did not have hypertension that was of interest to the study? To me, that is a very germane point.

DR. BORER: Beverly?

DR. LORELL: I think that another difficult point, and I think the sponsor was asked and responded in detail that the data really wasn't there, but I think in planning trials it might be helpful, in informing the FDA about trial design, to have more data about adverse events that occur with drug withdrawal. I think all of us nervous about beta-blocker withdrawal in this trial. Those data are not traditionally either rigorously collected, nor are they paid for in terms of normal reimbursement for inclusions of subjects. So, that would be the kind of thing I might be worthy to think about prospectively.

DR. BORER: Alan?

DR. HIRSCH: Well, as long as you asked, since we are going to be asked to give opinions regarding the potential pleiotropic effects of blood pressure lowering drugs, this focus on the

delta, whether it is 0.5 mm Hg, 1.0 mm Hg, 2.0 mm Hg is going to become increasingly important because there probably is both the traditional blood pressure effect as well direct vascular effects of these agents, and I think it is important to get this quality data at the beginning.

DR. BORER: Steve?

DR. NISSEN: Yes, I can't let that go unchallenged, Alan. I just find it absolutely not compelling that there is a mechanistic explanation for this, particularly in light of the ALLHAT data where a very similar drug that works through the renin angiotensin system was distinctly inferior to both diuretics and amlodipine in stroke reduction. You know, I have heard enough about angiotensin II being the Darth Vader of the cardiovascular system and I am tired of it. I don't think there is evidence for it, and you can scream and yell all you want about mechanism here but until somebody shows me robust evidence that drugs that work through the renin angiotensin system are superior at reducing any endpoint in prevention I am not convinced.

DR. THROCKMORTON: Steve, what would

robust data mean for you there? The sponsor and I think Tom laid out a bit earlier, and you can sort of think of lots of ways that blood pressure could vary between the two groups. You can think of it over time and you can think of it within day and just at the end of the trial. How many ways would you have a sponsor assess comparative antihypertensive efficacy to convince you that there was an effect above and beyond the effect of a given drug on blood pressure?

DR. NISSEN: I was actually responding to something a little bit different. I guess I was responding to the issue about whether or not there is something we know about the mechanism of action of drugs that work through the renin angiotensin system that makes them particularly desirable. I mean, that was one of the principal questions underlying the ALLHAT trial, and it was one of the real failures, the failure of an ACE-based regimen to prove to be superior. So, it is troubling me because if you poll physicians, physicians have all bought this pleiotropic argument. If you ask everybody what was going to happen in ALLHAT, they all said, oh, the ACE inhibitor is going to win. Well, it didn't win; it came in third.

DR. FLEMING: Steve, listening to you, could you remind me how did you vote for question number five?

[Laughter]

DR. NISSEN: Because, you know, the question was asked compared to an atenolol-based regimen was there, in fact, superiority for losartan? The answer is yes. What wasn't tested, however, were the other two agents, the agents which are much more likely to be used in this population which are diuretics and/or amlodipine.

DR. FLEMING: But in a sense it doesn't matter too critically what that control is when now we are talking about is it superior to the control. We are using the data from the LIFE study and what I am hearing from you is a reason for some caution as to the biological plausibility that an ARB is going to be superior in clinical endpoints, particularly when there is no difference in blood pressure control. That is the sense I am getting, that at least we should be cautious. I understand that and I am thinking doesn't that, in fact, give you more reason for being cautious and saying five is a compellingly positive study that establishes superiority?

DR. NISSEN: Superiority to something else. I mean, superiority is always made in context of something else. I wish this trial had been designed differently. I wish that atenolol was not the comparator. On the other hand, somebody spent a lot of time, energy and money to do this comparison and they ended up with a p value with two zeros in front of the one comparing these two regimens with respect to stroke and I think that ought to be described in the label and I wrote something to that effect. But I also wrote in there that it does not apply to comparisons of other agents because it isn't going to change my mind. I am not going to prescribe losartan as the first-line agent for prevention of stroke based upon the LIFE trial because they didn't compare against the agents that we all think are probably the most effective agents at stroke prevention.

DR. BORER: You know, in all fairness though, we are not being asked to select the first-line agent for stroke prevention. That is a guidelines issue. We are just being asked to say whether we think this regimen works better than not giving something. I think that what we have said is, yes, it works better than not giving something.

Beyond that, I think the consensus here has been we really don't want to go although you have suggested that perhaps we should be a little bit more descriptive.

DR. HIRSCH: Just one more point. I think what you have said, Steve, is that you don't believe this pleiotropic effect and I think we are in a stage where all history in pharmaceutical trials in blood pressure lowering has not ended with ALLHAT or LIFE. We have ambiguous signals and I think what we have struggled with today is the ambiguity. So, I would like to leave sponsors in the future and other investigators with that ambiguity so that additional data can come forth to the committee.

DR. TEMPLE: And the good news is they all do pretty well and you can treat people for $10.00 a year. I wanted to go back to what Doug asked because sometimes we are asked this. He asked about how important you think the washout period is. The purpose of the washout in this case is really solely to see what their baseline blood pressure is. In this case, as it always does in very large studies, baseline blood pressures were virtually identical and it doesn't really help you

much to have known that, except you are reassured that they are all hypertensive.

Since we are going to get asked this sometimes, how much do you actually care about knowing that, first, in a non-inferiority study where you answer should be you care a lot and, second, in a superiority study where that doesn't seem so clear? Anybody want to briefly comment on that? I know it is late.

DR. BORER: For all the reasons you have heard in answer to that question the first time it was asked, I think it is important to characterize the patients even for a superiority study.

DR. TEMPLE: So you know who it applies to.

DR. BORER: That is right, exactly. I mean, I could go on and on about this but I think that reason alone should be sufficient.

Let's go on to number eight which is our final question and probably will generate some discussion here. You have heard a discussion of qualitative and quantitative interactions among subgroups. For one relevant subgroup, African-Americans in the United States, atenolol is apparently superior to losartan in its effects on

the primary endpoint. Maybe. No biologic rationale for this apparent qualitative interaction with race has been identified by the FDA or the sponsor. Does the lack of this rationale matter to you? Then there are several other questions which we will get to.

I would like to begin here by saying I find the statement that there is a lack of rationale in one sense perhaps irrelevant and in another sense perhaps not exactly a fair statement. I didn't hear any description of renin sodium profiles or renin levels measured any hway in either of these subpopulations. I understand the label for losartan says it is reasonably well accepted from a great deal of information that has been published that black people who are hypertensive more commonly have volume-dependent than renin-dependent mechanisms than would be true in a white population. Here, we are giving a drug that is specifically aimed at the renin-dependent mechanisms of hypertension.

So, you know, I don't think it is fair to say there is lack of a rationale. On the other hand, I am not sure that it matters. We made an observation here and it is a pretty potent

observation. As I have said before at these meetings, I am not sure exactly how any drug works. I know there are pharmacological effects but I don't know how those translate into clinical benefits. So, I am not sure it is terribly important.

DR. TEMPLE: Just one observation. It is true for all renin intervening drugs, including beta-blockers for sure. None of them work very well alone in blacks. It is also true that when you add a diuretic the total blood pressure lowering of the combination is very similar in all races. So, I don't know what to make of that, except the diuretic makes you renin-dependent again, or something.

DR. BORER: Whatever--

DR. TEMPLE: That is fair, we don't have to understand it. We hardly ever do.

DR. BORER: But having said that, there are important parts of this question that I think we have to get to and I would like to generate some discussion before we close. Are there other data you feel illuminate the observed differences? Do you find this outcome surprising? Let's move beyond that--

DR. FLEMING: Well, before we do, before getting beyond 8.1 and 8.2 I would like to expand a bit more on 8.1 and 8.2 and, in fact, maybe mention up front that we have appropriately congratulated the sponsor on the conduct of a very important and informative trial, and we have appropriately congratulated and thanked the medical reviewer from FDA for an extremely informative summary. I would also like to thank the FDA statistical reviewer for providing a lot of insights which were the very issues I would have wanted to have better understood to answer this question.

As I see it, when I look at subgroup analyses, effect modification--I have probably already mentioned this, I really believe there are at least three factors to carefully consider. One is what is the strength of evidence in these data for effect modification? The second is, is it biologically plausible that there would be effect modification? Thirdly, is there independent confirmation?

On that first point, strength of evidence, I found it very informative that in the FDA statistical review what was pointed out was that it is not uncommon in the context of seeing globally a

13 percent reduction in relative risk in the entire group that in a subgroup that would be fairly small in size for you to see by chance alone lack of any effect in that subgroup. In fact, as the statistical reviewer appropriately pointed out, it was a 28 percent chance. That goes up to a 37 percent chance when you take into account the fact that you have a lot of different covariates that are used for subgroup analyses. It is something that we need to be reminded about. That is, if we are seeing effects that are 13 percent reduction in relative risk and we allow ourselves to slice and dice the data in many ways in subgroups, by chance alone you are going to find some subgroups that don't show any effect.

So, that in itself wouldn't constitute evidence that I would consider at all statistically strong evidence for effect modification. But as his review pointed out, this is more than that. This is a situation where there is a qualitative interaction of such a level that in the black subgroup the confidence interval is excluding equality. So, it is a very strong difference. His summary here provides a sense that it is something that would occur 0.003 in a fairly uncommon way.

With the insight from his analysis, I would say, first of all, this is fairly strong evidence but it is not in its own right, I would say, sufficient to say it is conclusive. So, I go to the issue of biological plausibility and it is relevant from my perspective. I have always said, you know, show effect modification to a clinical and they will come up with an explanation for why there is effect modification. I always say I an complimenting my clinical colleagues because their knowledge is so broad they are always going to be able to come up with some way--

DR. TEMPLE: In either direction.

DR. FLEMING: In either direction. So, one has to be somewhat cautious. But what you are saying, Jeff, to me is relevant and if there is, in fact, rational plausibility to blacks being less likely to have a renin response or other rationale, that is certainly relevant in weighing this out. But ultimately as well what is very relevant is, is this a pattern that has been seen frequently? I haven't been keeping score but my sense has been, in my years on this committee, that there have been a number of instances now, more so than what just seemed to be a chance alone event, where blacks

have had much less or very different effects than what the aggregate study has shown. In fact, I think it has also been interesting to see that U.S. populations show less effect but those may be related points, and in fact it seems to be in this study, the fact that U.S. results were less favorable and the global results were entirely driven by the blacks within the U.S. because the whites within the U.S. actually had a very robust effect. But also the other studies, the SOLVD, what was already known about losartan in hypertension, all of these factors, to my way of thinking, now create much more of a sense, and this is what is in 8.2, there does seem to be a sufficient amount of additional data that, with the strength of evidence just from this study alone and this repeated pattern in other studies, does give me a sense that there is something here that is very plausibly effect modification and I would be very interested in hearing from other committee members as to their sense about independent external data and what their sense is of how strongly this would be reinforcing.

DR. BORER: I would like to focus this discussion on what Tom said, that is, the data

rather than biological plausibility because renin angiotensin system activity in some populations notwithstanding, I must say again that it would be probably naive to suggest that the only pharmacological effect of an ARB is to block the angiotensin receptor. I am sure that there are multiple other pharmacological effects that we haven't even identified yet. So, I don't think we can really deal with the biological plausibility, but the issue of whether we are seeing a pattern here so that we should really take this seriously--if anybody wants to comment on that beyond what Tom has said? Steve?

DR. NISSEN: Well, it is particularly troubling when you look at the ALLHAT data, which I know we haven't reviewed yet, but you see the same signal. I think you see it, you know, in all kinds of other data. So, I think that drugs that work via the renin angiotensin system appear not to work as well in African Americans, blacks as they do in whites and this difference is really robust. Just as I was willing to give the sponsor the benefit of the doubt with an 0.001 p value for benefit in the overall population, I think the same should be said for inferiority, if you will, in the African

American population and I do think it ought to be in the label. Certainly if you give them the plus, you have to give them the minus.

I think the prescribing physician has to be told about this just to amplify. You know, in this trial it was a small group of people but in the U.S. the number of African Americans with hypertension is not small. They are actually over-represented. What I worry the most about in whatever you do here is that it is very hard to get negative messages to the prescribing physicians, and the reason is that pharmaceutical detail people don't emphasize the negative messages. They are not going to come in and say, "now, be sure you don't give this drug to African Americans." So, when you give a positive label, you know, there is going to be some leakage here and I think it is not 12 percent, it is more like 20 percent of the U.S. hypertension population that is African American. They are tough to control. I don't know whether the drug is actually worse than placebo here. I have no way of knowing that. What I sure know is that there is a very, very large disparity and it worries me, and I think it has to be in the label and has to be emphasized in public education.

DR. BORER: I just want to point out that Steve answered another part of 8.3 that I would suggest that we accept as our answer, unless anybody disagrees with it, which is 8.3.5, "cannot tell" because we don't know whether L is greater than or less than or equal to imputed placebo.

DR. THROCKMORTON: Sorry, just to break in there, Jeff, if someone has a strong feeling about that it would be very useful for us to hear. Part of the questions at the beginning of the disease and part of the discussion about beta-blockers relative to placebo, and things, were to either provide comfort or not. If you conclude that, in fact, losartan is inferior in some population to atenolol, are you concerned to any substantive extent that it is less than placebo?

DR. BORER: Tom?

DR. PICKERING: Yes, I was impressed by the FDA analysis this afternoon that there is a significant difference between the blacks and the whites. I don't think one can say that losartan was harmful.

The other thing is I don't think you can explain it by differences in blood pressure, from what we heard, which were relatively minor. So,

this may be another example of a blood pressure independent difference going in the other way, so to speak.

DR. BORER: Are you ready to answer the next point?

DR. PICKERING: I am not sure which.

DR. BORER: He is saying that he believes that this is a real effect and he is not sure that losartan can be said to be harmful. I would guess that you really can't say anything about the relation of losartan to imputed placebo given that.

DR. HIRSCH: It is not a matter of harmful; it is just relative order of efficacy here.

DR. LORELL: I think one of the challenges for the FDA, and I am glad I don't have to do it, is how to correctly word a message that in this trial for black Americans losartan was inferior to atenolol and whether you have to address issues beyond stroke. Because I think one of the concerns in the data that we were presented from the FDA is that there is a consistency on every measure including cardiovascular mortality, MI and even total mortality. So, it is an odd conundrum to be in; you might need to say more about black

Americans than you needed to say in terms of the overall labeling.

DR. BORER: Can we make a clear statement about this? The FDA medical reviewer concluded that the data suggesting that there is a difference between the atenolol regimen and losartan regimen did not reach the level of robustness that would allow you to say that losartan was harmful, which would mean losartan is worse than placebo, but it does look as if losartan is less good than atenolol. Do we all agree with that?

DR. FLEMING: Well, I am really uncertain. What I do feel very confident about is that something needs to be said because there is considerable evidence here that there is effect modification by race. I think where we are here is that we believe there is evidence in the global data set that losartan has efficacy. There are differences in opinion on the committee as to whether it is superior to atenolol. Certainly, I would feel extremely uncomfortable for the impression to be given that in blacks losartan is superior to atenolol. My own sense is I don't know whether it is truly inferior. The confidence interval says it is inferior but that is truly data

dredging to say that that confidence interval that indicates that atenolol is superior to losartan in blacks is in any way reliable for inferiority against atenolol but it surely is, from my perspective, very strong evidence against superiority of losartan in that population. I am left more with "the can't tell." I would actually encourage FDA, that is in a position to really see globally what is happening in a lot of very relevant studies, to look at this.

To come back to what I said before, I see three very relevant elements here. One is what we know from this trial; another is plausibility; and, thirdly, relevant external data and there is a lot of it that could be very helpful and it is what is persuading me, and I am hearing reinforcement of that from my clinical colleagues, is substantial. I would at this point really wish to see much more clearly what an analysis would show from relevant agents, and agents in similar classes to losartan to come up with a better sense of the manner in which race is an effect modifier before at least I would be comfortable drawing a conclusion about whether it is harmful. I don't know. I am not saying I believe these data establish that losartan

is harmful in blacks, but it surely leaves me completely uncertain about its benefit and I think, as Steve said--I think it was Steve that said it, this label has to make it very clear, as a result, that these conclusions about efficacy shouldn't be extrapolated to conclusions within blacks until we know a lot more.

DR. LORELL: Tom, may I ask you a question? From the data, and understanding this has to be read by real-world patients and doctors, would you be comfortable with language emphasizing that there is lack of superiority and maybe inferior?

DR. FLEMING: Well, I would like to get some insight from all of you. You are getting at an important issue, which is question 8.4. When I looked at 8.4 I ruled out the first and last options. I didn't feel the results were so strongly negative that there should be a contraindication, although I am leaning toward the warning. I think the sponsor had taken the third option. They were talking about a description in the clinical trials section. Contraindication to the use of losartan, to my way of thinking, would be justified if we had concluded that there was

something bad about its use in that population. My own sense about this is that there is enough evidence here to suggest that there is substantial uncertainty and, certainly, I believe we shouldn't come away with the conclusion that the results of efficacy in the global population would be attributed to the black subgroup.

So, either the warning or the description, but I was inclined to think in terms of the warning as being necessary to make sure that this was clearly understood.

DR. HIRSCH: Could I jump in here and emphasize one more point? What is so wonderful about LIFE is that we are measuring hard outcomes in a prospective clinical trial. This is different from what we had, differences in effects of ARBs and ACE inhibitors on blood pressure responsiveness and surrogate endpoints that didn't respond quite as well. So, to me, I find it relatively unnerving that, you are right, from the robustness of the data we don't really know if there is lack of superiority, inferiority or harm. But not knowing and having so many signals going in the wrong direction I think should really give us caution. We see hepatotoxicity at a small rate that doesn't

quite achieve significance, and that gets back to our responsibility for including enough individuals who are African Americans or blacks to finally answer these questions, especially now when we are measuring hard endpoints. So, I am leaning towards the precaution or warning and, again, it has implications for future trials since we have a first early signal.

DR. BORER: Bob?

DR. TEMPLE: We have confronted subgroups with uncertain results on other occasions. You may remember that in MERIT, where we could think of no conceivable rationale for the failure of the U.S. population to have a survival benefit we, nonetheless, included wording and took a lot of stuff for it internationally, but made it clear that the apparent lack of benefit was not a sure thing; that sometimes things work out when you look at subgroups; and presumably would say something similar to that here although I hear a higher level of concern here than I did in MERIT because at least in MERIT the major endpoint went the right way even if mortality didn't.

DR. BORER: Yes, this wasn't a lack of benefit; this was a clear distinction in the

direction of effect of the comparators.

DR. FLEMING: Not too surprisingly, stroke and the composite show exactly the same pattern.

DR. LINDENFELD: Could I just suggest a choice that is not in here? I think what we are all concerned about is that physicians understand that there is this real concern about black patients. I wonder if that couldn't just be in the approval, in non-black patients. Then you can discuss the results but, rather than putting it back in a warning section, is there anything wrong with the indication for this being in non-black patients for a regimen of losartan--would anyone have any objections to that?

DR. TEMPLE: Are you distinguishing between use of the drug or who this study result applies to?

DR. LINDENFELD: Who this study result applies to.

DR. TEMPLE: It would be hard to think that one say on the basis of this you mustn't ever use this drug in black patients.

DR. LINDENFELD: No, no, I wouldn't say you mustn't use it; I would say who you should use it in. There is a difference.

DR. TEMPLE: Again, are you saying about use of the drug altogether or who the outcome data apply to?

DR. LINDENFELD: Who the outcome data apply to.

DR. TEMPLE: That is what I hear everybody saying, that there ought to be some clear reference to this in some part of the label, to be figured out which part.

DR. LINDENFELD: But I understand you could have it right up front in the initial indication.

DR. THROCKMORTON: But that is a step beyond what Tom was saying. Tom was saying he is not sure you can say it is worse than atenolol. You are saying you can't tell it is better than nothing. Is that correct?

DR. LINDENFELD: That is correct.

DR. TEMPLE: There is no question from everything you have said that you think the observation ought to be clearly described in the clinical trial section. That, of course, means no one will notice it. So, there is some feeling for putting it somewhere else. I have heard one suggestion that it actually ought to be part of the

indications to the extent that the indication refers to outcome data. That is one possibility. The other, perhaps is a warning or precaution. I must say, it feels more like a precaution to me given our uncertainty, but whatever. So, those are two possible choices. I take it you don't think putting it just in the clinical trials is noticeable enough. Would that be a true statement?

DR. HIRSCH: Precaution is more like it. I think, again, where this precaution warning comes from a little bit is the history we have been trying to do for the last ten or twenty years, which is to elucidate the LVH and hypertension in African Americans in particular as a reason to treat because of the high risk of stroke. So, we have been teaching physicians to have a reflex, to notice this and to treat but this may not be the first choice. So, I think it is a precaution or warning.

DR. BORER: Can I ask, just to sort of bring this to some closure, for an opinion from each of the members of the committee about how this finding should be described, whether it should be a contraindication, a warning, a precaution, some statement in the indication as JoAnn has suggested,

one or the other, a description of the clinical trials, or forget about it? John?

DR. NEYLAN: So, this is a non-voting issue?

DR. BORER: Well, there is no binding vote here. We are giving advice to the FDA.

DR. NEYLAN: Okay. My feeling would be that this would be very useful information to the prescribing physician and that information might get lost somewhat if it was merely put in the description of the clinical trial. I favor the use of non-black in description of the changed indication and also a precaution, rather than a warning, further detailing this effect.

DR. BORER: Tom?

DR. PICKERING: I don't think it should be a contraindication. There are a lot of black patients, particularly with diabetes, who need multiple drugs and this could certainly be one of them. I do think there should be some warning or precaution, I don't know the difference, about the effects not being demonstrated in black patients.

DR. BORER: Steve?

DR. NISSEN: I am little bit of the odd man out here because I would not have commented on

the LIFE trial in the indications section at all. I would put the entire description of the trial in the clinical trials section because I think that is about all the conclusion I can come to. I would describe what happened, and I have written something and we are not going to get to it and that is fine, which describes the population that was studied and what was found and also describes the finding in the black population, a simple, fair description of what LIFE showed. I also added the comment that the comparative efficacy of losartan in other populations, in comparison to other antihypertensive agents, has not been tested, as a way of letting physicians know that this is really only a trial in which atenolol was compared.

That is why, Tom, I voted the way I did. I felt that there wasn't enough information to give a general indication for the use of losartan but only a comparative indication in comparison to an agent which I happen to think is a relatively weak agent, but an agent nonetheless. In addition, I would say something in the warning section as well about the African American population, and I would do that in part because in America hypertension is not, you know, some small, isolated, unimportant

group. Those of us who treat patients know that these are very large numbers of African Americans with hypertension. They can be difficult to treat. And, I think the physician needs to know as much as they can about what works and what doesn't work, and I think there is a pretty strong suggestion here that agents that work through the renin angiotensin system, not just in this trial but in others, don't work very well in African Americans and I want my colleagues to know that so that they will choose other regimens preferentially in such patients.

So, my advice to the agency is to describe LIFE in the clinical trials section, not in the indications section. Describe it in a fair and balance way, and I have written something which you can look at later if you are interested. But then also to put that warning in there. I think we have done due diligence and we have given the sponsor, you know, what they have earned here, which is I think they beat atenolol and I am willing to give them that. I am just not willing to say that this is the way to reduce stroke because I don't know if losartan is the best way to reduce stroke.

DR. BORER: Alan?

DR. HIRSCH: Well, this should not be in the indications section. All patients of any ethnicity, race or gender should have access to the agents they require based on their particular clinical characteristics. I think precaution is appropriate. I would like to again sort of give kudos to both the sponsor and the FDA reviewer for pointing out the data so clearly.

DR. BORER: Beverly?

DR. LORELL: I agree with a precaution.

DR. BORER: Tom, did you want to say anything else? No? Mike?

DR. ARTMAN: Yes, I think rather than just a precaution, it should be a warning. I think it needs to be clearly stated.

DR. BORER: Susanna?

DR. CUNNINGHAM: I would prefer either a warning or precaution.

DR. ARMSTRONG: Precaution.

DR. BORER: JoAnn, do you want to add anything?

DR. LINDENFELD: No, I still like the population that benefited in the indications because I think then people have to see it when they are presented with the data.

DR. BORER: I voted that this drug should receive in indication paralleling the indication that was requested, with some modifications that are all in the record. I am not going to rescind that opinion; I believe that that is correct. But if I believe that, then something has to be said that clearly demarcates the potential lack of efficacy in this population. So, I would favor a precaution in bold black letters somewhere in the label, and I would think about, although I am not sure without having the time to do some word-smithing how to do this, if it actually even doable, the additional solution that JoAnn has suggested, which is describing the population for which the drug applies to the new indication very narrowly. I am not sure that that is a practical solution but I think that is something to consider in addition to a precaution.

I think we have covered all the items on the set of questions here. I think, in summary, the consensus of the committee has been that the evidence that is presented is sufficient as stated in number four, with all the caveats that we all gave. The strength of evidence is sufficient for some new indication, appropriately circumscribed,

to be granted in the labeling. Is there any other issue that you want us to raise before we adjourn?

DR. TEMPLE: Thank you. This has been fascinating for all of us too.

DR. BORER: Then we stand adjourned.

[Whereupon, at 5:45 p.m., the proceedings were recessed to resume at 8:30 a.m., Tuesday, January 7, 2003.]

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