DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

Cardiovascular and Renal Drugs Advisory Committee Meeting

THURSDAY, FEBRUARY 24, 2005

8:00 a.m.

Food and Drug Administration
CDER Advisory Committee Conference Room
Room 1066
5630 Fishers Lane
Rockville, Maryland 20005

P A R T I C I P A N T S

Steven E. Nissen, M.D., F.A.C.C., Chair
Lt. Cathy Groupe, RN, BSN, Executive Secretary

Committee Members:

Blase A. Carabello, M.D.
Susanna L. Cunningham, Ph.D., Consumer Representative
William R. Hiatt, M.D.
Frederick J. Kaskel, M.D., Ph.D.
John F. Neylan, M.D., Industry Representative
Thomas Pickering, M.D., D.Phil.
Ronald Portman, M.D.
John R. Teerlink, M.D.

Special Government Employee Consultants (Voting):

Jonathan Sackner-Bernstein, M.D.
Ralph B. D'Agostino, Ph.D.

FDA Participants:

Robert Temple, M.D.
Norman Stockbridge, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. NISSEN: I think we have all our committee members. My name is Steve Nissen. I am a cardiologist in the Cleveland Clinic, and we are going to do some introductions first so that you all know who is on the committee. Let's start with John, over there.

DR. NEYLAN: Yes, I am John Neylan. I am the industry representative on the committee, from Wyeth Pharmaceuticals.

DR. CARABELLO: Blase Carabello, a cardiologist from Houston.

DR. HIATT: Bill Hiatt, University of Colorado, vascular medicine.

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

DR. PORTMAN: Ron Portman, pediatric nephrologist from the University of Texas in Houston.

DR. TEERLINK: John Teerlink, heart failure specialist from University of California

San Francisco and San Francisco VA.

LT. GROUPE: Cathy Groupe, the executive secretary for the Cardiac and Renal Drugs Advisory Committee.

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

DR. SACKNER-BERNSTEIN: Jonathan Sackner-Bernstein, cardiologist from North Shore University Hospital in New York.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician from Boston University and the Framingham study.

DR. STOCKBRIDGE: I am Norman Stockbridge. I am the Acting Director of the Division of Cardiorenal Drug Products. To my right would be Dr. Temple, but it is completely unreasonable for us to start on time and expect him to be here.

[Laughter.]

DR. NISSEN: Dr. Temple usually is awake by ten o'clock in the morning so I expect him later. Lt. Cathy Groupe is going to read the conflict of interest statement.

Conflict of Interest Statement

LT. GROUPE: The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda 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:

In accordance with 18 USC Section 208(b)(3), full waivers have been granted to the following participants, Dr. Ralph D'Agostino for consulting for two competitors on unrelated matters for which he receives less than $10,001 per year per firm; Dr. William Hiatt for consulting and speaking for a competitor on unrelated matters for which he receives between $10,001 to $50,000 per year per firm; Dr. Steven Nissen for consulting for the sponsor and for four competitors on unrelated

matters for which he receives less than $10,001 per year per firm; Dr. Thomas Pickering for consulting and speaking for two competitors on unrelated issues for which he receives less than $10,001 per year per firm; Dr. Ronald Portman for consulting for two competitors on unrelated issues for which he receives less than $10,001 per year from one firm and between $10,001 to $50,000 per year from the other firm; Dr. Sackner-Bernstein for consulting for a competitor on a related matter which was general in nature for which he receives less than $10,001 per year.

In accordance with 18 USC Section 208(b)(1) a full waiver has been granted to Dr. John Teerlink for his role as an independent and blinded adjudicator, consulting and steering committee member on unrelated matters for two competitors. He receives from $10,001 to $50,000 per year from one firm and less than $10,001 per year from the other; for his role as an endpoint committee member on a related matter for a competitor for which he receives from $10,001 to

$50,000 per year; for his role as a sub-investigator on a related matter for a competitor for which the contract was less than $100,000 per year.

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

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participants 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.

We would also like to note that Dr. John Neylan has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Neylan is employed by Wyeth Research.

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.

DR. NISSEN: Dr. Stockbridge, I believe you have some opening comments.

Welcome and Comments

DR. STOCKBRIDGE: The first thing I wanted to say was sort of in the form of a public service announcement. Last week someone, using the name of a Cardiorenal Advisory Committee member but claiming to be from the Division of Cardiorenal Drug Products, made calls to several parties, one on an investigator side and another a pharmaceutical company, clearly trying to get some kind of information. If anyone else ever hears about a case like that I would like to suggest that you bring it to my attention so we can coordinate the investigation of any new case with the current one.

The other thing I wanted to say is that two days ago the division took an action to approve candesartan for use in heart failure and I have

made sure that everybody, this morning at least, got the relevant parts of the labeling that resulted largely from the CHARM-Alternative trial. So, the question about whether candesartan works in heart failure is not what you have been invited to comment on. Instead, there is a fairly simple question--it only takes three pages for me to ask it--

[Laughter.]

--about use of candesartan together with an ACE inhibitor. Thank you.

DR. NISSEN: Thanks, Norman. Let's then just proceed to the sponsor presentation. If it pleases the committee, I think what we would like to do is let the sponsor go ahead and go through their presentation and then maybe hold all the questions together because it is going to be, I think, easier to integrate everything. However, if anybody has burning questions after any of the individual presentations, please let me know and we will try to make sure you get clarification.

Sponsor Presentation:

Regulatory Overview

MS. LANCASTER: Good morning, Mr. Chairman, members of the committee, members of FDA and ladies and gentlemen. I am Cindy Lancaster, and on behalf of AstraZeneca I would like to thank the division and the committee for giving us the opportunity to present the results of our clinical program for candesartan cilexetil in heart failure.

Atacand has been approved since 1997 for the treatment of hypertension and, more specifically, approved in the United States in 1998. Atacand is currently marketed in 92 countries and to date we have 20 million patient-years of exposure available.

Let me begin by sharing a list of individuals who are here today to participate in these proceedings. These are the sponsor representatives. We have also invited our expert external advisers to share their experiences with the heart failure clinical program. Dr. Pfeffer served as a co-chair on the CHARM executive committee. Dr. Young and Dr. Dunlap served as

CHARM U.S. national leaders. Dr. McMurray served as he principal investigator for the CHARM-Added trial. Dr. Granger served as the principal investigator for the CHARM-Alternative trial. They also served as members of the CHARM executive committee.

In addition, Dr. Lewis, Dr. McLaughlin, Dr. Kronmal and Dr. Hennekens are also available to assist today. Dr. Hennekens is here in his role as the chair of the CHARM data and safety monitoring board.

To set the stage for the forthcoming presentations, here is a brief history as of 1996 of the product's development and key previous interactions with the FDA in regard to the heart failure clinical program. Three pilot studies were conducted to help identify the optimum dose and evaluate neurohormonal effects, LV systolic volume and tolerability of the 32 mg high dose under the U.S. IND, prior to the initiation of the CHARM program.

In 1998 AstraZeneca met with the Division

of Cardiorenal Drug Products to discuss the design of the CHARM program, and gained agreement that the program would support a claim for heart failure. The CHARM program was initiated in 1999, and in March, 2003 we completed the program. Later in 2003 a pre-sNDA conference was held with FDA to discuss the content and format of the application. The heart failure supplement was then submitted to the FDA in June, 2004 and a priority review was assigned for CHARM-Added.

An approvable letter was issue by the FDA at the end of December for the CHARM-Added study. As Dr. Stockbridge stated this morning, on Tuesday of this week the division granted approval for the use of candesartan in heart failure primarily based on CHARM-Alternative. As such, today we are here to specifically discuss CHARM-Added and approval based on the results from this particular study. To that point, let me first provide a little background on the CHARM program.

CHARM-Alternative and CHARM-Added were part of the most comprehensive trial program

completed to date with this class of drugs for heart failure. The CHARM program consists of three separate but complementary randomized, double-blind, placebo-controlled, parallel group studies including 7,601 patients.

Alternative was conducted in patients with ejection fraction less than or equal to 40 percent and not on an ACE inhibitor. This Tuesday's approval was primarily based on this study. Added, which is the focus of today's discussion, was conducted in patients with ejection fraction less than or equal to 40 percent and receiving an optimized dose of ACE inhibitor. Preserved was conducted in patients with preserved left ventricular systolic function.

The primary endpoint for each trial was CV death and heart failure hospitalizations. The data demonstrated a statistically significant and clinically important benefit for candesartan in the low ejection fraction studies, Added and Alternative. The primary endpoint for Preserved was not statistically significant. These results

from Alternative, supported by the Added study, formed the basis of Tuesday's approval by FDA for candesartan in heart failure. Additionally, to date candesartan has been approved in 18 countries for the treatment as add-on therapy based on CHARM-Added or without an ACE inhibitor based on CHARM-Alternative.

Specifically, in the United States the indication approved on Tuesday states Atacand is indicated for the treatment of heart failure (New York Heart Association class II-IV and ejection fraction less than or equal to 40 percent) to reduce the risk of death from cardiovascular causes and reduce hospitalization for heart failure.

In addition, the clinical trial section mentions CHARM-Added as a supportive study in the first sentence of the text you see on the screen. Also note there was a 15 percent lower risk of cardiovascular mortality based on both CHARM-Alternative and CHARM-Added together. Furthermore, symptoms of heart failure, as assessed by New York Heart Association functional class,

were also improved.

Based on CHARM-Added, AstraZeneca requests approval for candesartan as add-on therapy when a patient is already receiving an ACE inhibitor. CHARM-Added was designed to allow an investigator to optimize the dose of ACE inhibitor treatment on an individual patient basis when either placebo or candesartan is used for the treatment of heart failure. Treatment resulted in a statistically significant and clinically important benefit when candesartan was added to an evidence-based dose of an ACE inhibitor.

The FDA has posed the question does CHARM-Added provide compelling evidence that candesartan should under some circumstances be recommended for use in patients on an ACE inhibitor.

To help answer this and other questions posed today, we have conducted supplemental analyses, the results of which will be presented here to assist with these proceedings. Next, Dr. Young will present the rationale for use of ARBs in

heart failure. The ARBs and ACE inhibitors have distinct and complementary mechanisms, and data from pilot studies are supportive of the beneficial effects demonstrated from treatment with candesartan added to an ACE inhibitor.

Following that, Dr. McMurray will present information on the selection of the recommended dose of an ACE inhibitor in CHARM-Added. Dr. Pfeffer will then provide a summary of efficacy for CHARM-Added as well as the analyses for maximum ACE inhibitor doses defined by the FDA. Dr. Hainer will present safety information. Dr. Young will then present the benefit/risk profile. That will conclude our formal presentation. Now, Dr. Young?

DR. NISSEN: Any clarification issues for anybody or can we go ahead and move on? If not, let's do it.

Background and Rationale

DR. YOUNG: Thank you, Cindy. Dr. Nissen, ladies and gentlemen of the panel, the FDA and the audience, it is an honor for me to be here today so we can all reconsider an extraordinarily important

healthcare challenge and review data which supports a new pharmacotherapeutic strategy for chronic heart failure.

I need not detail the devastating impact of chronic heart failure's morbidity and mortality. Particularly concerning is the high prevalence of this syndrome and the number of hospitalizations precipitated annually which is increasing, and in those patients associated with even higher mortality rates during follow-up.

This survival data from the Framingham cohort study is important as it demonstrates that though some progress has been made over time heart failure mortality is still great. Even in the so-called modern era of heart failure, the last decade, which would have included ACE inhibitors and to a lesser extent beta-blockers, the 5-year survival rate for men with CHF is still only about 40 percent and women fare only slightly better.

Germane to today's CHARM program presentation is question 1 from the FDA, and specifically question 1.4, are ACE inhibitors and

ARBs sufficiently different that CHARM-Added can support use of candesartan with ACE inhibitors?

To answer that question we need to consider the pathophysiology of heart failure and the relationship of ACE inhibitors and ARBs to the renin-angiotensin-aldosterone system. It had been gratifying to see the insight gained over the last 30 years into the pathophysiology of heart failure and this has helped us design better therapies. Particularly important is understanding implications of the renin-angiotensin-aldosterone system.

Indeed, the vast majority of drugs beneficial in this system, including beta-blockers, attenuate adverse effects of angiotensin-II. Emphasizing that point is this RAAS cascade. I know everyone here has their own favorite RAAS cascade. This happens to be mine. Here we can see the potentially detrimental effects of angiotensin-II effected through the AT-I receptor, as well as some putative beneficial effects of angiotensin-II effected through the AT-II receptor,

specifically increasing kinin and nitric oxide activity.

These observations have significant implications when we consider ACE inhibitor and ARB use in heart failure, and particularly their combination. First, angiotensin-converting enzyme is not the only molecule affecting production of angiotensin-II. During long-term ACE inhibitor prescription chymase activity, for example, can increase levels of angiotensin-II even at doses of ACE inhibitors which completely inhibit this enzyme.

ACE inhibitors have another important effect. They are bradykinin potentiating factors. Indeed, when first isolated from the Brazilian pit viper venom, the molecule was labeled BPF. It is also important to remember that candesartan, the agent of focus today, is a selective angiotensin-II type I receptor blocker that is tightly bound and long acting.

Again keeping in mind the last diagram, we can illustrate how ACE inhibitors mediate benefit

in heart failure remembering the BPF and ACE escape issues. Here we see the ARB effects which result in more specific and complete blockade of the angiotensin-II type I receptor. Here, the rationale for combination ACE inhibitor and candesartan therapy is the fact that angiotensin-II produced by chymase activity will be attenuated without abrogation of ACE inhibitor BPF effects while allowing potentially beneficial effects of AT-II receptor activity.

There is robust basic scientific evidence that supports these concepts. For example, in canine heart failure models ACE inhibitor and ARB combination improved hemodynamics, collagen volume fraction and mRNA for collagen 1 and 3 compared to either agent alone.

In Pfeffer model rats with heart failure the combination of valsartan and fosinopril was more effective in suppressing myocardial remodeling assessed by collagen production and decreased infarct size, while valsartan and benazopril improved more subsequent left ventricular

hypertrophy and lusitropic properties noted in these pathophysiologic models. In obese and hypertensive rats, blood pressure, left ventricular hypertrophy and renal function were improved more with the ACE inhibitor/ARB combination than with use of either agent alone.

We also see clinical evidence that a combination of an ACE inhibitor and an ARB could be beneficial. For example, this now classic report of the ACE inhibitor escape phenomenon demonstrates the time-dependent increase of angiotensin-II despite almost complete reduction of plasma ACE activity over time.

This is one example of several very elegant demonstrations of a complicated interaction between ACE inhibition and AT-I receptor blockade in heart failure patients. This experiment specifically focused on the contribution of bradykinin to vasodilation in patients on enalapril compared to losartan. Specifically, all subjects received an infusion of a bradykinin receptor antagonist before an ACE inhibitor or ARB was

given.

This is a complicated diagram but focus on the change in mean arterial pressure and change in systemic vascular resistance. The top line is the ACE inhibitor; the middle line the ARB. What this study shows is that in patients with chronic heart failure infusion of a bradykinin receptor antagonist attenuates the blood pressure lowering effects of long-term enalapril therapy when compared with losartan treatment indicating loss of the BPF activity of the ACE inhibitor.

Additional information has also become available supporting the hypothesis that an ACE inhibitor/ARB combination will produce incremental benefit with respect to significant clinical outcomes, albeit in a non-cardiac vascular bed. The first three small clinical studies listed on this slide explored in type 1 and 2 diabetics the value of adding valsartan, candesartan or irbesartan to substantive doses of an ACE inhibitor and consistently demonstrated, when a crossover trial design was used, significantly greater

reduction in proteinuria with the contribution of an ACE inhibitor and ARB.

The COOPERATE trial was a small but significant clinical outcome study in nondiabetic renal insufficiency patients when a maximally effective dose of trandolapril, and this was determined as the dose above which there was no further reduction in proteinuria, was combined with 100 mg of losartan. There was significantly greater reduction in proteinuria with the drugs combined, but most important, with the combination there were significantly fewer primary endpoints of combination of developing end-stage renal disease or a doubling of creatinine.

With respect to clinical effects of combination of ACE inhibitors and ARB in heart failure, a ValHeFT pilot study demonstrated that adding valsartan to 20 mg of lisinopril effected more reduction in some hemodynamic parameters.

RSOLVe was a very important pilot study of candesartan in heart failure patients. Its primary purpose was to determine if this ARB in varying

doses could be added safely to 20 mg of enalapril and then if long-acting metoprolol could be added to the ACE inhibitor/ARB combination.

Exploratory efficacy endpoints were included and this slide demonstrates the important finding that BNP dropped significantly in the combination group at the 43-week follow-up point. The combination of candesartan and enalapril also more favorably affected aldosterone and angiotensin-II levels, not shown on this slide.

The combination ACE inhibitor/ARB pharmacologic effects seemingly translated into greater beneficial cardiac remodeling, demonstrated by this data also from the RESOLVe pilot study. Candesartan alone and enalapril alone had about the same effect on left ventricular end diastolic and end systolic volumes during the course of this trial, whereas, a more substantial effect was apparent with the combination.

Another small clinical study demonstrated the additive effects of ACE inhibitor and ARB on heart failure symptoms and exercise capacity. Here

we see a significant increase in peak exercise oxygen uptake and improvement in New York Heart Association symptomatic classification when 50 mg of losartan was added to either lisinopril and enalapril.

Setting the stage for the CHARM program, and particularly the CHARM-Added study is this clear imperative to develop better strategies for heart failure treatment. Certainly, attenuating the adverse effects of RAAS is important. There is now substantial preclinical and clinical evidence that the combination of an ACE inhibitor and ARB will be effective interventions. This is supported by clinical outcomes data in diabetes and chronic renal insufficiency patients, as well as hemodynamic, neurohormonal, cardiac remodeling, symptomatic and exercise changes in heart failure patients.

To discuss in more detail the rationale for very important design characteristics of the CHARM-Added study is Prof. John McMurray of the University of Glasgow, in Scotland. John is the

global principal investigator for the CHARM-Added trial. As we consider in more detail the CHARM-Added program design, Dr. McMurray will specifically address the issue of baseline ACE inhibitor choice, dose and utilization in our study. This will address several additional questions posed by the FDA. Then Dr. Pfeffer will subsequently present our outcomes data. So, if there are no clarification questions, we can turn to John to deal with the ACE inhibitor issue.

DR. NISSEN: Can we move on? Okay.

ACE Inhibitor Choice, Dose and Drug Utilization

DR. MCMURRAY: Mr. Chairman, ladies and gentlemen, Dr. Young has explained to you that ARBs and ACE inhibitors have pharmacologically distinct mechanisms of action. He has explain to you the scientific rationale for combining the two. He has shown you the mechanistic data to show that there may be benefit from using the two different types of drugs together. But to show that there is an important improvement in clinical outcome when you combine the two drugs you obviously have to conduct

a trial like CHARM-Added, and what I want to consider is the way we approached this question when we designed CHARM-Added. In particular, I want to show you the approach we took to ensuring that the background dose of ACE inhibitor was optimized because to test this hypothesis in an outcomes study it was important that candesartan was added to a good dose of an ACE inhibitor, to optimum background ACE inhibitor therapy.

So, in line with the questions that we received from the agency, I am going to speak to how we did this in the CHARM protocol, and I am going to tell you how we tried to optimize background ACE inhibitor dose, and I am going to show you what our investigators actually did. So, I am going to talk about which drug and what dose. I am going to show you the evidence-based trials on which we based our recommendations and then also address a question raised by the agency which is about higher than evidence-based doses. I will come back to that at the end of my presentation.

So, what did we do when we designed

CHARM-Added? What did we write in the protocol? What did we tell our investigators at all the meetings that we spoke at? Well, at the time that we were designing the study there were five ACE inhibitors that you could call evidence-based. In other words, five ACE inhibitors that have been used in large-scale clinical outcomes studies--captopril, ramipril, trandolapril, lisinopril and enalapril. These are the five ACE inhibitors that we recommended to our investigators that ideally they should use in their patients.

What about dose? What did we say about dose? Well, here are some words from the protocol. I am sorry, this is quite a long slide to read but I will just draw your attention to the last sentence. We say here the investigators are reminded that these trials--so we referred to the trials I just mentioned--had target ACE inhibitor doses higher than those commonly used in clinical practice. We have an appendix, which I will come to, which showed the doses. We also said at that time that the recently reported ATLAS trial, which

compared a very low dose of ACE inhibitor to a higher dose, that trial suggested that there is more morbidity benefit from using a higher dose of ACE inhibitors. So, we were very strong. We felt that to test the hypothesis it was very important that our investigators used the target doses, if possible, of the ACE inhibitors that had been shown to be of benefit in the large randomized trials. You can see here those trials and the target doses that were recommended. These were what were put in the protocol. These were what we spoke about at the investigator meetings.

So, that is what we planned. What actually happened? Well, in addition to those two things we also asked, once the investigators had individually optimized ACE inhibitor dosing in their patients, that the patients should be on a stable dose of an ACE inhibitor for at least 30 days before randomization.

So, I want to now look at what our investigators actually did. Well, if you remember, I said there were five ACE inhibitors proven to be

of benefit in large-scale randomized trials. We were pleased to find that, in fact, in 80 percent of the patients in CHARM-Added those five proven ACE inhibitors were the ones that were used.

The agency also recently asked us to look at all approved ACE inhibitors. In fact, there are two additional ACE inhibitors. There are seven FDA-approved ACE inhibitors for the treatment of heart failure. In fact, it was 90 percent of patients in CHARM-Added who received an FDA-approved ACE inhibitor. So, that is something about the drugs that were used.

What about the doses that were used by the CHARM-Added investigators? Well, we asked our investigators to tell us that they actually felt that they had tried to individually optimize the dose of ACE inhibitor. We did that by asking them to check a box before randomization on the CRF. We wish we had collected more information about this but we didn't.

But I will show you what I believe is evidence to support the view that our investigators

did a good job in trying to use evidence-based doses of ACE inhibitor. On this slide you see the mean dose of ACE inhibitor used in those landmark trials. You also see the mean dose of the same ACE inhibitors used in CHARM-Added. For example, in the SOLVD treatment trial the mean dose achieved was 16.6 mg. In CHARM-Added the mean dose of enalapril used was 17 mg. Broadly, I think this slide shows that our investigators generally did achieve the sorts of doses of ACE inhibitor seen in the forced titration trials.

I am just going to focus on enalapril a little bit more, and the reason I am going to do that is two-fold. Firstly, enalapril is by far the most evidence-based ACE inhibitor in heart failure and, secondly, it is the one where we have the most information about doses achieved during forced titration.

You see on this slide all the trials that force titrated enalapril in heart failure. You see the mean daily dose achieved which was generally between 15-18 mg, and in CHARM-Added our patients

received 17 mg and enalapril was the most commonly used ACE inhibitor in CHARM-Added.

Perhaps an even more important slide I think is this one because it shows you the ACE inhibitor doses used in other recent important heart failure trials looking at treatments given in addition to an ACE inhibitor. So, on this slide you see two of the recent key beta-blocker trials and you also see the RALES trial and you see the baseline dose of ACE inhibitor used in these trials. In every case for these key ACE inhibitors the CHARM-Added investigators had their patients on a larger dose of ACE inhibitor than in these other trials. We think that that tells us that our investigators did heed our advice; did follow the instructions in the protocol; did listen to what we said at the investigators meetings.

Here is another important slide and it really goes to the heart of what we were trying to do in CHARM-Added. Here you see all the evidence that we can find about the use of ACE inhibitors in ordinary clinical practice in the community and in

hospitals. You can see again that the patients in CHARM-Added got much higher doses of ACE inhibitor than were used in ordinary clinical practice.

I want to now turn to the interesting question raised by the agency, what if we were to go to even higher doses of ACE inhibitors than those proven to be of benefit in the clinical trials? That is actually quite a difficult thing to look at because though there are many dose-response study for ACE inhibitors, most of these haven't addressed that question. What they have looked at is actually very small doses or medium doses compared to evidence-based doses. They haven't looked at the question that we were asked, which is what happens if you go above evidence-based doses?

It is interesting to think about that question because the first part of it is really is it possible to do that? Can patients get to these much higher doses? Secondly, even if they do, is there additional benefit? Well, I am a heart failure specialist and I know there are other

people here who are, and we know that in our practice you can get some people to bigger doses than have been used in the key landmark trials, but I think individually it is very hard to get a handle on how many patients, what proportion of your patients can get above those doses.

It is interesting just to note that in the SOLVD treatment trial only about half the patients got 10 mg twice a day of enalapril. In the CONSENSUS study it was only about a fifth of patients who actually got up to 20 mg twice a day. The one trial in the literature that has actually tested this question is shown on this slide. That is a study that compared an evidence-based dose of enalapril, 20 mg a day, to a much larger dose, 60 mg a day. You can see the details of this trial here. You can see that about a third of patients could get this larger dose of enalapril. But what is of interest is that there was no statistically significant or clinically important difference in blood pressure, heart rate, ejection fraction or NYHA class in the group who got the larger dose of

enalapril than in the group who got the evidence-based dose of enalapril. There was also no significant difference in any of the clinical outcomes measured, though this was a relatively small trial but just so you can see what happened. Here is the endpoint of death or admission to hospital with worsening heart failure. You can see the two treatment groups and I think you will agree that in this small study there is no difference between the two treatment groups.

To summarize, Mr. Chairman, ladies and gentlemen, in CHARM-Added we believe that our patients did receive an evidence-based ACE inhibitor; 80 percent of them got a proven ACE inhibitor. We believe that they did get doses comparable to those obtained in the forced titration studies, for example 17 mg of enalapril. The doses patients in CHARM-Added got were much higher than doses used in other recent add-on trials, and clearly higher than doses used in ordinary clinical practice. And, I have shown you what little evidence there is about whether going

to higher dose of ACE inhibitor has any additional benefit.

So, to conclude, in our protocol and at our investigational meetings we advocated the use of evidence-based ACE inhibitor treatment, and we believe our investigators did do that. In other words, we believe that CHARM-Added did test the hypothesis of whether adding an ARB to an evidence-based dose of ACE inhibitor would provide further clinical benefit, and my colleague, Dr. Pfeffer, will speak to the evidence that that is the case when he presents the efficacy findings from the CHARM-Added study. Thank you very much.

DR. NISSEN: Any clarification? Yes, Bill?

DR. HIATT: Just a quick question, when you presented the dose of ACE inhibitors how different was the median from the mean?

DR. MCMURRAY: The medians were slightly smaller for one or two ACE inhibitors but they were generally similar.

DR. HIATT: So, the mean data were

representative of the distribution of use--

DR. MCMURRAY: They were.

DR. NISSEN: Before we go on, we have had two people join us a little bit late so perhaps they could introduce themselves. Dr. Temple?

DR. TEMPLE: Bob Temple, regularly late, Office Director.

DR. CUNNINGHAM: Susanna Cunningham, University of Washington.

DR. NISSEN: And you might tell them what your role is here.

DR. CUNNINGHAM: I am the consumer representative on the committee.

DR. NISSEN: Thank you very much. Let's move on unless there are other questions of clarification.

DR. TEMPLE: I have a question.

DR. NISSEN: Yes, sir?

DR. TEMPLE: The point was made that the doses used in CHARM-Added were similar to doses used in a variety of add-on studies. But our view was that that isn't really relevant unless it is

another drug that works the renin-angiotensin system. The question here is whether it is sort of like giving another extra dose of your ACE inhibitor. So, the fact that RALES used lower doses really doesn't matter particularly.

DR. MCMURRAY: I understand that, Dr. Temple. The dose of ACE inhibitor in CHARM-Added was larger than in any of the other add-on trials. We had the same view that you do. I mean, we tried to design a study to test the question and I was only showing that slide to try to emphasize that I think our investigators did try and do better, certainly have done better than in ordinary clinical practice and actually did better than other investigators in other clinical trials.

DR. TEMPLE: Yes, I take that point but the immediate question is whether you are just adding a little more of the same. So, it really only matters in the ACE inhibitor trials.

DR. NISSEN: Other clarifications?

[No response.]

Fortunately, I visited Scotland so I

understood every word without English translation.

DR. MCMURRAY: Thank you very much.

[Laughter.]

Efficacy

DR. PFEFFER: Mr. Chairman, members of the panel, ladies and gentlemen, I am glad to be representing the CHARM investigators to present the efficacy data, and I will be concentrating on CHARM-Added. But I would first like just to remind you that this was a program of research, and you met Dr. McMurray who led the CHARM-Added, which I will be talking about. Dr. Granger is here. He led CHARM-Alternative. Dr. Slim Yusuf led the CHARM-Preserved, and I co-chaired this with Dr. Carl Swedberg.

The program of research had some interesting aspects which relate to CHARM-Added particularly. By definition, by protocol the program was three individual projects, each asking its own question in its own population; each with its own sample size; and each was united under the banner of the same investigator, same form, same

dose titration; same committees. But one of the aspects of the protocol I call your attention to is that by definition the protocol stated that we would follow the last patient randomized for a minimum of two years. That means the greatest exposure we have is in CHARM-Added for the longest observation of those on the experimental medication.

For each of the projects--but we can concentrate on CHARM-Added--it is the same; the primary endpoint was cardiovascular mortality or hospitalization, unplanned hospitalization for management of heart failure, all adjudicated centrally.

The secondary endpoints for each of the projects was to look at all-cause mortality or hospitalization for heart failure, and another prespecified secondary endpoint was to add nonfatal MI to our primary endpoint of CV mortality or hospitalization for heart failure.

The dose titration regimen for all the protocols was the same. The investigator had the

option, after assessing patient status, of starting either at the first step or the second step. So, effectively, they could have started either with 4 mg or 8 mg of candesartan or matching placebo in a blinded fashion. Investigators were asked to titrate at 2-week intervals according to clinical standards and whether or not they wanted to proceed. As you can see, 71 percent of our placebo patients were able to be titrated to the full dose and 61 percent of the candesartan, which is quite comparable to other trials with forced titration.

The analyses that I will present within our analysis plan--and if I leave our analysis plan I will specify that--were all intention-to-treat. It is all time to first event for the primary and secondary endpoints. We will be using log rank test for comparisons; the Cox proportional hazard models to estimate the effect size. You will be seeing effects over time as a Kaplan-Meier. For the secondary endpoints we are using a hierarchical closed test procedure.

Inclusion criteria for the whole program

were symptomatic heart failure patients above the age of 18, and they had to be stable for at least 4 weeks, and II-IV. For the CHARM-Added we had the additional criteria that if a patient was class II they could be admitted but they had to have a history of a cardiac hospitalization in the previous 6 months.

For the program, patients were to be excluded if their creatinine was greater than 3; potassium greater than or equal to 5.5; and known contraindications to inhibitors of the renin-angiotensin system or use of an ARB.

I think Dr. U's report demonstrates that we did achieve balance in the randomization process so I just want to highlight that approximately 17, 18 percent of our patients were over 75 years of age and 21 percent were female. The predominant New York Heart Association class was III. The background of co-morbid diseases is well-known to this group, with about a third known diabetics; hypertension in about a half; and atrial fibrillation in just over a quarter; and a prior

myocardial infarction in about 55 percent.

Concomitant medications is an important point for any study. Our enrollment started in 1999 and ended in 1999 for this trial. Around 1990 were very exciting times with the proof of beta-blockers continuing to mount. As I mentioned, Dr. Swedberg was one of the co-chairmen and he has been on the vanguard of beta-blocker use. So, our investigators were well on top of the wave at the time so for a study randomizing in 1999 I think we have the highest use of a beta-blocker at 55 percent. We did allow the use of spironolactone at the physician's discretion, and our exposure will be on 17 percent on patients.

Here are the results of the primary endpoint. CV death or hospitalization for heart failure is reduced by 15 percent, showing the confidence interval here. This is a significant reduction. This relative risk really represents 44/1000 events reduced, and that event is either a CV death or a hospitalization for heart failure. The number needed to treat over the time course

would be 23 to prevent either a CV death or first hospitalization for heart failure.

I will just use this opportunity to say that this is the first hospitalization for heart failure and, as this group knows, this is a revolving door. Once a person has that, they are much more likely to come back again. Subsequent total hospitalizations will be discussed.

Well, here are the components of the endpoint. The endpoint was a composite of CV death or hospitalization for heart failure. This is basically what I was showing on the Kaplan-Meiers but if we look at the contribution of both components, they are a 16 percent reduction in risk of CV death and a 17 percent reduction in the risk of a hospitalization for heart failure. As everyone knows, if you add the components, it exceeds that because a person can have a hospitalization for heart failure and subsequently die, and that was a common finding more often in the placebo group.

Here are the components looked at

individually. Here is the Kaplan-Meier for CV death. We are also showing the non-CV death but the impact on CV death over time--I have shown you that data. Here is the impact on hospitalization and this, of course, is skewed by the survivor bias. Obviously, there were more placebo patients at risk to have this but despite that fewer candesartan patients were hospitalization for heart failure, at least a first hospitalization.

Our secondary endpoints, prespecified, were to look at all-cause mortality, not the adjudicated but all-cause and add that to the hospitalization for heart failure. As you can see, this secondary endpoint was also achieved and the components of this are also shown where both contribute to this important secondary endpoint.

Another prespecified secondary endpoint was to add nonfatal myocardial infarctions, and we add an equal number. We add 13 and 19 to the primary endpoint--I may have this wrong; I can't do it from this one. We add very few--

[Laughter.]

--equal numbers, but the point is how few it is relative to the primary endpoint.

Subgroups. We do this with caution and I am showing 13. I could show many more. The analysis plan had several others. These are the ones we thought would be of interest to the clinical audience. Thirteen are on this. There were no interactions, which allows me to say that the benefit we have been discussing was not modified by these subgroups.

There was really at the time, when we first analyzed our data and presented our data in the year 2003, clinically a very major issue addressed, and that was beta-blockade. A study prior to ours had given an indication from a subgroup analysis of the potential safety issue. With that knowledge, our data monitoring board chaired by Dr. Hennekens, and our investigators and the world clearly wanted to know what was the exposure with beta-blockers.

I will remind you that in CHARM-Added everyone is on an ACE inhibitor, 100 percent. So,

when we talk about beta-blocker, it is ACE inhibitor, beta-blocker, plus candesartan or placebo. Here is the experience. There was no signal of loss of efficacy so the effectiveness was not modified by the presence or absence of a beta-blocker.

This is a safety analysis--was there a mortality signal of using this now triple therapy--the so-called triple therapy, ACE inhibitor, beta-blocker, candesartan--and no signal of a safety issue. So, this was an important group looked at, at the time.

Spironolactone was an opportunity for us to query potential issues, with 17 percent of patients on spironolactone. We had 436 and there was no interaction here. This is a non-prespecified sub-subgroup that I put here with trepidation, just to say everyone is on an ACE inhibitor, beta-blocker, spironolactone, placebo or candesartan, and it is only 237 patients but there is the data in that non-prespecified sub-subgroup. If we do that, we must look at safety and the best

measure of safety would be all-cause mortality and we are showing that here with no signal but, certainly, the confidence is based on 237 people in the sub-subgroup.

So, this part of my presentation is really the standard CHARM-Added and we believe we have addressed the hypothesis that we set out to test, that for patients with symptomatic heart failure already being treated with an ACE inhibitor and other conventional therapies the addition of candesartan improved clinical outcome, and improving clinical outcome by our definition was reducing the risk of CV death or a hospitalization for heart failure, and we can confirm that with our secondary endpoint of reducing all-cause mortality and hospitalization for heart failure which was also reduced.

In response to the agency's very pointed and very stimulating questions, I will present some other data. One is to put CHARM in external perspective. There have been three major outcomes trials with ARBs in patients with depressed

ejection fraction and symptomatic heart failure. One was a head-to-head comparison and in that the dose of the ARB was not found to provide clinical benefit or to be even comparable.

Here is the closest study to CHARM-Added. This is the ValHeFT experience which has been presented to this group. In the ValHeFT it was conventional therapy and an ARB. For the composite outcome, one of their co-primaries of morbidity and mortality, there was a significant reduction. In the CHARM study there was a significant reduction. So, I think the external validation of adding an ARB, without looking at subgroups but looking at the total group, gave very similar information. The reason we have more events here is, again, because of the longer exposure and longer follow-up.

The other questions from the agency which we will try to address the best we can--Dr. McMurray told you how the study was conducted and we did find that investigators were using a variety of ACE inhibitors. So, if I look at those ACE

inhibitors, as Dr. McMurray showed you, there were 12 including enalapril and four of these did not have an FDA approval so we couldn't find the dose that would be used.

So, now just talking about the agents themselves with the different use of the agents, we used an analysis of was there a difference in the outcome of those who received an ACE inhibitor that had FDA approval or those that did not. That analysis is a non-prespecified one that I am showing here. Here are the patients that had the FDA approval using an ACE inhibitor, and here are agents that were not approved. Again, the best estimate is the overall. So, as far as the agent, we did not see any difference.

The real probing question that we have seen through your questions is the dose issue. To get at that, I have to say the first analysis that the investigators and the sponsor did was the prespecified one. Prior to unblinding, the academic group made a list of the evidence-based therapies and the doses. We had made that

definition called the recommended by the evidence-based. When we did that, there were 1291 patients who at baseline were receiving that dose.

I will talk about that dose in a moment but I think one of the questions about trial design and trial conduct that has to be addressed right up front was in order to test the addition of the new medication, candesartan, the study medication, did the investigators sustain the levels that Dr. McMurray was so proud of, or did they just reduce that to start the other inhibitor of the renin-angiotensin system--a very important and valid question.

To do that, I will just be talking about the five most commonly used, which is approximately 80 percent of our patients and is representative, and the dose, and look at the titration time period. While patients were being titrated to either placebo or candesartan there was no down-titration of the ACE inhibitor. That was something that was conveyed to investigators. If your patient is stable on these doses of an ACE

inhibitor, that is what you should be sustaining. If you have issues you should be down-titrating the experimental medication.

I also have some additional data here on the use of the ACE inhibitors over time, and I think it is quite reflective of our baseline numbers, that there was no attrition of the use of ACE inhibitors. So, we are looking at the added value of candesartan. It is on top of holding good doses of ACE inhibitor over the time frame.

So, what was the analysis? This is the prespecified one from the investigators. These are the 1291 patients who at baseline were receiving doses equivalent to those in the evidence-based trials, and these are the patients who were not. That does not mean these patients weren't receiving optimal dose for them; it is individualized care. But just making this definition, there was no interaction here. The observation of the overall benefit means that this benefit was not modified by the baseline dose of the ACE inhibitor using this definition.

In subsequent communication with the agency, there were requests to create additional subgroups. Since our forms were designed to know the ACE inhibitor and the dose, we are able to comply with those requirements. The agency asked for different doses, a definition of maximum where now the lisinopril dose is increased and some of the other agents are increased. So, we go from having 1291 who met our definition to now 721 who met the new subgroup criteria.

If we look at the results of that, I think you can see the consistency that there was no modification of this benefit of candesartan that I have been describing based on the ACE inhibitor dose at baseline with these two definitions of ACE inhibitor dose.

In subsequent communications with the agency another subgroup was defined, and we were pleased to be able to comply. This one raises the captopril to 300 mg and we did have 2 percent of our patients at baseline. More importantly, it raised the enalapril dose to 40 mg and we did have

10 percent of our patients on enalapril at that dose. So, overall now we are talking about 20 percent of the patients, 529, who met the new definition.

Here are the results of this new subgroup. The 529 and the remainder had the same efficacy so this candesartan benefit on reducing risk of cardiovascular death or hospitalization for heart failure was not modified by any definition of ACE inhibitor dose at baseline, our prespecified one and the two definitions that the agency requested.

Because we are a program of research, we can give one more, and that is the zero dose of an ACE inhibitor. So, we have a whole trial that you have evaluated and that trial is zero, CHARM-Alternative, 2028 patients not receiving an ACE inhibitor.

So, I think we have run the whole spectrum here and you can see the results. Now if we pool the two, the benefits that we are describing of candesartan were not modified by the dose of the ACE inhibitor from zero to predefined levels to

subsequently defined maximum levels at baseline.

That allows us to conclude that we really have an additional opportunity to help patients who are already on an ACE inhibitor and, more than 55 percent, on a beta-blocker. That really is the clinical question. When CHARM was designed that was the issue, can we make an improvement in the practice of medicine? We didn't know the answer. We now share that answer with you and we think we do. We reduce the patient's risk of cardiovascular death or hospitalization for heart failure on top of other therapies, irrespective of the dose of the ACE inhibitor, and we offer that opportunity to reduce cardiovascular morbidity and mortality.

That opportunity does come with some responsibilities, and Dr. Hainer will discuss the risk of inhibiting the renin-angiotensin system in doses that improve morbidity and mortality, and then Dr. Young will come back and describe the risk/benefit. Thank you.

DR. NISSEN: Thank you, Mark. Are there questions right now? Yes?

DR. HIATT: Just a quick one on slide 28. Is that a typo, the maximal FDA-revised for lisinopril? Did the dose go down from 40 mg to 20 mg? Is that true?

DR. PFEFFER: That is not a typo. We were responding to definitions provided to us.

DR. PICKERING: Could you give us a breakdown of which beta-blockers the patients in CHARM-Added were taking, in particular how many were on carvedilol?

DR. PFEFFER: Yes, I could do that and I would like to do that. I said 55 percent at the start and obviously that number increased to the mid-60s by the time it was over. If I can show the beta-blockers that were used at baseline, the predominant beta-blockers were metoprolol and carvedilol, 81 percent. These doses were sustained over time, but the number of patients alive on a beta-blocker increased over time.

DR. SACKNER-BERNSTEIN: In light of that slide, you did a nice job of showing the effect of coronary heart disease on top of approved ACE

inhibitors, trying to make sure that we really were evidence-based. Can you show us a similar analysis for approved beta-blockers as background therapy?

DR. PFEFFER: I don't think I can, Jonathan, but with 80 percent of the people on the approved, I would think the numbers would be the same--if I have this information, and I don't think I have.

DR. NISSEN: We are going to have lots of time for questions. If there ar clarifications, let's do that.

DR. TEMPLE: Just one thought, I just wanted to say that with all these after the fact analyses, don't try these in your own home.

[Laughter.]

DR. NISSEN: We have some very solid advice. So, we are kind of going to finish the sponsor presentations and then we are going to have lots and lots of time for questions.

Safety

DR. HAINER: Good morning, Dr. Nissen, members of the advisory panel, FDA, public guests.

I am Jim Hainer from AstraZeneca, and I would like to begin by stating that the candesartan safety profile in the CHARM program relative to placebo--the findings were really quite consistent across all three CHARM studies. For the purposes of this presentation I will, like my other colleagues, review now the safety of candesartan in chronic heart failure when added to evidence-based doses of ACE inhibitors, the CHARM-Added trial.

Let's start then with two points that are really important to safety monitoring. First, the CHARM provided explicit monitoring directives for the clinicians. Second, the CHARM protocol was particularly specific about monitoring for hypotension, renal dysfunction and hyperkalemia, events expected for any drug which inhibits the renin-angiotensin system when added to an ACE inhibitor.

These directives included monitoring of blood pressure, creatinine and potassium at multiple intervals. These were baseline, within 2 weeks of dose adjustment, at the end of dose

titration, annually and, of course, at any time in the judgment of the responsible clinician. These monitoring directives are entirely consistent with usual clinical practice in caring for heart failure patients.

With that said, let's look then at hypotension, renal dysfunction and hyperkalemia. Hypotension was reported as an adverse event in 23.2 percent of the patients receiving candesartan and evidence-based doses of ACE inhibitors and 14.5 percent among those receiving only ACE inhibitors. Hypotension was reported as one reason for treatment discontinuation for 5.4 versus 3.5; for hospitalization, 4.3 versus 1.7; and for serious fatal adverse events 0.2 versus 0.1 percent.

Note here, expressed as proportions of patients, that discontinuations due to hypotension in patients 75 years and older, those taking spironolactone or beta-blockers, were similar to the overall discontinuation rates. The rate for candesartan was about 3.5 times higher though among patients entering the trial with a baseline

systolic blood pressure less than 100 mmHg.

Renal dysfunction was reported for 15.4 percent of the patients receiving candesartan and ACE inhibitors; 9.4 percent among those receiving only ACE inhibitors. Renal dysfunction was reported as one reason for discontinuation in 8.2 versus 4.2 percent; for hospitalization, 4.5 versus 3.0 percent; dialysis, 1.6 and 1.6; and for a serious fatal adverse event, 0.9 versus 1.5 percent.

Discontinuations due to renal dysfunction in patients 75 years and older and diabetics taking spironolactone or with systolic blood pressure less than 100 were similar to the overall discontinuation rates in the trial.

For patients entering the trials with a creatinine already greater than 2, the rates were high in both groups but the rate for candesartan was really no higher than for placebo.

Next, hyperkalemia was reported in 9.6 percent of the patients receiving candesartan and 3.6 percent receiving placebo. Hyperkalemia was

reported as one reason for discontinuation in 3.8 versus 0.9 percent; for hospitalization, 1.2 versus 0.7 percent; and for a serious fatal adverse event, 0.2 versus 0.0 percent.

Despite the potential for hyperkalemia to increase rates of sudden death and fatal ventricular fibrillation, both rates were somewhat lower in the candesartan group, specifically 11.2 versus 13.7 and 0.7 versus 1.3 percent respectively. Discontinuations due to hyperkalemia in diabetics and patients taking spironolactone was similar to the overall discontinuation rates in the trial. The rates were higher in patients 75 years and older and those with potassium greater than 5. In patients entering the trial with a serum creatinine of 2 or greater, the rates were high but similar in both groups.

Now, having led with this data, highlighting these three specific areas of interest, let's examine whether they translate into global adverse consequences. Any adverse event was reported in 80.4 percent of the patients receiving

candesartan and evidence-based doses of ACE inhibitors and 78 percent among those receiving ACE inhibitors. Of particular interest, serious adverse events were reported in 75.9 percent in both groups, of which serious fatal events were 29.5 and 32.5 percent in the candesartan and placebo groups respectively. Treatment discontinuations due to adverse events were 24.3 and 17.6 percent. Dose reduction due to adverse events were 17.2 and 9.7 percent respectively.

Listed here are the common serious fatal adverse events by treatment. Sudden death occurred in 11.2 percent of the patients receiving candesartan and 13.7 percent amongst those receiving placebo. For heart failure the corresponding figures were 5.8 and 8.8 percent respectively. Other causes of death were far less common. Of note, there was no trend toward a consistently higher risk in the candesartan group.

Now, safety concerns also surround the concomitant use of other heart failure treatment drugs, as already alluded to by Dr. Pfeffer. To

that end, Dr. Pfeffer presented this slide which demonstrates the benefits of candesartan on the primary prespecified endpoint of cardiovascular mortality or heart failure hospitalization, both overall as well as for subgroups of patients receiving spironolactone or spironolactone plus a beta-blocker.

One logical concern is that the reduction in heart failure hospitalization may not be reflected in all-cause hospitalizations. But, in fact, these data show no significant increases in all-cause hospitalizations either overall or in these subgroups.

A second logical concern is that the reduction in cardiovascular mortality might not be reflected in all-cause mortality. But here, again, these data show no significant increases in all-cause mortality either overall or in any of these subgroups.

These trends in hospitalizations are further reinforced by the cumulative number of hospital admissions for any cause shown here in the

candesartan and placebo groups and, as Dr. Pfeffer pointed out, even though the risk remains larger for the candesartan group. Importantly, there is no increase in the non-cardiovascular rate for hospitalization in the candesartan group.

Next, if you can recall the all-cause mortality data for CHARM-Added, note how they are reinforced by the cumulative number of deaths from any cause in the candesartan compared to the placebo groups.

Having now examined the safety of candesartan in chronic heart failure when added to evidence-based doses of ACE inhibitors, I want to conclude with two final slides. First, let me summarize the safety findings and conclusions. As expected, due to greater renin-angiotensin inhibition, rates of hypotension, abnormal renal function and hyperkalemia were greater with candesartan. But these predictable adverse events did not translate into any increase in all-cause hospitalization or mortality, sudden death, renal failure or ventricular fibrillation. These data

show that candesartan is safe and generally well tolerated by patients with heart failure receiving evidence-based doses of ACE inhibitors.

Second, understand that AstraZeneca is firmly committed to risk minimization. We also wish to maximize opportunities for benefits. In order to ensure proper use of candesartan with heart failure receiving ACE inhibitors, AstraZeneca will implement all of the following risk minimization activities: Administration and dosing instructions which are consistent with those that guided the CHARM-Added investigators; labeling which includes precautions and warnings regarding these adverse events; collaboration with major societies involved in the treatment of heart failure patients; and educational activities to ensure that healthcare providers understand the risks as well as the benefits of using candesartan in heart failure. This includes focused training of sales force; and expert scientific liaison groups; continuing medical education activities; and prominently displaying information on all

promotional materials regarding the risk of using candesartan in heart failure.

With these measures in place, candesartan can be safely used as another important treatment option to reduce cardiovascular events in patients with heart failure who are receiving ACE inhibitors. I will turn now to Dr. Young once again who will elaborate on the issues of benefits and risks of candesartan in the treatment of chronic heart failure.

DR. NISSEN: If there are any burning questions on this presentation let's have them, otherwise I think we are ready to launch into full questions after Dr. Young.

Risk/Benefit Summary

DR. YOUNG: Thank you, Jim. It is now to overview our data and quickly consider the impact we can make on ill patients with significant heart failure.

Our CHARM program in its entirety, and specifically the CHARM-Added study, the broad patient population, comprehensively characterized

the risks associated with treatment, particularly the combination of an ACE inhibitor and candesartan. We believe that we have clearly delineated net benefits for this therapeutic strategy in CHF patients with depressed left ventricular ejection fraction.

Particularly important, CHARM-Added addressed the previously unresolved question of whether adding an ARB to an ACE inhibitor in patients with low EFV heart failure provided incremental benefit by reducing risk of cardiovascular death or heart failure hospitalization. Interesting and also important is the fact that we have demonstrated added benefit in patients receiving evidence-based doses of ACE inhibitors proven effective in previous clinical trials, and we also believe we have demonstrated a favorable benefit/risk profile.

This benefit/risk profile is best summarized in this slide. Overall there was a significant 15 percent relative risk reduction for the primary endpoint, cardiovascular death or heart

failure hospitalization, over the 41-month median follow-up. When analyzing the data per 1000 patient-years, this translates into an absolute risk reduction of 25 patients having a primary endpoint event over that period of time, as summarized in the third column on this table.

Importantly, no increased risk for all-cause mortality or all-cause hospitalization or the combination was noted. These observations were all less in the candesartan treatment group, again noted in this table. This should assuage concern about adverse events precipitated by this therapeutic strategy.

Thus, candesartan, at a target dose of 32 mg daily, significantly reduces the risk of cardiovascular death or heart failure hospitalization when added to an ACE inhibitor, irrespective of agent and irrespective of dose. Given our understanding of heart failure, it is prudent to look at the most common adverse events in this population--hypotension, hyperkalemia, abnormal renal function. Proposed instructions for

the use of this strategy are consistent with those provided to the CHARM investigators and good clinical management of any patient with heart failure.

We will emphasize attention to volume status, blood pressure, renal function and potassium levels, and recommended monitoring of these measures will be with initiation of candesartan dose titration and periodically thereafter the same as we manage all of our patients with heart failure.

In conclusion, we believe that the addition of candesartan to an ACE inhibitor treatment of heart failure patients, as was done in the CHARM-Added trial, will result in substantial cardiovascular morbidity and mortality benefit. The positive risk/benefit profile is further supported by numerical reductions in both all-cause hospitalization and all-cause mortality. We believe these findings support the use of candesartan with or without an ACE inhibitor at varying doses for the routine management of heart

failure so that candesartan can be prescribed for managing these patients with left ventricular systolic dysfunction.

Dr. Nissen, ladies and gentlemen of the panel, thank you very much. I will ask Dr. Mark Pfeffer to come back to the podium so that we can direct any questions to the group.

DR. NISSEN: Thank you very much. I must compliment the sponsor. It is rare that we finish ahead of time. We don't have a break scheduled until ten o'clock so I think we can maybe start taking some questions and we will take our break a little bit later. Blase?

Questions from the Committee

DR. CARABELLO: Mark, based on ValHeFT I have routinely avoided the use of an ARB in patients already receiving a beta-blocker and an ACE inhibitor. Now CHARM-Added seems to ameliorate that. So, what is the difference? Is this the two agents? Is this the kind of beta-blockers that were used in the two different studies? Is this a statistical glitch among the two studies? How can

we reconcile those two studies?

DR. PFEFFER: Well, Dr. Carabello, I can't be definitive but I can give you my opinion on that. I, like you and every clinician, wanted to be adding an ARB on top of other therapies to reduce adverse outcomes in patients and that beta-blocker subgroup gave us pause. It really did because what we do know is that beta-blockers have a profound benefit and they do on top of an ACE inhibitor. So, that was the conundrum in 1999.

Then, with the publication of our experience, I think it really showed that maybe that was a hazard of a subgroup. It turns out, if we look at the numbers in our experience, there were even more patients having events. if I could show that, because we had more patients on a beta-blocker and greater exposure time when we are giving you our subgroup, prespecified subgroup, it is based on more events. Just to give you an idea of the two trials, the deaths, which is really what we are concerned about, the total deaths were 226 in ValHeFT and really 370. So, I think there is

more confidence in our subgroup based on the increased number of events.

You then asked about the agent. I think there is an excellent answer to that because there was a very large study, called VALIANT, which used that agent in a large number of people on triple therapy, actually more patients on triple therapy than here, and did not show an adverse safety interaction with beta-blocker, ACE inhibitor and that agent.

So, I think there was a pause because safety doesn't require the same boundaries of statistics that efficacy does, and that pause I think is now erased by what we showed you for candesartan and that other study. So, I do think the message for clinicians--and this is really the important thing, the message for clinicians should be ACE inhibitors at the optimized dose, beta-blockers and then this addition of candesartan in the strategy we have shown can reduce morbidity and mortality.

DR. NISSEN: Go ahead, Tom.

DR. PICKERING: As a follow-up to that, you said 31 percent of the beta-blockers were carvedilol and I wasn't able to see what the proportion was in ValHeFT and, you know, there is the COMET study that suggests that there may be a difference between different beta-blockers in heart failure. I wonder could that be one possible explanation.

DR. PFEFFER: I am here for the CHARM data. I really don't have detailed knowledge about ValHeFT and I would say, based on the small numbers we are talking about, if we start dividing that up by the agents it would be even more unreliable, but I don't have that information.

DR. NISSEN: Ralph, you had a question?

DR. D'AGOSTINO: In Table 59 of the recent material that you sent and our response to C-25 and C-29, I am trying to understand--I know this is all post hoc and I should not be excited about looking at post hoc analyses, but I am trying to understand what happens as you go from maximum dose no to yes. If I look at slide 25, what seems to happen is when

you are dealing with the no--this is the recommended and you are dealing with the no you basically have the placebo and drug pretty much the same. There is only something like a 12 events difference. When you move to the yes you have a 43 events difference, and the change is all basically in the candesartan. Its events drop down. The placebo, whether no or yes, 165 in terms of the events per 1000 follow-up years and the candesartan goes from 151 to 131.

Then when you move to the next slide, slide 29, here the no for analysis one has in terms of the placebo rate 172 versus 152, when you go to the yes where the candesartan has 145 to 133. Again, when you go from the no to the yes it is the candesartan that is showing the reduction. The same with analysis two. In analysis two if you look long enough you will find an analysis that will produce statistical significance. So, my question is it seems to be the action in the candesartan. Does that say anything about the added benefit to the ACE?

DR. PFEFFER: Well, Dr. D'Agostino, I know enough not to discuss statistics with you on this--

DR. D'AGOSTINO: Granted, we shouldn't have done this.

DR. PFEFFER: I think you are asking me is there a pattern here, and I think there is no pattern here and I think the interpretation--may I have the slide, please? You are asking is there a pattern in the no's. Obviously, by every definition we are making a new definition of no. But I think the way to handle this is in any definition was there a hint of an interaction, and the answer--

DR. D'AGOSTINO: The interaction test is notoriously lacking in power, which is the problem.

DR. PFEFFER: But let's look for consistency here, is there a consistent message? If anything, we are not making the message that we are even better on top of an ACE because we also have this 2000 experience here of zero. That is the definite no. So, I think we run the range of no's from low doses, from zero doses to higher--as

we go here we have a higher and higher dose of no really, the no group, because of the higher dose of ACE inhibitor. So, I personally don't see any consistency here and I don't see any pattern. But if you do, then I would be worried--

DR. D'AGOSTINO: Well, I am just trying to sort out why you would say that candesartan adds to the ACE inhibitor. What is the revelation in the data that would say that?

DR. PFEFFER: I think it is this point right here that candesartan adds to an ACE inhibitor. A 100 percent of these patients are on ACE inhibitor. I will remind you that from the clinician's perspective--I will go back to what Dr. McMurray was saying, from the clinician's perspective, 96 percent of our clinicians checked the box that says I believe I have optimized their care. Now, that is a box. We then upped the ante. We made the evidence-based medicine definition. The FDA made these definitions. So, really the best way to look at our data is overall and I don't see a pattern here with the different definitions

of doses.

DR. NISSEN: I wanted to ask a question related to CS-12. You may not have this but I sure would like to see it. This is a little unusual Kaplan-Meier plot. It is cumulative number of hospital admissions and I would like to see time to first hospital admission for any cause because that is a more traditional analysis.

DR. PFEFFER: Yes, and Dr. McMurray has done a lot of analyses of pharmacoeconomics so for that we needed cumulative numbers. For safety, and this was presented in our safety presentation, we think the burden is the cumulative. That is something I was alluding to also although our analysis plan didn't let me show you that because we were timed to first. I think in the clinical scenario we are really trying to keep the revolving door. And, this is showing all admissions for any cause and we thought this was the strongest safety statement we could make about the population. I don't know if I have hospitalization as time to first event. I don't know that I have that.

DR. NISSEN: Let me tell you why I am asking the question. I want to understand if there is an early hazard. That is where time to first is very helpful. That is, when you are titrating up candesartan and you are getting these admissions, there is a fair number of admissions for hypotension and for hyperkalemia, and I want to see whether the pattern shows an early hazard within a more favorable effect later on because I think it is very important for clinicians. I assume somebody has done that analysis.

DR. PFEFFER: That is a very important point. We can show early efficacy. We were showing that. And time to first hospitalization for any cause--let's see if I can get that for you.

DR. NISSEN: That would be really helpful.

DR. D'AGOSTINO: The graphs they do show seem to have a consistent hazard. That is a good question if you go to all-cause hospitalizations.

DR. NISSEN: I did a little Tom Fleming type back of the envelope calculation and I want to see if I am right about that, but there are a fair

number of those hypotension hospitalizations and I am guessing that they are early, that when you are trying to titrate up the drug you run into some difficulty. So, I think to inform clinicians about how to do this it is very important to understand whether there is in fact and early hazard.

DR. PFEFFER: I totally agree. I don't think that is the case and I would like--somebody is showing me CV hospitalizations but I need all hospitalizations to reassure. CHF hospitalizations won't reassure you and I need all hospitalizations to reassure you.

DR. PORTMAN: To turn from cardiorenal to renal for a second, based on DOQI guidelines and Framingham studies and so forth, we know that microalbumenuria is an important cardiovascular risk, independent risk. Do you have data on the prevalence of microalbumenuria? Was there improvement with the ACE/ARB or just the ACE alone in microalbumenuria? In fact, did you even see resolution in a portion of the population in microalbumenuria?

DR. PFEFFER: I have to say that that is a sub-study which is being run out of McMaster University and that as of this moment I don't have the results on the 600 people who were in what we call micro-CHARM. My friend Dr. McMurray is closer to that data. Do we have that?

DR. MCMURRAY: No, we don't.

DR. PFEFFER: We have yet to see that data, sorry.

DR. KASKEL: With regard to kidney, those patients with creatinines less than 3 and maybe above 1.5 are still at risk for dysfunction and you had hyperkalemia as one of the early changes. I am just wondering if there are any other guidelines that might be helpful to prevent hyperkalmeic episode in patients with diminished renal function.

DR. PFEFFER: Definitely, the patients with impaired renal function are much more vulnerable. They are also the patients at highest CV risk. Here is where cardiorenal really should be cardiorenal; we should be getting together more. So, we identified the same risk and now that we

have learned how to use the MDRD equation we are suddenly realizing we have more patients at risk. But that was true for placebo as well as for candesartan. All the augmentations are related to baseline renal function, more so on candesartan, but you need the same monitoring for someone with impaired renal function whether or not you add candesartan because they are at high risk also.

Let me see if I can show you something like that. I would like to show you the EGFR and just to show the adverse experience, just to share that with you. I believe I have a better opportunity to show you that than all-cause hospitalizations as a function of time. May I have the EGFR? We do have that information and it is concerning for both placebo and candesartan. I think the message we have to get out there for education is that we should be looking at renal function and we should be alerting ourselves to vulnerable patients. I will have that for you a little later.

DR. SACKNER-BERNSTEIN: Getting back to

Steve's point about how we can create a way for clinicians to understand how to utilize the drug and manage the patients who are getting the drug, as well as the point you just made about renal function, I am wondering if you could provide us with some insight as to what happens to patients who develop worsening renal function specifically during the titration. I look back to the SAVE trial where you did such a nice job of talking about the prognostic importance of heart failure hospitalization and subsequent course. What can you tell us about worsening renal function?

DR. PFEFFER: I am going to ask Dr. Lewis but I do want to show the slide that I was just alluding to. Let me just show this first. I will get back to the EGFR and then we will continue the thread of what happens to people.

So, here cardiologists have learned how to do EGFR, and it is a risk for discontinuation of any causes and candesartan augments that risk. But this also tells us how carefully we have to monitor the placebo patients with impaired renal function.

Your specific question about discontinuation due to renal function and outcome, I am going to ask Dr. Lewis, our renal consultant.

DR. LEWIS: I am Dr. Lewis, a Vanderbilt nephrologist. I would first like to remind the panel that there is a great body of data in renal literature that inhibition of the renin-angiotensin system benefits people in terms of preserving renal function across a wide range of kidney disease and across a wide range of GFR, including CKD for the lowest GFR groups, which has now been reported from several of the major clinical trials.

There are two settings in which inhibition of the renin-angiotensin system can cause renal dysfunction. One is that patients have ischemic renal disease or fixed renal artery stenosis. The second, more relevant to the CHARM study, is if a patient has decreased effective arterial blood volume. That occurs in two settings, decreased cardiac output which, of course, these patients were at risk for, and decreased intravascular volume, which they were at risk for because of the

use of diuretics.

In both those settings the kidney becomes critically dependent on efferent arterial resistance to maintain GFR. It is a hemodynamic effect. One would predict when a patient has decreased effective arterial blood volume and develops renal dysfunction that the stopping of the agent, the inhibition of the renin-angiotensin system, would repair that renal hemodynamic and the patient should recover. It should be a reversible event.

Evidence to support that--first I will remind you that Dr. Hainer showed you that the number of patients requiring dialysis was equivalent in the two groups, on his safety slide. Also, if I could have slide 48, looking at the ultimate outcomes for people who had renal dysfunction?

So, these are the patients who had any kind of renal dysfunction event during the course of the trial and what happened to them. I have already told you that they had an equivalent amount

of dialysis. As you can see, 38 percent of the placebo group was alive at the end of the trial and 55 percent of the candesartan group was alive at the end of the trial. So, I think the signals we have from the CHARM-Added is what you would expect from the physiology, that this was a reversible event.

DR. SACKNER-BERNSTEIN: Just to clarify, what was the definition of renal dysfunction in that analysis?

DR. LEWIS: The definition of renal dysfunction in this analysis was if an investigator indicated in a narrative form that the patient had renal dysfunction of any sort. The narratives were scanned very closely. There was an appendix about renal dysfunction attached to the protocol that had precise instructions for a given change in renal function. So, for more than 1 mg/dL increase to a level greater than 2, the investigator was instructed to respond to that. But for the purposes of the safety analysis we used any change of renal dysfunction that the investigators noted.

DR. SACKNER-BERNSTEIN: Part of the reason I am bringing this up is because of a little bit of discomfort that I have about how to know the optimal way to interpret changes in creatinine. Certainly, if you take a heart failure patient and you treat them with an inhibitor of the renin-angiotensin system you would almost hope to see an increase in creatinine, consistent with the hemodynamic mechanism you defined, as reflecting the fact that you are achieving a pharmacologically relevant level of inhibition. That is the way most people, I believe most people think about the use of these agents in a chronic setting such as this trial. In the acute setting there is a growing body of literature that increases in creatinine during treatment of acutely decompensated heart failure in a hospitalized setting portends a worse long-term prognosis.

In trying to bring those two observations together I found a relative paucity of data to look at what happens to people in a chronic setting where serum creatinine goes up by 0.3 mg/dL, 0.5

mg/dL during initiation of therapy. Should clinicians be looking for that physiologic effect on efferent arterial as something that is a good sign or is it potentially a bad sign?

DR. LEWIS: I think this is a great issue. I am actually giving cardiology grand rounds at Vanderbilt next week so I am going to address this issue.

DR. SACKNER-BERNSTEIN: What day? What time?

DR. LEWIS: I think this is so good because I think we really are learning more because I think what your paradox is--first let me say that in renal trials, as well as in cardiology literature, you are exactly right. The patients who most benefit from inhibition of the renin-angiotensin system in the first three months--in terms of, you know, don't go into end-stage renal disease or hard outcome--in the first three months of exposure to the inhibition of the renin-angiotensin system do two things. They drop their proteinuria and they drop their GFR by a

hemodynamic mechanism because we have shown reversibility. It is 3-5 mL. It is not clinically significant but it is a signal, like you said, in heart failure patients that they are responding to the inhibition of the renin-angiotensin system.

I think the reason why you have the paradox is that the patient in the hospital who, despite you doing all you can do for them in a hospital setting has a very poor cardiac output, is the patient who has decreased effective arterial blood volume and you can't make it any better because they have reached a point where, short of a heart transplant, you can't make their cardiac output any better. When you give that patient an ACE inhibitor or an ARB you can't get their heart to be better. Nothing is going to get that heart to be better. In that setting the kidney is giving you the message that the patient has reached an end-stage heart situation.

DR. MCMURRAY: Jonathan, I can actually answer your question directly because we are all interested in this in heart failure at the moment.

I will show you a slide that shows you the change in GFR over time, but it is in a slightly different way than my own personal slide of this issue in CHARM-Added because what you see in CHARM-Added is you see a sort of steady decline in GFR over the three and a half years of follow-up. The placebo group and the candesartan group run in parallel. But if you plot those two lines together what you see is this initial little drop in the candesartan group and thereafter they run parallel with the placebo group.

So, it is interesting to me because I think, unlike the nephrology issue, we don't see protection or preservation of GFR over time with an ACE inhibitor or with an ARB or with the combination. We see this initial little decline in GFR but then the two lines run absolutely parallel. It intrigues me why the kidney in heart failure seems to be a bit different than the kidney in, say, diabetic nephropathy.

DR. NISSEN: I would be very interested in seeing the U.S.-non-U.S. analysis. There are some

obvious differences there. I presume you have a slide that drills down on that, or maybe by region if that would be possible. Do we have that?

DR. PFEFFER: Yes, I think this is the observation that you are discussing. This is one of multiple subgroups.

DR. NISSEN: Of course, and obviously I recognize the hazards of this but, to me, it is a rather striking difference. We have seen this now in a fair number of drug development programs where the effect is seen outside the U.S. but not in the U.S. and I want to understand it.

DR. PFEFFER: Well, first you would have to believe that that is a truism. So, if you just take the countries it bounces around like crazy. You would expect that. One of the real strengths of CHARM is that we have 7599 patients with long-term follow-up, and if there is something about carrying a U.S. passport you would expect to see a consistent message. So, we really are coming to you with three trials.

I would like to show you this slide. This

is the point, and it was just over the line at 1.019. On this scale it looks like it is on line, just over. But there was no inconsistency here.

But let's look at the total program. If there is something about being a U.S. citizen that means you are not going to see the benefit of candesartan, let's look at all patients. When we get down to the 7,500 patients U.S.-non-U.S., I think you would agree with me there is nothing here. More importantly, I think when you look at studies was the U.S. represented? The U.S. was the major contributor to the CHARM program.

DR. NISSEN: Were the overall event rates different in the U.S. and other countries?

DR. PFEFFER: I am going to represent Dr. Granger because he has done a complex analysis that only the Duke group can do of the CHARM data, looking for the modifiers and predictors of outcome. Despite hundreds of man and women hours, the things you know about--ejection fraction, diabetes, age--I asked Chris what else have you done; put in re-vascularization? No. Race? If

anything, we don't have enough African Americans to talk about but the point estimate goes the right way. The other issue in the model, if you now force the U.S. into the model it does not come out as a predictor.

DR. TEMPLE: We are sort of watching this. It keeps showing up or at least you notice it when it does show up, which is probably more to the point. Sometimes there are oddities to it. In both RENAL and IDNT the action was all in the Asian population, Asian including Israel and a variety of places you don't usually think of as Asian. But when we actually looked at the end-stage renal disease endpoints it didn't look that way anymore. So, the long-term follow-up no longer was as conspicuous in the U.S. population. So, I don't know what you make of something like that but these things are jarring when they show up.

DR. NISSEN: Let me tell you why these things catch my attention and bother me. Obviously, the FDA is charged with regulating drugs in the United States and we are presented with a

certain number of trials where the U.S. contribution was a minority of the population and where sometimes the point estimates like this are quite variable. One of the things I always worry about is, you know, are these patients somehow different? Is the underlying care, particularly if there are a lot of Eastern European and other countries involved different? I am just trying to get an understanding of this because I know this must come up for you a lot. It always gives us pause for thought considering the fact that this is a drug that we are considering for use in the United States. So, any advice, Bob?

DR. TEMPLE: No, it is just hard to know what to make of it. My bias is that if people are treated badly they probably benefit more from a drug that they are actually getting. So, maybe the U.S. is too well--you know, you could say, well, in the U.S. they really all got their ACE inhibitor and in the other places they all lied.

DR. PFEFFER: That is a very U.S.-centric view--

DR. TEMPLE: I am not alleging that it is true. I am just saying what is the worst thing you could imagine.

DR. PFEFFER: I am not speaking about CHARM now but in almost every database the presumption was that U.S. are better treated, better outcomes. I have many friends in Canada and every time we have sliced it Canadians do a little bit better, so less procedures and do a little bit better so it is hard to even support the hypothesis.

DR. TEMPLE: I am in no way saying it is true. I am just saying, you know, what is the worst thing you can imagine?

DR. NISSEN: One way to test this which would be very helpful to me just to get comfortable here is what the actual event rate was in the U.S. versus the non-U.S.

DR. MCMURRAY: To answer your question directly, if you look at the two low ejection fraction groups pooled, and I am only saying that because I think that is the type of heart failure

we all know most of all, if you look at the placebo groups, if you compare U.S. to non-U.S. the event rates are almost identical. One is 41.7 percent, the other is about 42 percent. So, the event rates in the conventional type of heart failure that we are all familiar with are virtually identical.

DR. NISSEN: What are they in the CHARM-Added?

DR. MCMURRAY: Someone is going to have to do the mathematics very rapidly for me. I put the two low ejection together simply because it was large numbers but, again, you can see they are almost exactly the same.

DR. D'AGOSTINO: Yes, they are almost identical. It is a smaller group. The confidence bands are large; lots of multiple comparisons.

DR. NISSEN: And I do recognize that. You know, this is not by any means definitive. It is an observation that pops out and you want to try and understand it. I mean, if we saw an event rate in the non-U.S. that was radically different from the U.S. that would be a signal to me that this is

meaningful, and we don't see that here.

DR. MCMURRAY: I was going to comment that on so many trials showing this with drugs and drugs being different--I mean, carvedilol was brought up earlier and that is an interesting example. In the large trials done outside the U.S. the effect size of carvedilol was smaller than in the U.S. carvedilol trials.

DR. TEMPLE: Well, you tend to notice it when the U.S. doesn't do well--

[Laughter.]

--so there is probably some selection. We have actually done an internal analysis and there is some suggestion of it but it is mostly driven, I think and I don't know if Norm agrees, by the two studies that formed the hypothesis, RENAL and IDNT. Those didn't look so conspicuous. You know, you are not supposed to use the ones that form the hypothesis, but it is certainly an interesting question.

I have one other question. If you look at hyperkalemia can you show any relationship to what

dose of diuretic people were on? Should the dose of diuretic be higher in people who are getting both of these drugs?

DR. PFEFFER: I was bragging about our case report forms. We had doses of the ACE inhibitor, doses of the beta-blocker. We did not have doses of diuretics which changes during time, so I could not tell you that.

DR. TEERLINK: Mark, was there entry criteria for blood pressure in this trial?

DR. PFEFFER: I mentioned that Dr. Yusuf was part of the executive committee so let's make this broad; let's make this inclusive; let's not have a blood pressure level as long as people are talking to you and are not symptomatically hypotensive. So, we did not have a cut-off for a low blood pressure.

DR. TEERLINK: The reason I ask is because, obviously, given that we are only considering additive therapy here and clinicians only have so many millimeters of mercury to spend, and in slide CS-4 there is a conspicuous increase, as one would

expect, in terms of the increase in hypotension in patients who start out with a blood pressure that is already borderline low. Then we also recognize that many adverse events can spin off that hypotension so you can have hypotension that then leads to renal failure and then leads to other aspects. Is there a blood pressure--and we can choose 100--at which the risk to benefit of candesartan in addition to other therapies is no longer favorable?

DR. PFEFFER: John, it is a tough question because one person's blood pressure of 98 and another person's blood pressure of 98 are totally different, as you know. So, by opening the door and allowing these patients in we have a total experience of about 120 patients. They are vulnerable patients. A patient who walks around with symptomatic heart failure and blood pressure less than 100 is more likely to have an adverse event, and more likely to discontinue due to hypotension. So, it is the person you want to put on the medications and are unable to.

So, everything I have been showing you is intent-to-treat but I will show you, John, in direct answer to your question that for hypotension, if you came into this trial with a blood pressure less than 100 systolic, and only 54 of the placebo patients did and they not infrequently had to be discontinued, but then trying to add the active therapy, we discontinued their medication. Now, that is not a demerit. Investigators tried. This is a blinded study medication. They discontinued and everything I have shown you has been intent-to-treat.

DR. NISSEN: Another way to look at it is that in spite of allowing these patients in the trial it didn't undermine the results. So, I presume those people didn't end up on much candesartan.

DR. PFEFFER: They didn't. That is why I was bringing back the intent-to-treat not the per protocol.

DR. HIATT: I have a slightly different question. I tried to resolve the results of this

development program with the other ones, particularly the valsartan. I think a number of questions can be raised in that regard but I am struck by the interaction in ValHeFT between ACE inhibitors, beta-blockers and the addition of an ARB showing a worse outcome in contrast to your data. Could you speak to that?

Then I have a follow-up question related to that, and that has more to do with the pharmacokinetics of these different agents. Valsartan has a very long half-life; candesartan has less. I am worried about the receptor interactions and how they might differ because are all these ARBs created equal is sort of where I am going with this.

DR. PFEFFER: These are key clinical questions and you can imagine the question in the year 2003 when we came up with these results. I have no more insight than the distinguished panel but I will give you my personal views. The question was of the agent, and I would have to say, no based on the VALIANT experience where a good

number of patients were on so-called triple therapy and harm was not seen.

We are showing no harm and benefit. I think that is the message. If you look at overall the entire ValHeFT experience there is consistency. It is just when you get to that particular subgroup. And that is where I gave you the numbers. You have to look at the robustness of one subgroup and another. We happen to have more events because we had a higher use of beta-blocker and longer follow-up. But beyond that I would be speculating.

DR. HIATT: Can anyone from the company sponsor distinguish some of the PK potential differences--dwell time on the receptor, those kinds of things, between these different agents?

DR. PFEFFER: I am sure somebody from the company can tell you about the PK differences.

DR. NISSEN: What do you say we do that after the break so you, guys, can kind of gather your thoughts together? I am actually give you some thoughts; I was on that ValHeFT panel and also

on a panel that reviewed candesartan compared to losartan, and I will give you some thoughts about that that might help you understand this. Let's break for about 15 minutes. We are doing very well, everybody.

[Brief recess.]

DR. NISSEN: If everybody can take their seats we will try to get started again.

Bill, before the break you asked about differences in any ARBs, and I can offer a little bit of perspective. Sometimes there is a little institutional memory around here and I served on the advisory panel for ValHeFT and we also looked for comparative data between losartan and candesartan. I think both were helpful to me in understanding some of this. At the time the ValHeFT data were presented there were a number of us on the committee that were very suspicious that the result, the beta-blocker hazard--you know, the triple therapy hazard observation was spurious. One of the reasons is that that particular analysis, as I recall, was not really prespecified

so it was an exploratory analysis. You know, I opine that you really couldn't--shouldn't make any regulatory decisions on that basis; that it was hypothesis generating at best and that, again, if you look at enough trials and enough people and enough subgroups you are going to see something like that happen once in a while.

I must say, it was very intense. The final vote was 4-4, which meant that we actually had an even number so we didn't actually make a decision on the primary indication for valsartan. Even though the nominal p value looked very good and the data looked very good for the overall study, at the time I felt like people were being unduly influenced by the observational data on the subgroup. I think now, in retrospect, that probably was spurious. That is my own personal interpretation that it was just simply an unusual result.

DR. HIATT: Where I was sort of going with this, is there really a difference in dosing between ARBs, or are there different pharmacologic

differences that we should be recognizing between ARBs?

DR. NISSEN: There is some subtlety here. Again, there are obviously things that are class effects and there are things that are not class effects. We looked at two trials comparing losartan and candesartan, and this committee voted I think unanimously that there was evidence that the blood pressure lowering effect was greater with candesartan than with losartan, both given in their full therapeutic doses.

DR. TEMPLE: Well, the labeled full therapeutic dose.

DR. NISSEN: Yes.

DR. TEMPLE: I think we all had the impression that losartan probably should be higher but wasn't pushed.

DR. NISSEN: Yes.

DR. TEMPLE: Whatever the reason, they beat them.

DR. NISSEN: Yes. But what we can say is that 32 mg of candesartan had a very big effect on

blood pressure, bigger than the full doses of another ARB. So, it is like any other therapeutic class, there are sometimes agents that are somewhat more potent than others, that perhaps have more affinity for the receptor. So, if you want to test the hypothesis that blocking at the AT-I receptor produces an added benefit you want to probably do it where you are really blocking the receptor as well as you can block it, and I think that is one of the things that CHARM did. They got to a really very robust dose of a very potent angiotensin receptor blocker so it really does test the hypothesis.

DR. TEMPLE: Of course, our concern has been you can only test it if you really are on whatever the full dose is, but a full dose of the ACE inhibitor. That is what has been addressed here. In the case of ValHeFT, that was sort of a very Bayesian episode. We actually approved the use on what was not a primary analysis at all. I mean, that was just an accidental 7 percent of the people that weren't on any other drug. That is

what we approved, even though that was only 300-some odd patients in a 5000 patient trial because the result was so conspicuously large. The beta-blocker thing, we were skeptical about it too but it was the mortality outcome and we just didn't feel we could say anything about it.

DR. SACKNER-BERNSTEIN: Also, in terms of the mortality in ValHeFT, I wasn't part of the committee but the randomization in that trial was stratified based on background beta-blocker therapy which does add some robustness to that analysis, just to clarify that.

DR. HIATT: Before I leave this question, is there anyone from the sponsor who can talk about the differences in the pharmacokinetics and dynamics of these different ARBs? I mean, I was struck that valsartan has a longer half-life. It is certainly a less potent drug but then it is just a matter of milligrams. If you can get them to the same equivalent dose you should overcome that but, if anything, candesartan maybe should be dosed more frequently. So, I am just questioning whether there

are any other pharmacologic properties between these agents we should be discussing today.

DR. NISSEN: That is a fair question so can somebody just tell us about PK and PD data?

DR. YOUNG: I can give you a clinician's perspective because this is important when we are setting up a lot of these clinical trials and we are looking at this, and all these are different molecules and it gets at this issue of variability from an ACE inhibitor to an ACE inhibitor, from a beta-blocker to a beta-blocker, an ARB to an ARB, and there are differences, some of them subtle and some of them may translate into outcomes data that are important.

But with respect to the ARBs, candesartan is the most tightly bound of the ARBs. It has an insurmountable binding property, sort of a non-competitive type of binding property that lasts well over 24 hours. You can detect effects in binding activity after 24 hours, and what happens is that the PK levels will go up and drop and the half-life will appear to be less when you are

looking at it from a PK or a drug exclusionary phenomenon, but if it is still tightly bound to the receptor you won't have candesartan coming off the receptor and causing it to go back up.

DR. HIATT: And that was my understanding. That is where I was going with this. I wanted to say that because I think valsartan does not have that same kind of receptor affinity. Am I correct?

DR. YOUNG: It does not; you are correct.

DR. HIATT: So, if it really is bound across the 24-hour dosing cycle and has a very high affinity there could be a pharmacologic basis for a slightly different clinical result.

DR. YOUNG: And I stress the word "could be."

DR. NISSEN: Yes, Tom?

DR. PICKERING: I would like to discuss further the issue of hyperkalemia and spironolactone use. I think the issue here is really one of labeling and whether it should specifically say anything about whether patients should be also taking spironolactone or not. If

you look at slide CE-17, there doesn't seem to be any advantage of being on spironolactone in terms of the primary outcome variables. Although there is a trend in the lower panels for improved mortality, I guess it is not significant.

The other one was CS-8 which shows that the hyperkalemia occurrence is increased in patients taking spironolactone in diabetics, and so forth. I guess the reason for the concern was the publication in The New England Journal about what happened after the RALES trial was published, that the hospitalization rate for hyperkalemia rose from 2.4 per 1000 to 11 per 1000 with an increase in mortality. You know, obviously, in this trial everything was very nicely controlled and people were doing what they were supposed to be doing, but what will the consequences be when it sort of gets out into the real world? So, perhaps we could discuss that.

DR. PFEFFER: Certainly, inhibiting renin-angiotensin system does have its issues and, fortunately, one of my colleagues wrote the

editorial that accompanied that New England Journal article. So, let me ask Dr. McMurray to talk about that.

DR. MCMURRAY: We share your concern. In fact, I think the only reason I wrote that editorial was that we had already published our own experience with the misuse of spironolactone which became widespread after the publication of the RALES trial and I think that was a lesson from the Ontario experience and, indeed, from 13 other case series that have been published reporting the same thing in smaller numbers of individuals. The striking thing about that was that essentially it boiled down to two problems, the use of the wrong dose of spironolactone, much higher than the small dose used in RALES which was 25 mg a day, and also misuse in the wrong patients. So, RALES was a study targeted at a carefully defined group of patients and the Ontario experience with spironolactone was used in a completely different patient population, much older; many patients with preserved rather than low ejection fraction; more

diabetics, and so on.

So, one of the points I tried to make in that editorial was that RALES was a very unusual trial in one respect, and that was that it was a trial done with a generic drug that had no sponsor and the usual care in terms of risk management, in terms of educational programs, in terms of meetings and so on, to emphasize how you must use the drug; you must monitor what happens to patients. I think perhaps I would look more to the experience with ACE inhibitors where they were used in a more responsible way because there was a sponsor acting behind them to ensure that the program education was carried out. Unfortunately, that didn't happen after RALES. Certainly my personal interpretation would be that the reason there have been major problems is because people didn't go through the usual process of introducing a new treatment and ensuring it was used as carefully as possible.

DR. TEMPLE: There is, of course, no labeling of any spironolactone product reflected in RALES despite my attempts to embarrass people into

producing one.

[Laughter.]

For fairly obvious reasons, it was unsuccessful.

DR. PICKERING: But if this gets approved there is going to be labeling that could or could not say something about concomitant spironolactone use.

DR. TEMPLE: Indeed, it could. Actually, my question from before goes. I mean, everybody has moved down to low doses of diuretics because they are worried about hypokalemia. Maybe they should make a comeback in the face of all this potassium retention. Higher doses do work slightly better than 12.5. That seems worth exploring too.

DR. NISSEN: Actually, it does reflect a real problem for clinicians in managing heart failure. The computer term for it is combinatorial explosion, which is you have four or five therapies and how do you combine, what kind of combinations and permutations of them can be used in individual patients. It is not so easy. I often don't know

what to do so I am looking for guidance from FDA.

DR. TEMPLE: So, you don't think anybody can just make a single pill that will just do it?

DR. NISSEN: Yes, I don't think so. I wanted to explore something else with you, guys. Obviously, one of the reasons we are here is because the agency reviewer and the agency has some concerns about has the hypothesis been proven that on top of maximal doses of ACE inhibitors candesartan produces an incremental benefit. This all could have been resolved if you just picked enalapril, you know, pushed it to the heart failure doses and then everybody would have gotten the same ACE inhibitor and we would know exactly what they got.

I know what your answer is going to be. Your answer is going to be you wanted to make this a real-life trial with the real-life drugs that people use, but it does, in fact, undermine a little bit our ability to interpret the experiment. Did you, guys, consider actually just specifying the ACE inhibitor, pushing it up in the way they

did in the ACE inhibitor trials and then, once you got to the maximum tolerated dose, randomize?

DR. PFEFFER: Well, I gave you the names of the people involved in the planning so you can imagine we did consider it. The other issue would be I could imagine if we came back here with the same findings on the most commonly used medication, which was enalapril, somebody--I am not saying who--

[Laughter.]

--would say what about the other ACE inhibitors, the other approved ACE inhibitors? Then we realized that to dictate the use of an ACE inhibitor, with the VA system telling us what ACE inhibitor you have to use, my healthcare system telling us what ACE inhibitor you have to use, we really did make the decision to optimize the individual dose and see if adding on improves outcome.

DR. NISSEN: Although you did allow use of ACE inhibitors that were not approved for heart failure. Was the assumption that everybody would

feel okay about that, that even though the drug wasn't actually approved--

DR. PFEFFER: Well, this was FDA approved. We are talking about 26 countries. I was reminded in this international trial that the U.S. is one country.

[Laughter.]

DR. NISSEN: Yes, we are getting reminded of that all the time now. Other questions? Yes, Jonathan?

DR. SACKNER-BERNSTEIN: Just to get back to the U.S.-non-U.S. finding, there are a couple of different ways that I was trying to look at this to see if I could understand it. Obviously, it could just be a statistical fluke, which my own bias says is the most likely. But one issue that has come up before is the possibility of drug interactions. So, I am assuming that you looked and found that U.S. and non-U.S. subjects were treated similarly. A second one has to do with whether the statistical power was sufficient within the U.S. population, and I think we addressed that by the question

earlier. The third question has to do with what is unlikely but possible, that perhaps the people in American who have systolic dysfunction are already treated with an ACE inhibitor. There is a potency issue about the way candesartan works compared to the way it works in similarly described patients outside of the U.S.

One of the ways I would like to get a handle on that is by seeing what the AE effects were. If you were to tell me that by region the North Americans had a very low rate of renal insufficiency, a very low rate of hypotension, then I would have the bias that perhaps we are looking at a differential potency in a population. I wouldn't understand why. Perhaps I am putting myself at risk of attack from pharmacologists but that is the way I have thought about this and I am wondering if you looked at that data.

DR. PFEFFER: Let me first start by what it is. I reject that there is anything here personally. So, if you are asking me to defend what it is, I can't do that because I think there

was nothing there.

But if you want to explore something where I don't believe it, I can tell you there are a lot of differences between U.S. patients and non-U.S. patients at baseline. You heard that their outcomes are pretty much the same, and you heard that in the trial of 7599 in the program the effect of candesartan was pretty much the same.

But just to explore, in CHARM-Added, yes, there were some differences, fairly minor, in the medication use but here is medication use. Now, I mentioned that being at the recommended dose, and I think Ralph pointed out that the arrow went in a good way so you can see the inconsistency, there are more people at the recommended dose. So, there are a lot of inconsistencies here.

Let me show some more differences between U.S. and non-U.S. We do more procedures. That is no revelation. Coronary procedures, we are very good at that. That did not influence anyone's outcome. We do more angioplasty. We have ICDs and pacemakers. So, procedures we do more of. I am

off the cuff going to ask Dr. McMurray, did we do any quality of life? Did U.S. patients feel better with all this hardware?

DR. MCMURRAY: Only in the U.S.

DR. PFEFFER: Quality of life was only done in the U.S. Now, for AEs we can give you this by North America. Is that okay? So, we can go across the border and I think it is important to look at placebo. Placebo in the U.S. were more likely to tick a box, and we really asked these questions--renal function, 6.3 versus 2.9. I am not going to make anything of it but numerically more. Obviously, the agent increased that in both North America and the rest of the world. Here is the hyperkalemia, increased in North America; increased by the same factorial in the rest of the world.

So, Jonathan, I don't see that there is a clue here that they are under-treated, over-treated; that the SAEs are helping us with this. I go back to your first statement of fluke but I don't even say fluke because I don't make the

observation.

DR. NISSEN: It is intriguing though, Mark. I mean, some of the therapies like defibrillators do have an impact and, you know, the fact that there were more defibrillators used in the U.S.. You know, one of the mechanisms of death--you know probably better than I--in these patients is sudden death. So, it is possible that there is a competition for benefit between defibrillators and more effective heart failure treatment. If, in fact, there is more defibrillator use in the United States there may be less opportunity for benefit from candesartan. So, some of these hypotheses, and they are just hypotheses--I basically agree with you but when you see an observation, it is our responsibility obviously to explore that and make sure we understand it, that there is some strong signal here and I think there is not a signal; I think there is an observation. I think you can see how the defibrillator use could certainly drive some of this.

DR. PFEFFER: And defibrillator use is something that in the year 2005 we are much smarter than in 1999. I don't know what the balance would be around the world now but these are heart failure patients and I have some of my heart failure colleagues telling me to turn these things off sometimes too. So, I don't have the answer for that.

DR. TEMPLE: Of the U.S. differences you showed, one of them is sort of tempting. More U.S. patients were on the full dose so maybe that would explain why the addition didn't work as well, but your overall data shows that people who were on a full dose on the whole did better.

DR. PFEFFER: I mentioned that as an example of a confounder. The point estimate for being on full dose moved in the right direction. More U.S. were on the full dose so it is a perfect confounder--

DR. TEMPLE: Right.

DR. PFEFFER: A fluke, and I just think it is a great example. Dr. Granger has something to

add.

DR. GRANGER: We did look at this. One of the obvious things is procedure use and prior re-vascularization. When we looked at prior ICD or prior re-vascularization the point estimates were almost identical for the treatment effect of candesartan. So, it doesn't appear to be that.

DR. NISSEN: I would have guessed that having angioplasty would increase the event rate because we all know that angioplasty is bad for you--

[Laughter.]

--but I guess you didn't see that.

DR. PFEFFER: We don't know how long ago the angioplasty was or where it was done.

DR. NISSEN: Did you enroll any patients at the Cleveland Clinic?

DR. PFEFFER: Cleveland Clinic was a vigorous proponent of conducting the CHARM trial and Jim was the U.S. lead investigator. He probably asked you about some of your patients.

DR. PICKERING: Could I raise the issue of

African Americans? I think you had 2.8 percent and the issue is if this gets approved what are we going to say about its use in black patients? Because there is evidence that blocking the renin-angiotensin system may not be so effective in African Americans. At two meetings ago we reviewed a drug which was basically killed because of adverse effects, angioedema, which is commoner in African Americans, and there seems to be a total void here. Should clinicians be using it in African Americans or not? Or, what are we going to say?

DR. PFEFFER: I think we have as much confidence in our data as any that have been presented here, and let me walk through that.

This is self-designated as black--self-designated. In CHARM-Added, of the 70-something patients there is the point estimate. I am not saying that it is this way or that way. That was Alternative. That was not on an ACE inhibitor. In CHARM-Added, in the few patients we had you can see the point estimate here. But if

you go through our whole program I think there is a consistent message here that designating yourself as black and then being enrolled in our study there is no loss of efficacy, and my interpretation would be we are offering an opportunity to reduce someone's risk regardless of this designation, and that is the best estimate even the point goes this way. When we do the total, we are talking about over 300 patients.

DR. NISSEN: While other people are thinking, Mark, let me tell you what triggered my request for the time to all-cause hospitalization. I did some sort of simple numerics and I see there were 56 fewer deaths or CHF hospitalizations in the primary endpoint. So, you avoid 56 deaths in the primary analysis. Then I looked at the hypotension and there are 33 more people hospitalized for hypotension. So, at least in your mind, until you see an analysis you have to say, well, you kept 56 out of the hospital and from dying but you had 33 that had excess hospitalizations and you have 20 excess hospitalizations for renal dysfunction and

then you have another 10 in the hyperkalemia.

So, when you add all the numbers up, you know, you sort of see an analysis that says, well, you are keeping people out of the hospital for heart failure but you are admitting a lot more to the hospital for AEs, so isn't the hospitalization data kind of a wash? I know it is not the correct analysis because once you have that first heart failure or hospitalization you may have more. That is why I am so keen on seeing that.

DR. PFEFFER: I think it is a key number to get you but we do have it without Kaplan-Meiers and Dr. McMurray would like to tell you about total hospitalizations.

DR. MCMURRAY: I am afraid I don't have a slide of this but I do have the numbers so you might want to write them down. I was intrigued for my own interest to figure out how it balances up. On the benefit column what we actually have, and I will give it to you per 1000 patients treated over the duration of the study--on the benefit column there were 46 fewer patients hospitalized for heart

failure. There were 100 on ACE fewer heart failure hospitalizations and 35 fewer cardiovascular deaths.

On the risk side there were 26 more patients hospitalized with hypotension, but when I say with hypotension that means hypotension was just on the list of possible causes for that hospitalization. For example, amongst those there were people with septicemia, people with GI bleeding, and this is true for all the AEs. There were 16 extra hospital admissions for renal dysfunction and there were 8 extra hospital admissions with hyperkalemia. Again, some of those groups overlap but we weren't able to quite tease that out.

In summary, the balance was substantially in favor of candesartan and, in fact, I can give you sort of a handle on that because we have done an economic analysis in Europe and a resource utilization economic analysis, and over the course of the study for every 1000 patients treated with candesartan there were 1900 fewer days in hospital

with worsening heart failure. There were significantly fewer days in hospital for any reason whatsoever in the candesartan group. So, yes, of course, there is a trade-off but it is substantially less on the benefit side in terms of morbidity and resource utilization.

DR. TEMPLE: I just added up your numbers leaving deaths out of it for the moment, not that you necessarily want to. There was a 46-patient benefit for heart failure hospitalizations.

DR. MCMURRAY: Forty-six patients, yes.

DR. TEMPLE: And 49 extra hospitalizations for hypotension, renal dysfunction and hyperkalemia.

DR. MCMURRAY: Okay, the difference there is--well, there were several differences. First of all, you have picked patients as opposed to admissions and, secondly, on the risk side when I said hypotension, when I said renal dysfunction, when I said hyperkalemia I really do mean that if those terms appeared anywhere on the long list of reasons for admission we counted that just in case

it could be a risk. Also, there was overlap. The best estimate I can give you of overlap, and I really don't know the proper numbers but the best estimate of overlap is two-thirds of those patients were counted more than once.

DR. TEMPLE: Okay, but those were extra hospitalizations in the treated group.

DR. MCMURRAY: Extra hospitalizations, yes. So, the contrabalancing number for that is 188.

DR. NISSEN: Bob, I understand what he is saying and I want to just see if I can rephrase it. You know, if you take the number of patients that had a hospitalization for either heart failure or a drug AE, it is fairly balanced. But once you got admitted once for heart failure you are very much likely to be admitted again and again. So, what they showed us was the Kaplan-Meier for cumulative incidence of all-cause hospitalization. And I understand that. And it is very important and I am not minimizing it at all. But, you know, it did strike me that there was a cost for that, and the

cost is that a fair number more patients--when you talk about AEs I look at hospitalized AEs rather than I do incidental AEs that are sort of discovered on a laboratory test. If you have hyperkalemia sufficient to land yourself in the hospital, that is a pretty serious AE, and if you have hypotension that gets you in the hospital, that is a pretty serious AE. So, that is why I am so keen on seeing that time to first event because that is an important objective. Now, I know that over time the hospitalizations are clearly less in the candesartan arm. But I am going to guess that--

DR. TEMPLE: Yes, and the implications are different. One is transient, you fix it and it is over--

DR. NISSEN: Yes.

DR. TEMPLE: But being hospitalized for heart failure means you are on the way to troubles.

DR. NISSEN: You are on a downward spiral. Don't misunderstand me, I am not placing equal weight on them.

DR. MCMURRAY: I was trying to give you actual numbers.

DR. NISSEN: Yes. Obviously, FDA is going to have to write a label and we have to understand this as well as we can in order to help them understand it.

DR. PFEFFER: Dr. McMurray was looking at pharmacoeconomics and multiple admissions. I think what he was explaining is that for hyperkalemia and hypotension, we can count both of those for the same admission just to be on the safe side. But I have also learned something--when I go over there and sit down I become a little smarter, and people have now fed me the numbers for the total hospitalizations as a function of time with your question about the early hazard. I didn't know this answer so it is new for me too, and it was a very appropriate question, what happens in the first month. May I share that slide or do I read numbers--I don't have a slide; I read numbers.

So, at the first month, which is that up-titration phase, for hospitalization for any

reason, 69 of the candesartan patients and 80 of the placebo. At 6 months it is 297 and 304. Then, as a function of time we get better, as you see. That doesn't mean we didn't hurt somebody early but in the overall, all-cause hospitalization for any reason numerically people were on the candesartan. Then you did see the curve of the cumulative hospitalizations.

DR. NISSEN: It actually does sort of support the hypothesis that you are really picking up the benefits once you get outside of that early sort of titration. Once you have proven you can tolerate the agent, then you are starting to accumulate lots and lots of benefit.

DR. PFEFFER: Well, I really have trouble with when was the benefit. I know you spent some time on that last week--when is the benefit. I don't know what statistical tool one uses to do that besides your eyeball. So, why don't we look at our two low EFs combined? You know, we did a lot of statin work, as you have, and for the most part, except for a few studies, you need a little

time to see the benefit unless you are very, very aggressive with your statin use. Treating heart failure, symptomatic heart failure, you tend to start to see things early.

So, Dr. Nissen, I don't know what to make of this, of when, but I do think we are starting to see the benefits that you would ask for in a medication for the treatment of people with symptomatic heart failure and, yes, there are other things that we must be vigilant to look for. It happens in placebo too so I think we need to raise our standards of how to monitor patients whether they are on the triple therapy or not.

DR. SACKNER-BERNSTEIN: In terms of the endpoint of heart failure hospitalization that was part of the primary endpoint, I am wondering if you might comment on how you can be confident that you captured all the heart failure hospitalization that occurred appropriately. Literature, including the RESOLVe trial has shown that about as many as 11 percent of heart failure hospitalizations are associated with pulmonary processes. So, I am

curious about how you made sure that the endpoint committee saw all the hospitalizations that an investigator may have thought were just bronchitis or pneumonia and may have actually been given IV diuretics. Another issue is that of worsening renal function which certainly can be a sign of worsening heart failure, and in many of those cases patients aren't treated with IV diuretics, which I understand was part of the definition for heart failure hospitalization. So, I am curious about those two and, with respect to the first one, it would also be interesting to know if there were baseline imbalances in underlying pulmonary disease between the two groups that may play into the potential risk there.

DR. PFEFFER: Thank you, Jonathan. Yes, you are right. We set the bar high so that as we stand here we can feel that when we are talking about hospitalizations for heart failure they all reach a certain level, which means there are other admissions which probably were for heart failure but didn't reach our predefined definition, just so

that we could have some common definitions around the world. As you know, it required overnight and it required intravenous use.

Now, around the world we were told before we even started the project by some investigators that in my country I might admit somebody who has an unplanned deterioration and I might just double the diuretic dose orally. So, we knew this and our steering committee made that decision to raise the bar at that level just so that we could take out some of those less severe.

Now, we have, of course, analyzed our data in both ways, investigator reported versus the core. I would like to be able to show that but I can't. But I can tell you the results are the same. As a matter of fact, Dr. Yusuf was beside himself because CHARM-Preserve looks a lot better on investigator reported. So, if you open the window a little bit more you will get more admissions and it did not change our results.

DR. SACKNER-BERNSTEIN: But that addresses only part of my concern. The other part is that

people who come in, or have a discharge diagnosis, however you want to label it, say, with pneumonia but in fact they were treated with intravenous diuretics and they did have some lower extremity edema, are we sure that all of those cases were reviewed by a committee? Because there the investigator may not have considered heart failure so it wouldn't fall into the investigator designated, and it didn't get to the committee and didn't form part of the primary analysis either.

DR. PFEFFER: No, the net to catch these, these would have gone to our committee. As a matter of fact, there were swings both ways and it was the flavor of this such that the white count was elevated and, even though they got a diuretic, what was the flavor? I had a very interesting chuckle over this because Dr. Swedberg who was my co--this was all done by fax machine--one of the first we said no to was a person just like you are describing, who got antibiotics and got pneumonia and had a diuretic, and we sent for more information from the site. It happened to be his

site and it happened to be one we rejected.

Could I have the slide I was just looking at, the investigator reported? So, that is a bigger window. This is the information from the investigator reported for all the studies. So, this is this definition we are not using. Now, if we use this definition, that allows Dr. McMurray to do his pharmacoeconomic analysis because his pharmacoeconomic analysis does not care what Scott Solomon, in Boston, says, and there it becomes even more impressive and you can see the multiple admissions. So, the window is even larger if you use the broader category.

DR. MCMURRAY: I can tell you the difference in the numbers, Jonathan. If you look at the investigator reported admissions, in the placebo group the adjudicated admissions were 356; the investigator reported were 437. In the candesartan group the adjudicated number was 309 and the investigator reported was 381. That is just in CHARM-Added that I am talking about.

We also saw--and I can't quite remember

but I can get it for you if you want--a very strong trend, if not a statistically significant difference to a lower number of admissions for pneumonia as well, reminiscent of the SOLVED trial. I can dig those numbers out.

DR. D'AGOSTINO: Just a comment, we don't want to make too much of this discussion because the adjudication process was to remove all of this uncertainty.

DR. NISSEN: Oh, I completely agree but, you know, since we are sort of exploring risk and benefit, I mean, in many ways it sort of doesn't matter why you are in the hospital, you know, I mean, from a patient perspective.

DR. D'AGOSTINO: I think in the cost benefit, and so forth, and if we did quality of life you would focus on this very much but in terms of the endpoint analysis, we don't want to say there is even a better result.

DR. NISSEN: No, I completely agree with that but, you know, my view of this in part is that you stand in the patient's shoes and, you know,

being in the hospital is not a desirable outcome; it is not pleasant for patients; they don't like the idea. So, I would like in a study, even though it is not a prespecified endpoint, to understand all-cause hospitalization because these are, in fact, very meaningful to patients in terms of what they put up with and it is not the primary analysis by any means.

DR. PFEFFER: In our endpoint committee we commonly say that we are doing this for the trial, the patients in the hospital, the patients admitted. If we say it is not for heart failure but something else, the patient is admitted, I think that is why the best analysis would then be the hospitalizations for any reason.

DR. HIATT: A slightly definition question is that a central issue before the committee is whether adding candesartan to background ACE inhibitor provides some unique benefit or is it simply that you should push the dose of the ACE inhibitor and that would erase the benefit of candesartan? Clearly, you have shown those

different analyses and at different levels of heart failure doses of ACE, and the FDA briefing document, Table 37, shows this sort of counter-intuitive dose-response curve that candesartan plus high dose ACE beats high dose ACE with a relative risk reduction of 20.6 percent. For candesartan plus low dose ACE versus low dose ACE the relative risk reduction is only 8.5 percent. I am assuming that is a statistical fluke of multiple subgroup kinds of analyses, but it does kind of go in the wrong direction.

So, I guess I would like you to comment on that. Then that begs the second question which is if then you extrapolate this, perhaps somewhat illogically, into a community setting and not every patient is taking an appropriate dose of an ACE inhibitor they more match the low dose ACE, and would that then suggest that the addition to candesartan for those patients really wouldn't be beneficial, begging a third question, is the sponsor going to do anything about optimizing ACE inhibitor dosing post-approval?

DR. PFEFFER: We think to stand here in 2005 and say we have advanced the practice of medicine you have to stand on the shoulders of those before you who have advanced the practice of medicine, and that is ACE inhibitors and beta-blockers.

I think the group you are describing--I would like to add CHARM-Alternative to this, if I could have the slide that I have been using, because I think it does make a point looking for consistency in subgroups, and I would call each of these new definitions of somebody else's definition of what an ACE inhibitor is and what the right dose for their patient is. You talk about me, being in Boston, telling somebody whether they had an infarct or not in Poland, this is us telling the doctor what dose of ACE inhibitor they should use for their patient. So, here are the three definitions. I think what you are talking about is--

DR. HIATT: Well, this clearly plays into your hand. Obviously, all this suggests is that if

you push the ACE inhibitor dose the candesartan benefit is even more robust.

DR. PFEFFER: But let me add again that our 2028 patients who had zero ACE inhibitors and they had a profound benefit, that the agency has already agreed with us about.

DR. CARABELLO: It would seem very hard to say that ARB and no ACE is great and ARB and lots of ACE is great, but ARB and a little bit of ACE isn't so good. I can't logically see how that could come out.

DR. HIATT: Me neither, but that is what we are here for. So, thank you, Dr. Carabello.

[Laughter.]

DR. NISSEN: I was going to say that is why it is quite relevant. Even though the agency has made a decision already on the Alternative, it is quite germane to our discussions and why it is appropriate that you should be reviewing that because, you know, I do think this was a package of trials designed together that should be considered as contributing to our understanding together. So,

even though you have already made your minds up about this, it is quite relevant and I am glad you asked about it.

DR. PFEFFER: Dr. Nissen, I don't have the slide you asked for but you brought up the point about multiple hospitalizations and that the patient doesn't care what they are in the hospital for so I just want to show that again, if I may--

DR. NISSEN: We saw that once I think.

DR. PFEFFER: But to me that is a risk/benefit analysis too and you have to realize this is in the context of more people available to be hospitalized. This you haven't seen so I will do this one. It is a slide you have not seen.

Here are to total hospitalizations for the whole program and, yes, there is a counter but that counter ends up with numerically fewer. We are here for CHARM-Added but in the whole program but we are double and triple counting people coming in for hypotension and renal dysfunction that would be double counting. But it is real and we are the first to say it is real. As a matter of fact, Dr.

McMurray has taught me that when you use an inhibitor of the renin-angiotensin system in doses that save lives there is a responsibility, and we are prepared to use that in a responsible fashion.

DR. SACKNER-BERNSTEIN: In terms of the analyses that were alluded to about the low dose versus high dose ACE background and throughout the briefing document I think those are most convincing to me, that patients who could only tolerate a low dose of ACE inhibitor were probably sicker. I think if you look at all of the analyses--remember, the patients weren't randomized but based on low or high dose, it is most logically explained and most internally consistent if you look at it--

DR. HIATT: The rates were the same. I am looking at it right here.

DR. SACKNER-BERNSTEIN: You are looking at one table. There are subsequent analyses that have to do with risk of AEs, that have to do with risk of the other endpoints. I think when you look at the totality of those, post hoc analyses, it looks like the low dose ACE patients are just a sicker

bunch, which would make sense as to why the doctors couldn't get them to high dose because they are more brittle. I mean, that is my interpretation and I think it is worth looking at the tables in that respect.

DR. D'AGOSTINO: I don't think that is the case with the data though. I think the ones who are not on recommended dose, and so forth, the two groups look very much alike. It is when you start doing the right thing that you see the candesartan looking better, and I am not sure we should make much out of that for reasons that we talked about before, but it is there.

DR. PFEFFER: I have to take objection to the low dose because this is our doctor in the field saying this is the dose for that patient.

DR. D'AGOSTINO: Well, it is the recommended dose.

DR. PFEFFER: Yes, and we didn't find a distinction. I think Dr. McMurray really shared with you all the information we have on could I go even higher on an ACE inhibitor, and if somebody

can and had improved clinical outcome, let's do that. But until we have that, we now have in our hands a way to reduce CHF hospitalizations and CV deaths.

DR. NISSEN: I have a question for you about the hospitalization. I don't know what you do in Boston, but it is common at our place--we have an emergency room, sort of a little short stay area where people can get admitted--not admitted, they are actually there for about 12 hours and they can get IV diuretics and so on. Were you able to capture those non-admission admissions, and how did you treat them?

DR. PFEFFER: In 1997-8, when this was being designed we heard a lot about my clinic infuses dobutamine as an outpatient and you would miss these patients, and we heard a lot about we have a special place for these patients and they are not admitted. We would not have captured that. So, if that is such an abundant part of the heart failure scene, we would not have captured that because, again, we set this bar for something

across the globe that we could come here and defend.

DR. SACKNER-BERNSTEIN: In terms of the background ACE inhibitor dose that you showed in the CHARM-Added study in one of your slide presentations--I guess it is slide number CE-24 where you show the mean daily doses of five different ACE inhibitors over time in the Added trial, I look at that and then I look at Table 48 in the sponsor's briefing document, page 96 through 98, and I see some evidence that maybe the mean dose doesn't tell the whole story about the level of ACE inhibitor use over time. In Table 48 it appears that as you look at each visit up until the last visit where, obviously, not everybody had the full 42-month follow-up since the median was only 41 months, but if you look out to month 38 you see that there is some consistent trend at each visit for a slight bit of disparity between the maintenance of that same level of ACE inhibitor dose over time. So, I am hoping you can put these two pieces of data, these two analyses together to

reassure me that the patients really were receiving continued appropriate doses of ACE inhibitor with the addition of candesartan.

DR. PFEFFER: I would like to put this table up. This is the data from CHARM-Added. We have been talking about baseline use because that is not confounded. I particularly went into the time during the titration phase because that is really an issue. Anything post randomization really is totally confounded by somebody being admitted for hyperkalemia; somebody having an MI; somebody saying I don't like you anymore, I'm not taking any medications; somebody having cancer and saying, you know, I am done with these medications. So, that is totally confounded. But I can show you the numbers here. I take some comfort that we are not taking a nosedive in the use of the ACE inhibitor over time but, Jonathan, I don't know how best to do that. These people at 36 months are very different than people at the other times.

Now, I do have a slide of the daily doses of the top four. This is as a table and I do have

a graph of this. So, yes, there are some people who stopped; stopped all their medications. Some people stopped our study medication. But this is trends over time for the use of the four most commonly used ones in our study.

DR. MCMURRAY: We did an analysis that I suppose we shouldn't have done but, like you, I was intrigued by that very question so here you see the sort of analysis you saw before looking at ACE inhibitor doses but no longer at baseline but for people who were maintained on big doses of an ACE inhibitor for the duration of the study. We have done that analysis also by looking at people who stayed on the dose until just before the events. Whatever way you look at it, I think you see the same thing that you saw when you looked at baseline dose. So, I think looking at baseline dose is probably the important dose to look at because of all the things that Mark said.

DR. NISSEN: Other questions from the committee?

[No response.]

This is good; this is unprecedented. I have a procedural question. Are we obligated to answer the questions to the committee after the public hearing or could we begin that now?

DR. TEMPLE: I don't know. I suppose if public input is going to be meaningful you should probably have it.

DR. NISSEN: Yes, I think so too. Since we told people it is at one o'clock, since no one has actually signed up to offer an opinion, could we do that now? Would that be acceptable procedurally? I don't want to break any rules. I never break rules.

DR. TEMPLE: I don't know. Is there actually anyone in the room planning to get up?

DR. NISSEN: Anybody?

DR. TEMPLE: Of course, it is not one o'clock so they wouldn't all be here. Why don't you check? I don't know the answer.

DR. NISSEN: We are going to check.

DR. TEMPLE: We don't want to violate anything.

DR. NISSEN: This may be the first time in five years of doing this that I actually make the flight that I originally intended to fly out on, which is extraordinary. Of course, we could get bogged down on the questions. One never knows.

DR. TEMPLE: It could snow.

DR. NISSEN: Yes, we do have a little bit of weather to contend with. So, while we check, if anybody does pop up with an additional question? The sponsor did a great job. I must also comment to Dr. U that that was perhaps the most comprehensive review that I have read in five years of doing this. There wasn't anything in there that I wanted to find that I couldn't find. So, that actually I think in part contributes to the fact that there are not as many questions here. And I thought your presentations also were very complete. It makes it easier.

Let's take a coffee break for about ten minutes and we will get the answer to our questions and we will move on if we can.

[Brief recess.]

Committee Discussion and Questions

DR. NISSEN: We have an answer to our question so we would like to get started again. We will abandon our unscheduled break and we will get moving. What we are going to do is we are going to allow anyone who wants to speak at the open public hearing to speak now. We are going to then make another announcement at one o'clock so that if anybody has come in especially to speak at one o'clock they will have that opportunity. If I may, let me announce if there is anyone in the audience that would like to address the committee, please step up. Seeing none, we are going to go ahead and do the questions to the committee, and we will try to get done what we can before lunch and we will pick up after lunch.

Let's begin with the background statement. This states that we are asked to opine on the candesartan development program for heart failure in a series of three studies, enrolling a total of 7601 subjects.

The division expects to approve the use of

candesartan in patients with heart failure who are not, for whatever reason, taking an ACE inhibitor. And we have already heard that that has been done. CHARM-Alternative shows that candesartan is effective in patients intolerant of ACE inhibitors and at least CHARM-Added is supportive of this use. The question for the advisory committee is whether CHARM-Added provides compelling evidence that candesartan should, under some circumstances, be recommended for use in patients on an ACE inhibitor.

The questions address three possible bases for approval. Once there is general agreement on a possible basis for approval, the committee is invited to skip directly to question 7 and address the strength of evidence for this claim.

Here is our first question, when two drugs are presumed to operate by sufficiently distinct mechanisms, one generally does not worry whether therapy with the older one has been optimized before testing the addition of the newer one. Should one, in fact, test a new drug against

optimized background therapy? Let's take that 1.1 first. We are not going to vote on all of these. This is one for discussion. So, comments?

DR. HIATT: Based on the dose-response curve, and so if it is flat, then it optimizes any dose, and if it is not, then you have to consider optimizing the dose. Here, when I was reading this literature I wasn't convinced. I mean, it wasn't compelling that there was a huge dose response for background ACE.

DR. TEMPLE: I think this is a tricky question, a different question. If, for example, you were adding an ACE inhibitor to a diuretic what this question says is we don't actually care whether you are imperfect on the diuretic as long as it is a reasonably effective dose because the mechanisms are totally different and adding an ACE inhibitor to a diuretic isn't like adding more diuretic. But, for example, take the most obvious case, if you are already on an ACE inhibitor and you were testing whether another ACE inhibitor would be beneficial, I mean, there might be

theoretical reasons why that would be sensible but you would want to be sure that you are on a maximum dose otherwise it is just like giving more of the same drug and that is not very informative. So, that is what this is about. But I guess you were asking, Norm, whether we think you should always optimize the other therapy.

DR. STOCKBRIDGE: Right.

DR. NISSEN: Well, it is a little complicated because, in fact, there are some examples where a strategic approach to management of a disease might, in fact, dictate a different strategy. Let me opine about that. I happen to be a believer that in management of hypertension it is often desirable to use modest doses of several medications rather than push doses to the highest level because we have generally observed that in a lot of classes you really do get a lot more AEs when you push the dose. Tom might want to comment about that more than me. So, there are a lot of reasons why you might want to explore the value of an added therapy. The problem you get into is the

one that you stated. I mean, adding a second ACE inhibitor on top of submaximal doses of another ACE inhibitor, that is a no-brainer. You don't want to do that. Obviously, the reason that this whole question is germane here is that there was some discomfort in the agency about whether ARBs and ACEs are really different. We are going to get to that. We are going to drill down to that in a little bit. But I do think that you don't always have to insist on the maximally effective dose in one class before you test the efficacy of adding another class because there are other reasons why you might want to added it.

DR. TEMPLE: The other part of our reasoning though is, apart from what the best practice is and I think everyone would probably agree with what you said, you don't push till people are sick, the inferential quality isn't impaired, or at least that is the thinking. If you are testing an ACE inhibitor in heart failure if it adds, in the presence of a modest dose of a diuretic or a large dose of a diuretic, you have

evidence of an added effect and we have never thought it mattered that much whether you were on the maximum dose. It is a different theory because of the non-relationship of the pharmacology.

DR. HIATT: I do think I get the question and, you know, the problem here is I think that it gets a little bit into pharmacodynamics. In other words, is the dose-response linear or do you reach an asymtope? I mean did you push the dose of enalapril from 20 mg to 40 mg or 40 mg to 80 mg? Are you gaining a 0.1 percent incremental increase for every doubling of the dose? In that case you may be clinically at an effective dose at 20 and going to 40 and 80 doesn't really matter. So, I think even in this situation you can't just ask that sort of like, well, of course you need to optimize the ACE dose, or whatever. It has a lot to do with how the drug is actually operating clinically.

DR. TEMPLE: Okay, but we are focusing here on the dose of the thing that you are adding to. Yes, you should test the dose response for the

drug you are interested in. We get that with 6000-patient studies, you wish you did. But this is about what the dose of the baseline should be. You can think of reasons that aren't necessarily noble ones why someone might want to us a suboptimal dose if you have completely obliterated the problem and there is no room for improvement. That is one reason people might use--

DR. HIATT: Also you double the cost of therapy if you add another drug that could sort of have been maximized by a modest increase in the dose of the background therapy.

DR. TEMPLE: Well, our presumption has been that if the baseline therapy doesn't wipe out the disease, if it was an antibiotic or something, it doesn't matter that much whether you add a perfect dose of that or a modest dose as long as it is an effective dose. You wouldn't want a non-effective dose.

DR. NISSEN: Blase?

DR. CARABELLO: Surely we wouldn't even be discussing this if the average dose of enalapril

had been 2.5 mg. I mean, we would have said, well, of course the addition of another drug affecting the same system worked and it wouldn't prove anything. I mean, in order to prove effectiveness here there had to be some reasonable dose of the baseline medication. Whether that was maximum or not I don't know but it had to be a reasonable dose or we wouldn't believe it.

DR. TEMPLE: Yes, but that is the case where they are pharmacologically related and we totally agree that is why we are here. But we have thought that if it is something completely different--diuretic is the most obvious--it doesn't matter that much whether you have optimized, whereas, with an ACE inhibitor it really does seem to matter. So, we have made that distinction. The question is to find out whether you think that is a good idea.

DR. D'AGOSTINO: I was going to pick up on Bill's comment. If you are talking about a dose-response where that flattens out, I mean, you could interpret optimal to be at the beginning of

that flattening out though it is hard to avoid the context of the study, even though it is question 2. I mean, this study did try to get an optimal type of dose for the ACE inhibitor and then move on, and I think that is a very sensible thing to do if you are worried about the same mechanism, and so forth, that you bring it up to reasonable optimization, and it doesn't necessarily mean the optimal point but something that is a reasonably good level that the patient can tolerate, then I think the answer is yes.

DR. HIATT: And my interpretation in fact, even though I posed the question differently earlier, is that it doesn't look like a strong dose-response curve so usual care, as you were pointing out, or maximal care certainly is in the same range of dose response versus a 2.5 mg enalapril dose where you really may be below a threshold of clinical benefit.

DR. D'AGOSTINO: If you are deliberately below the optimal, and so forth, then you are in the bind that Bob is raising. You are not going to

be able to sort it out.

DR. HIATT: I was just saying I think you probably are in the flat part of the dose-response curve, and the data here actually support retained, if not better, efficacy of the higher dose of background ACE.

DR. NISSEN: The difference here, of course--having sat through a number of these where we looked at comparative trials--when you are comparing two therapies then we are talking about an entirely different animal. You know, I think it is very important that we make that distinction. We can smell a rat very quickly when somebody does a comparative trial and the drug they are comparing to is being used in suboptimal doses. That is not a fair comparison. You, guys, have many times said no, you don't get a superiority claim by beating a suboptimal dose.

DR. TEMPLE: But you do get a claim. It did work.

DR. NISSEN: Yes, it worked.

DR. TEMPLE: You don't get superiority.

DR. NISSEN: You don't get superiority.

DR. TEMPLE: If there is good evidence of effectiveness--

DR. NISSEN: Yes, if you can beat placebo, and so on.

DR. TEMPLE: Right. It is easier to interpret than a non-inferiority study by a lot.

DR. NISSEN: Yes, absolutely. But one of the things that obviously this sort of an analysis has to do is it has to survive a sniff test. If you look at the doses and if you say, hey, are these doses in the realm of what clinicians commonly use and what clinical trials have commonly used to treat this disorder, then it is probably a reasonable analysis. If it is clearly below that, then you have a real problem.

DR. TEMPLE: The distinction we were trying to make, and I don't think we did it so well, is that if you think the drugs are pharmacologically close then to show an added effect you absolutely have to have what appears to be as good an effect from the thing you are adding

to--

DR. NISSEN: Yes.

DR. TEMPLE: --as you can get. So, it really has to be the maximum dose, the dose beyond which there is no point in treating, otherwise adding to it could be just adding more of the same. We don't have the same feeling about pharmacologically different drugs.

DR. NISSEN: No, I think you probably heard what we had to say. The reason everybody is struggling with this one a little bit is that these two classes of drugs, ACEs and ARBs, are similar in some respects and different in others and now the real big question is are they more similar or more different? And, this one is that oddball case where you are interrupting the same pathophysiological mechanism but by two different pathways. So, it creates this problem for you and I see why have a problem here and I understand it. There are not a lot of examples of this but this is a very good one.

DR. TEMPLE: But if you think they are

pretty similar or can't say that they are not, then it becomes important to know that you have maxed out the dose of the ACE inhibitor.

DR. NISSEN: Does that answer?

DR. TEMPLE: I think it does.

DR. NISSEN: What are the implications if such optimization is not done? I think we have heard that; we have said that. We have all said I think very clearly that you are way under what we believe to be a reasonable dose and obviously that is one thing.

DR. TEMPLE: Right, but reasonable dose--if you think they might be the same, reasonable dose is not good enough. It really has to be a dose beyond which there is not much more point, as far as we know, in pushing it. Otherwise it would be like adding another ACE inhibitor to an ACE inhibitor. As you said, it is the no-brainer case.

DR. NISSEN: I wouldn't really necessarily say that I guess. And, part of the problem is that, you know, I wouldn't say as a standard here

that one would have to push the background therapy just to the level of tolerance, I mean, the idea that you have to literally go to the point where you are getting into trouble and then back off before you add a second therapy. That is why I used the word reasonable. You know, they could have tried to really force titrate these folks up to the highest tolerable dose and they would have probably got a lot of AEs if they had done that and there would have been issues with that, and that wouldn't have been a practical study design so I wouldn't set the standard that high.

DR. TEMPLE: I don't think we are suggesting that. The distinction is we care much more about the dose of the ACE inhibitor than we do about the dose of the diuretic.

DR. NISSEN: Tom?

DR. PICKERING: Yes, I think we are talking about three doses here for the ACE inhibitors. There are inadequate doses, adequate doses and then mega doses and you have been talking about the difference between adequate doses and

mega doses. The only study that showed a dose response was I think ATLAS where you went from inadequate to adequate. When captopril first came into use for hypertension in the '80s we were using doses of 300 mg and 400 mg and I remember there were a lot of reports of neutropenia and proteinuria, and it was said that this was because captopril had a hydril group and the other ACE inhibitors didn't. But I don't think we know what the long-term effects are of mega doses of ACE inhibitors and there could be adverse effects that we just don't know about.

DR. TEMPLE: We also know that those high doses didn't add to the hypotensive effect.

DR. PICKERING: Right. I am in favor of combinations of moderate, more adequate doses rather than trying to push to the absolute maximum.

DR. STOCKBRIDGE: But, again, that is not really the question. The question is if you want to assert that the mechanisms are different, that ARBs or this particular one has some property that you can't get out of an ACE inhibitor, the only way

to do that is with the ACE inhibitor maximized.

DR. HIATT: Optimized. But I think the other concern I have with this conversation is that we are talking about this in terms of milligrams, not in terms of patient optimization. We have heard earlier today that for some patients a "low dose" by milligram may be a maximal dose tolerated in a patient who is sicker. So, I would like to be a little careful. I don't necessarily believe that the box that they checked really defines that they were on optimal ACE dose. On the other hand, if the patient populations are somewhat heterogeneous, then we can't necessarily assume that they were all on optimal doses of ACE inhibitors and then the difference in milligrams is a reflection of the demographic of the population.

DR. TEMPLE: But imagine for the moment that someone had a theory that his ACE inhibitor had an effect that somebody else's ACE inhibitor didn't have. Now we know they are both ACE inhibitors so the bias that they are the same is stronger than here. If they took, I don't know, 25

mg of captopril and showed that you get a better effect by adding this drug to it, that wouldn't really prove a whole lot. That is just getting the dose of ACE inhibitor up to where it should be. So, for them to make that case I think you would say, well, we should be at the top of whatever the thing you are adding to is or close to it--you know, you don't have to make everybody ill. And, I think the point of this question is how close are we to that situation where it is obvious you have to get the dose up otherwise you are just showing something entirely trivial.

DR. HIATT: But they showed that. If you look at that subgroup analysis at the "highest dose" defined a couple of different ways the risk reductions were even bigger.

DR. TEMPLE: Yes, well, we are just asking what the principle should be.

DR. HIATT: Well, I think that the drugs are different enough.

DR. NISSEN: Well, we are going to get to that. We will get to that; that is coming up.

DR. TEMPLE: I just want to make sure you know why we are asking the question.

DR. NISSEN: No, I think it is a really interesting, highly relevant question. It is not the last time it is going to come up, I am sure.

DR. TEMPLE: Right. I should mention that when we analyzed--and maybe this was a mistake, who knows--when we analyzed ValHeFT it appeared clear that the drug worked when there was no ACE inhibitor, valsartan did, but the effect of the drug seemed to be better and better as you went further and further away from having the proper dose of the ACE inhibitor.

DR. NISSEN: Right.

DR. TEMPLE: So, it sort of looked like if you had the proper dose of an ACE inhibitor you didn't have any effect. Given these data, maybe that was all wrong but that is how that looked.

DR. NISSEN: Yes, and again we are going to come to that later, but the ValHeFT data, how relevant is it to our current considerations? I think you are going to ask us that later. Now, we

have a question that says did CHARM-Added have adequate optimization of background therapy with respect to ACE inhibitor use? I would like people to discuss that. Ralph?

DR. D'AGOSTINO: The protocol implied that they were after some optimal use and this question becomes do we believe the results that they are reporting to us but they were aware of that question.

DR. NISSEN: Yes. Blase, go ahead.

DR. CARABELLO: But even if they didn't, the subset analysis of the mega doses is very assuring.

DR. NISSEN: Yes, but that is not what we are being asked. I am going to answer it. My view is that, you know, everything I saw this morning tells me that they made their very best effort. Now, you know, could you quibble about it? You know, could you find some expert that would say it wasn't enough? But, you know, the enalapril doses in the high teens look about like you see in other heart failure trials. The other ACE inhibitors are

being used in what I would consider full therapeutic doses. The instructions to the investigators clearly emphasized what they were trying to do. So, I have to give the study points for making a very good effort at this and I don't see any compelling evidence that there was an effort not to optimize; every efforts seems to have been to optimize and I think they got to optimal or near optimal doses.

DR. STOCKBRIDGE: What do you mean every effort was made? They checked the box and then what did they do, press people to get them up as high as possible on their ACE?

DR. NISSEN: Well, we got a statement that was given to investigators which basically told them to push the ACE inhibitor and, again, they got to doses, Norman, that were pretty similar to the doses used in the classical ACE inhibitor trials. Presumably, in those trials the sponsor was very, very eager to get to the optimal dose. So, if you look at SOLVD versus this study you get about the same numbers, don't you? So, if the people doing

the SOLVD trial were under-treating, okay, but they were clearly not motivated to under-treat in SOLVD.

DR. TEERLINK: I think actually the efforts that the CHARM program made to optimize were quite considerable, and I think they are to be congratulated on at least looking on that as an issue. For future trials, obviously, it might be interesting to have them fill out a little more information on what is limiting the dose in this particular patient and have a CFR that says, you know, we can't go any further because of renal function, hypotension, hyperkalemia, and list some of the limiting things. You are still left with having to trust the investigator that they tried and they pushed as hard as they could, and that is true in all cases.

DR. TEMPLE: You can also see the doses they achieved and the various subsets of analyses.

DR. NISSEN: I may be missing something here, Norman, but do you not agree that the doses that they achieved were very similar to what were used in the classical heart failure trials?

DR. STOCKBRIDGE: Oh, I think that is true. What I think is missing is a protocol-driven effort to make sure that the doses were as high as they could be. You can take some comfort if you think the populations in this trial were similar enough to populations in the other trials that you are using as references for what looks like it, but you are stuck having to make the decision based on comparing mean doses across trials and there is nothing in the protocol about pushing the dose of the ACE inhibitor.

DR. D'AGOSTINO: This is exactly what I was trying to say earlier, that there is a protocol statement that they are going to optimize but there is no real indication about how they got it so we can believe or not believe what the investigators are telling us and then also the actual doses that were achieved.

DR. TEMPLE: Which is a separate question from whether the doses they got to were--

DR. NISSEN: Yes. Again, you know, I understand your argument and it is actually a very

relevant argument. I mean, what you are really arguing for is almost, you know, maybe there needed to be more of a forced titration strategy here to really, really push and I can understand why that wasn't done. You know, these are very fragile patients and, you know, I see some of these folks myself and I suspect that a lot of the patients that had blood pressures that were tolerated would have been pushed and those that were not able to tolerate higher doses of ACE are dominating why you get to these similar average doses in SOLVD and in CHARM.

DR. TEMPLE: It could even be that if people pushed the dose of the ACE inhibitor to where it should be you would decide that certain people weren't suitable for the trial because their blood pressure was already too low. That is okay too.

DR. HIATT: There could be an inherent bias. If you are going to put a patient in a trial like this, you may not really want to push the dose of the ACE because you want to get them in the

trial and you know that the ARB is going to lower blood pressure, raise potassium and this kind of thing. So, there could be an underlying bias to not optimize ACE, which gets really to the heart of this question.

DR. STOCKBRIDGE: You have other opportunities in the questions to address whether or not there is a claim that that related to--you know, I have worked this system as well as I can with an ACE inhibitor and now I am going to work it from a different angle. You get another opportunity to do that. This question was different. This question was about establishing that an ARB is so different in mechanism that you clearly get something on top of ACE inhibition. It doesn't matter what you do with the ACE inhibitor. You know, you could give it at high doses and you still couldn't possibly get the effect you get out of candesartan.

DR. NISSEN: Let me tell you one of the pieces of evidence that suggests to me that the system wasn't getting gamed here, the fact that

patients were enrolled with virtually any blood pressure. You know, if you really wanted to exclude people who might not have benefited, basically all those low blood pressure people where you might have had trouble adding candesartan, you would have just kept them out of the trial, and they didn't do that. So, it means that they were including people who might have been more vulnerable to the candesartan add-on as opposed to just sort of getting an ACE inhibitor.

DR. HIATT: I wouldn't have called that gaming at all. In fact, I don't think if they had done that, if they had in fact driven people up to maximum labeled doses or maximum ACE inhibition or something like that everybody in the trial and then established the benefit there--I wouldn't have said that that was the only way to use the drug. I wouldn't have said you had to have blood pressure that was high enough to start with that this didn't, you know, cause tolerance problems. But it really would have established that as a class you could get something out of it that you can't get

out of an ACE inhibitor. We all think we have really answered that question so my comment on the data is that there is enough preclinical and clinical data to suggest that they are more different than similar.

DR. NISSEN: Well, we are going to get to that.

DR. HIATT: Then we have answered the question.

DR. NISSEN: Any more comment on 1.3.1, the question of whether there was adequate optimization of ACE inhibitor use? Any more comment? Have you heard enough discussion? We don't all necessarily completely agree here but, you know, I think that there is some sense from the committee.

What about other treatments for heart failure? I will take comments about that.

DR. TEERLINK: I think this was a very interesting portion of the question because there are those that believe that actually beta-blockers work via suppression; that one of the major effects

of beta-blockers is that they suppress the renin-angiotensin system. So, does that actually count as a related drug or a non-related drug? If it is a related drug, well, then should we have really said that they had to optimize? I think this is not pertinent to the CHARM. It doesn't influence my thinking on the CHARM trial but in terms of future trials, which we are all trying to design, are we going to now require or would we want to suggest that those doses need to be optimized as well? And, what direction are we going to give those trialists to decide how to optimize those? My personal opinion is that a similar approach to what was done in this trial, with the addition of a clinical report form or something else that says, look, did you really push it as best you could, would be a reasonable approach in my opinion.

DR. TEMPLE: So, since there is at least some overlap of the pharmacology you are also interested in being sure that that has been reasonably well optimized so you know whether you

are just giving more beta-blocker or actually doing something different.

DR. NISSEN: There is a real problem here with contemporary therapy, not just in this area but in other areas as well, and that is as therapy gets better and better you get to diminishing returns and we always want to know when we get to that point. You know, in coronary disease if you look at trial after trial the event rates year by year seem to get lower and lower. So, companies that are designing programs to lower the risk of death and MI with lipid-modulating therapies are estimating lower event rates as we are adding on multiple agents.

DR. TEMPLE: The event rates get lower; the hazard ratios don't always get lower.

DR. NISSEN: No, they don't necessarily but we like to know that in evaluating an agent that given on a background of what we know to be effective customary therapy. Now this trial has the problem, of course, that it was at a transition point. Beta-blockers were coming on very rapidly

but they weren't fully penetrating the heart failure area. So, my answer to this is if you look at the time frame when this was done, having at the beginning of the trial 55 percent on beta-blockers, going up into the 60s during the course of the trial is pretty reasonable given the time frame when this was taking place, there was certainly more beta-blocker use than in ValHeFT which was an earlier trial. So, it does reflect that the background therapy looks pretty contemporary but I would be interested in other people's comments.

DR. PICKERING: I would like to bring up the issue of spironolactone again because I would be interested to hear what other people think. There didn't seem to be any clear benefit of patients in CHARM-Added being on spironolactone as well, and there is clearly the possibility for harm there. So, perhaps the concomitant use should be discouraged.

DR. TEMPLE: How can you tell that? They weren't randomized to spironolactone.

DR. PICKERING: I know but from what we

have heard--

DR. TEMPLE: They might have been sicker. I think that is really hard to know from this design.

DR. NISSEN: It is an unanswered question.

DR. TEMPLE: But also, for what it is worth, in mind with the other question, you want a reasonable dose I guess but it is not as important because you don't think it might be the same pharmacology as the drug you are testing.

DR. NISSEN: Bob, you know, there are clinicians that are going to look at the results of whatever we do today and they are going to have to answer the question for a patient with, you know, class IV heart failure. I think everybody is going to get an ACE inhibitor and a beta-blocker. Now we are being asked to opine whether adding ARB is good. Should you also add spironolactone? That is an everyday practical, important question on what is the benefit and what is the risk of quadruple therapy rather than triple therapy. What I see here is that we can't answer that question. We

don't have enough information.

DR. TEMPLE: You do know that RALES was done in a population that mostly got ACE inhibitors, diuretics and a fair amount of beta-blockade I think--

DR. NISSEN: Yes, but not ARBs.

DR. TEMPLE: But definitely not ARBs. So, we presume everybody is going to get ACE inhibitors before ARBs because, as Norm told you, we are all set to approve ARBs as a substitute for an ACE inhibitor as the initial therapy. Of course, none of these data tell you that you still need the ACE inhibitor. These trials never do. They always add on but they never subtract, or hardly ever subtract.

DR. CARABELLO: The answer to 1.3.2 is we just don't know. We don't know what the diuretic doses are. If you believe carvedilol is a superior beta-blocker, you know, we just don't know.

DR. STOCKBRIDGE: Well, the question was whether or not it was adequate, and we have asserted in the preamble to this question that if

it is an unrelated mechanism it sort of doesn't matter to us. So, you tell us that it does matter to you and that you don't have enough information. Is that right?

DR. CARABELLO: I don't know what adequate in terms of diuretics for instance would mean in this trial. We don't know. But that is not the question. The question is does it matter. That is the question you are asking.

DR. NISSEN: Actually, I am going to interpret the question a little bit differently. What you are saying is given what we know about therapies for heart failure, are we satisfied here that the background therapy used, you know, was evidence-based contemporary therapies. Now, we don't have any evidence on diuretic dose, Blase. We don't know what the optimal diuretic dose is for patients with heart failure. So, there are a lot of things we don't know here so within the realm of what we have evidence for, did this trial achieve reasonable optimization--adequate was the word you used; I will use the word reasonable but adequate

is fine--of background therapy? It looks like the background therapy there was at least as good as any trial done during this era, maybe even a little bit better and so I would deem it adequate. Now, maybe other people have a different view but I think--

DR. TEMPLE: Especially for the ones that aren't as critical.

DR. NISSEN: Yes.

DR. TEMPLE: I mean ACE inhibitors are a special problem.

DR. NISSEN: Yes.

DR. TEMPLE: Maybe beta-blockers are a special problem. But for the others you just need to know they are reasonable.

DR. NISSEN: Yes. You know, there doesn't seem to me to be any evidence that there was some under-utilization of an important concomitant therapy that might have benefited these patients and, therefore, reduced the benefits of this add-on. I don't see any evidence of that.

DR. SACKNER-BERNSTEIN: I also think it is

interesting to look at the wording of the question. Maybe you could just help me understand it better because putting adequate and optimized together is a little bit confusing to me. I have been interpreting the goal as being one where we are saying were the patients in the CHARM-Added trial were treated well with an ACE inhibitor, the way contemporary medicine says they should be.

DR. TEMPLE: No--

DR. SACKNER-BERNSTEIN: I don't mean well compared to clinical practice; I mean well compared to clinical trials.

DR. TEMPLE: No, that is not the question. This is not about virtue or whether somebody tried--

[Laughter.]

--it is whether somebody thinks another ACE inhibitor is going to have an additive effect to an appropriate dose of the first ACE inhibitor and for some reason they think it does something else. What would you want that first ACE inhibitor to be dosed at to be convinced that you are not

just giving 10 mg instead of 5 mg of the first ACE inhibitor, which would be a completely trivial thing. So, if the drugs are the same in their pharmacology, what we are hinting at here, asking you about is, is it much more important to know that you have pretty much gotten all you can out of that drug so that you know you are not just giving enough of the same old thing? So, for example, nobody would think that an A2B is like a diuretic so you don't care if you are on the absolute maximum dose of the diuretic. When you have an effect when you add it to a reasonable dose of the diuretic, it must be the drug that is doing it; it must be doing something different.

Our thought has always been we are not sure about that when it comes to ACE inhibitors. There are a lot of theories about how they are different and we saw them up there, and it is not implausible but we have been more concerned that people be on full dose of the ACE inhibitor, whatever that means, so that you know you are actually adding something and you don't know that

if they are not on the full dose of the ACE inhibitor.

Now, what full dose means is tricky. We haven't talked about this but if you get a 20-or so percent reduction in this outcome, do you believe that increasing the dose of the ACE inhibitor a little bit will give you a 20 percent reduction? No, I don't. I mean, we have some idea of what the dose response is; it is not that big. So, that also argues that finally getting the dose of renin-angiotensin inhibition right is a good explanation. The effect is too large for that, you could say. That is where we are trying to make the distinction.

DR. NISSEN: Let me give everybody an analogy that I think is really extremely relevant here. The relevant analogy is the HOPE trial and the PEACE trial. In the HOPE trial there was very little in the way of contemporary background therapy given very little use of lipid-lowering therapy, low use of other beneficial concomitant therapies, and ACE inhibitors produced a rather

robust benefit. The experiment was repeated with what we have reason to believe is every bit as good an ACE inhibitor but the therapy was contemporary and, lo and behold, when you added the ACE inhibitor on top of contemporary therapy there wasn't a whit of benefit. Some of us predicted that outcome as a matter of fact. So, why it is so relevant is that we do really want to know that a new therapy, regardless of mechanism of action, is incremental.

DR. TEMPLE: That is an interesting question.

DR. NISSEN: Yes.

DR. TEMPLE: It is not what we are trying to get at--

[Laughter.]

--but really going back to adding one ACE inhibitor to another, you wouldn't expect that to work if the dose of the first ACE inhibitor weren't appropriate and optimized because you would just be adding more of the same and it shouldn't work. It is like, you know, adding three antibiotics where

one is an adequate dose. You wouldn't expect any benefit unless it does something different.

DR. NISSEN: Yes.

DR TEMPLE: And it might. That is really what we are trying to get at.

DR. SACKNER-BERNSTEIN: So, as I was talking about before, I think that adequate and optimization is confusing. I am going to try and start again with the same thing. I think the question is are these patients in CHARM-Added well treated with ACE inhibitors? When I say well treated I look at that in two ways. One is are they following the evidence, the investigators, and using the doses that are used in clinical trials, and then look at that in combination with the little we know about the dose-related impact of ACE inhibitors in clinical outcomes. So, you put all those together, because there is not much dose response as you go up to higher doses, and you are at the doses that are used in clinical trials and I think you could say adequate optimization, yes, they probably were with ACE inhibitors.

DR. TEMPLE: Meaning that they probably got as much out of an ACE inhibitor as you can get out of an ACE inhibitor.

DR. SACKNER-BERNSTEIN: I thought that is what you meant by adequate optimization.

DR. CARABELLO: Yes, that is 1.3.1 but what about 1.3.2?

DR. TEMPLE: Well, we are asking how you feel about the other drugs, how important it is to optimize those. But we start with less strong feelings about that because it is not the same mechanism. We know it is not the same mechanism.

DR. PICKERING: I don't think we can answer your question about huge doses of ACE inhibitors because it has never been done and what we heard conforms to general clinical practice and we basically have to deal with the data we have. So, I mean, I think it is a hypothetical question.

DR. NISSEN: Yes.

DR. HIATT: Except that when I first tried to answer this question it was the concept that you were at an asymptote and I still believe that. So,

20 mg of enalapril versus 40 mg--like you just said, going from 40 to 80 is not going to give you 15 percent risk reduction in events. Therefore, they are optimized.

DR. TEMPLE: That is an entirely pertinent and perfectly plausible answer.

DR. NISSEN: It is a little tougher to answer 1.3.2. Let me tell you why, personally, it is a little tougher to answer it. You know, the effect of agents like carvadilol, as we all know, is very robust. Some people have suggested it is more robust than metoprolol. I don't think that that has been demonstrated beyond a shadow of a doubt in my mind. But, you know, we don't know for sure here that if you redid this study in 2005 and gave an ACE inhibitor to these doses, gave carvadilol and pushed it all the way up to the maximum tolerated dose that then adding candesartan would produce the same benefit. Like every experiment that is done, you have a background that involves a moving target and, given that moving target here, it leaves just enough uncertainty

about what might happen. So, I can't guaranty that that experiment done again with everybody possible on background beta-blockers--but the subgroup analysis from the beta-blocker group would suggest that that is not a problem. But it is not proven.

DR. TEMPLE: What I hear is a general statement, not because you are worried about the similar pharmacology, but you want to be sure there is still something left to treat after you have treated all these things. It is not a bad idea to have a pretty good dose of the other appropriate therapies.

DR. NISSEN: Now, given the fact that 1.4 will involve a fair amount of discussion and we are going to have to vote on this, it might be a really good time to take a lunch break. There is an alternative approach if we think we are moving really fast, which would be to defer lunch but we have to have a one o'clock public hearing anyway. So, any comments or thoughts about how you might want to proceed? What do you want to do, Ralph?

DR. D'AGOSTINO: I would like to just

continue.

DR. NISSEN: Continue? Okay. Any other folks? Again, this is precedent setting efficiency of this meeting and we are going to keep going.

So, we have our ACE inhibitors and ARBs sufficiently different that CHARM-Added can support use of candesartan with ACE inhibitors. What clinical data support your view?

This kind of gets to the heart of what is being asked. So, I want some discussion and we will take a formal vote on this.

DR. TEMPLE: Steve, I think the question actually needs to say are they sufficiently different that it would support use of candesartan even if the dose of ACE inhibitor wasn't optimized?

DR. STOCKBRIDGE: No, I think that is really not what I intended.

DR. NISSEN: Bob is re-interpreting you.

DR. STOCKBRIDGE: Later questions invite the committee to say it doesn't matter whether or not the mechanisms overlap. There is a way to get the thing approved for use with an ACE

inhibitor--there are other ways to do this. This question was really intended to get at do you know from some other data or perhaps from this that ACE inhibitors and ARBs are so different in terms of their clinical outcomes that--

DR. TEMPLE: You should treat it like a diuretic.

DR. STOCKBRIDGE--that you should treat it like it was a diuretic. If the mechanism is different, then the dose doesn't matter.

DR. TEMPLE: Right.

DR. NISSEN: Blase?

DR. CARABELLO: I just want to be clear that throughout these discussions we are talking about CHARM-Added. I mean, we are not proposing that any of our deliberations extend to the person with preserved systolic function.

DR. NISSEN: That is right.

DR. CARABELLO: That hasn't been spelled out and that should be clear.

DR. NISSEN: So, this is a pretty tough and pretty important question and let's see whether

people want to talk about it. I have my own thoughts. Blase?

DR. CARABELLO: I am convinced. I would say yes and the clinical data to support it are--

DR. TEMPLE: That is not the question--

[Laughter.]

--that is why I tried to add this. If you believe the dose is optimized and it showed an effect, it really doesn't matter whether they are different drugs or not. You don't have to answer this question. This question only goes to the point if this is just like a diuretic and the two drugs are totally different, then you didn't have to optimize it. So, the question here is are they so different you would like to treat it as if it is a diuretic. I think that is the only way the question makes sense.

DR. NISSEN: Okay, I think I understand the spirit of what both of you are saying. It is a very touchy and difficult area.

DR. TEMPLE: Clearly.

DR. NISSEN: And that is why it is being

asked of us.

DR. TEMPLE: Right.

DR. NISSEN: So, you know, we are being asked to opine about this. Maybe I can help the discussion a little bit by making a couple of comments. There is a principle involved that comes up in medicine not infrequently. The principle involves the sequential block of a metabolic pathway. I will give you an example from the infectious disease literature. Trimethoprim-sulfamethoxazole blocks the same pathway at two different places and there is very good evidence that when you do that you end up with an antibacterial that is more effective than either agent is alone, and I can think of other examples of that. So, that is why this one is tricky. It is because it is a pathway and you are asking if you block that pathway at two points yielding the same final common denominator, particularly if those pathways involve some slight differences--

DR. TEMPLE: And some similarities.

DR. NISSEN: --and some similarities, are

the similarities more prevalent here or are the differences more prevalent? So, it is really is the glass half full or is the glass half empty? I would say that because the principle of sequential block is a very important one and has been reaffirmed in some other models, and particularly when you consider things like bradykinin and I happen to think bradykinin actually does have an important role to play, and because of the evidence of escape, and I think there has been some reasonable evidence that escape occurs when you give an ACE inhibitor, now you are talking about something that is beginning to come apart as a common mechanism. So, you know, I personally lean toward the view that in this particular application these drugs are somewhat different. They are certainly not as different as a diuretic is from an ACE inhibitor but they are somewhat different.

DR. TEMPLE: But if you believe that then any dose of the ACE inhibitor, even if it was half the doses here, could be perfectly good enough.

DR. NISSEN: Yes, and I wouldn't go that

far, Bob. You know, if we were sitting here today and the average dose was 2.5 mg of enalapril I would be having a whole lot more trouble.

DR. TEMPLE: How about half the dose that they achieved?

DR. NISSEN: Okay, 10 mg. I mean, I think that this does speak to whether we really do think they were in an appropriate range for having the full biological effect or most of the full biological effect.

DR. TEMPLE: But if you think they need full biological effect, then the answer to this question is no.

DR. NISSEN: I said most of the biological effect.

DR. TEMPLE: That is what it turns on. If you really think they are different, then you don't have to optimize. You don't have to have the full effect of the ACE inhibitor. That is only if you think they are or might be sort of the same drug, and you might not know the answer to that.

DR. NISSEN: Again, what we have is a

partial overlap situation here and that is where the rubber hits the road.

DR. TEMPLE: Right.

DR. CARABELLO: But that is what I said before. I mean, I think the answer is yes they are sufficiently different and the proof of that is that when you have maximized the dose of one you still get benefit from the other. If they were working exactly the same way how could that be true?

DR. TEMPLE: Well, that is fair but that is because you think they did maximize it and you not only think they did but you think they needed to so as to convince you, as you have just become convinced. That is fine. We have no trouble with that. That is a different theory though. That is a theory that says because they might be more or less the same, to make a convincing case that one adds you have to use the full dose of the first one. Whereas, if it was just a diuretic you wouldn't need to do that. So, answering this isn't whether they make it or not. That is not the

question.

DR. NISSEN: So, answering the question in the spirit in which it was intended, I don't think they are sufficiently different. That is, if we were talking here about what was clearly a non-adequate dose of ACE inhibitors, then the mechanism is not sufficiently different. In other words, if we are being asked to approve an add-on like an ARB in a situation where we really thought inadequate doses of ACE inhibitors had been used I think this would be very difficult to justify. So, my answer to this is no. Well, we will vote eventually.

DR. PICKERING: Also, it is not just a single pathway. I mean, I think there is fairly good evidence that however big a dose of ACE inhibitor you use you still don't really knock that angiotensin-II level so, as we heard earlier, there are the bradykinin effects and the chymase effects. So, I think there is very good evidence that for the complete blockade of the renin-angiotensin system you need multiple sites of action and this

is what this does.

DR. HIATT: I agree with Tom completely on that. And, I think, Steve, your example of those 2.5 mg--I would say you just wouldn't know or you could conclude either way. In this situation I think we do have enough evidence at higher doses. So, I would vote for different enough.

DR. TEMPLE: Remember, the question is asking whether you even need the evidence at higher doses. See, if you are satisfied that it works and they are different because they used the higher dose, that is not answering the question.

DR. NISSEN: Yes.

DR. TEMPLE: That is a different question, a perfectly good basis for saying I think it works but it doesn't answer the question did we even need to bother.

DR. NISSEN: Can I shift the thinking a little bit? I am going to shift this, and let's suppose we had the same two drugs--

DR. TEMPLE: Mind you, we are hearing a lot about what everyone thinks.

DR. NISSEN: Yes. Let's say we have the same two drugs and the endpoint you are interested in is not heart failure but blood pressure. Okay? And, suppose somebody came in and said we want a label to add our ARB to an ACE inhibitor to produce incremental antihypertensive effect. And, suppose some submaximal doses of ACE inhibitors were used and they got a blood pressure back and they added in an ARB and they got a couple millimeters more blood pressure effect. Okay? Would you decide in that case that the mechanisms sufficiently overlapped that that would not be approvable because what should have happened is that the ACE inhibitor should have been pushed up to a higher dose? I mean, take it out of the context for the moment of heart failure. Have you given a label to anybody for adding an ARB to an ACE to further lower blood pressure?

DR. TEMPLE: No.

DR. NISSEN: You haven't done that? Okay. So, we are talking about something that has some relevance here. So, what do you think? What would

you, guys, think about that?

DR. HIATT: So, if you had three doses of ACE, low, medium and high, and ARB lowered blood pressure in all three scenarios I think that kind of answers the question.

DR. NISSEN: Would it have to be prespecified and would you have to--

DR. TEMPLE: No, that is the same distinction. If you added an ARB to a diuretic you wouldn't worry about whether it was 12.5, 25 or 50 because the mechanisms are totally different and you would say, oh, additive effect. But if you added 25 mg to a very low dose of an ACE inhibitor and showed that you could improve the blood pressure control by adding an ARB to it, that wouldn't tell you anything. You just finally got around to blocking the renin-angiotensin system.

DR. HIATT: At the low dose but what if you added it to the high dose?

DR. TEMPLE: That would be convincing. They would have to do that because you think the mechanisms are similar enough that you want

evidence that they actually add.

DR. STOCKBRIDGE: That is key. If you need the answer to that question, the business about what happens at the high dose of the ACE inhibitor, then you have to answer no to 1.4.

DR. TEERLINK: So, this becomes in some ways a burden of proof question.

DR. TEMPLE: Right.

DR. TEERLINK: All of us around the table I think acknowledge that there is ACE escape, that bradykinins are probably important to some different degree and so there are differences between ARBs and ACE inhibitors that are probably significant. My personal opinion though is that the overlap between them is sufficient enough that the burden of proof needs to be that they do need to do the trial in the context of adequate, optimized--

DR. TEMPLE: That is the exact point.

DR. TEERLINK: --so my answer to that would be I guess no.

DR. NISSEN: And, John, I think you

articulated that very well. Again, in the context of a hypertension study I guaranty that a sponsor would have a whole lot of trouble getting from a committee like this an added label for ARB on top of ACE without doing a forced titration of the ACE to maximal dose, and showing that even when you do that there is incremental blood pressure lowering by adding the ARB. So, if it is good for the goose, it is good for the gander. I mean, if the hypertension story says you have to prove that, I think we really do have to be convinced that the ACE was optimized before we can be comfortable.

DR. PICKERING: This has been done in hypertension. Jules Manard, from Paris, has studied I think maximum doses of ACE inhibitors and shown that you can still get an incremental effect on blood pressure by adding an ARB. I mean, it may not be as big as if you add a diuretic but it is there.

DR. TEMPLE: Well, that is okay. The point is whether you have to do that or not.

DR. KASKEL: Can I say something from the

kidney standpoint? There are some trials looking at ACE and ARB in progression of renal disease and treating the proteinuria, and the recommendations are to maximize the ACE and then start your ARB.

DR. CARABELLO: I would say that before this trial was done the answer to 1.4 was no. Now that the trial has been done, the answer is yes.

DR. TEMPLE: Well, you have to pretend you don't have the trial yet for this question.

DR. CARABELLO: But I am reading the question and it says that CHARM-Added has been done.

DR. NISSEN: We want you to be a bit more ignorant! Would you do that, please?

DR. CARABELLO: Change the question. CHARM-Added is included in the question; I am reading it. Now that CHARM-Added has been done, the answer to the question is yes. Before CHARM-Added was done the answer to the question was no.

DR. TEMPLE: Well, that is fair. That is fair.

DR. NISSEN: Blase, to really have answered the question here is what CHARM-Added would have had to have done: They would have had to force titrate the ACE inhibitor up to the maximum tolerated dose and then drop on the ARB. That would have ended this discussion once and for all. And, the reason that the agency is asking us about this and why there is some discomfort here is that that wasn't exactly the design. We understand why it wasn't the design and we are not criticizing it, but on a theoretical basis I understand better why you are asking this and I think that the design would have answered that question forever--it might have been done for hypertension but it hasn't been done for heart failure.

DR. CARABELLO: But I think the rescue is that there is enough data from the sponsor that at the very, very highest doses of ACE the stuff still works.

DR. NISSEN: We are going to get a chance to opine about all of that, you know, when we decide whether or not they have made their case.

DR. TEMPLE: These are going into it questions.

DR. NISSEN: Are you, guys, ready to vote? Let's start with Blase.

DR. CARABELLO: I think I have made it clear. I mean, a priori the answer is no.

DR. CUNINGHAM: I agree with Blase.

DR. HIATT: Yes, same a priori, it is no.

DR. PICKERING: Can you repeat the question? I am now totally confused.

DR. NISSEN: Are ACE inhibitors and ARBs sufficiently different that CHARM-Added can support use of candesartan with ACE inhibitors, with the implication what clinical data support your view?

DR. TEMPLE: It is could have supported even if you didn't think the dose was reasonable.

DR. NISSEN: Even if you thought the dose was inadequate. I really do think that is the spirit of the question. So, if you thought the dose of ACE was inadequate, would this have been sufficient data to support use of candesartan with ACE inhibitors?

DR. PICKERING: I didn't think the dose of ACE inhibitor was inadequate.

DR. NISSEN: I know, but if you did? If you did hypothetically?

DR. PICKERING: Well, if I did think that then I guess I would say no.

DR. PORTMAN: Based on those last conditions, no.

DR. TEERLINK: No.

DR. NISSEN: No.

DR. KASKEL: No.

DR. D'AGOSTINO: No.

DR. SACKNER-BERNSTEIN: No.

DR. NISSEN: So that was, indeed, unanimous.

DR. STOCKBRIDGE: Then you can't skip to 7.

DR. NISSEN: If you conclude that ACE inhibitors and ARBs are sufficiently different, skip to question 7. If the mechanisms overlap, then optimization of ACE inhibitors matters more.

The protocol for CHARM-Added required

subjects to be on an ACE inhibitor and possible choices were not limited to ones with established claims for heart failure. In designing a trial for an add-on claim, should the ACE inhibitors all be ones with an established claim in heart failure? Comments?

DR. TEERLINK: Is that intended solely for United States being one country or being the country?

[Laughter.]

DR. TEMPLE: That is interesting. I mean, if there were good evidence I might say that might be a half-way thing. I don't know whether there are data for the other ones or not. We only know what we have seen.

DR. TEERLINK: It would have been interesting actually if someone could have asked the sponsor in the question session, you know, in the United States what was the percent of FDA-approved ACE inhibitors and maybe that would have addressed the U.S.--

DR. TEMPLE: Well, the percentages

overall--

DR. TEERLINK: That is what I am saying, it is already 80-90 percent of the patients anyway, and I would anticipate it is even higher in the U.S. So, I do think I would ideally like them to be ones with established claims but it doesn't detract from my interpretation of the CHARM-Added trial that they weren't.

DR. NISSEN: Anybody else? Yes, Jonathan?

DR. SACKNER-BERNSTEIN: I wonder if anyone else is of the mind set of wondering whether it matters if the ACE inhibitor is proven to work for chronic heart failure versus heart failure post myocardial infarction. Obviously, the FDA-approved ACE inhibitors in all these analyses were those two indications lumped together.

DR. TEMPLE: That is correct.

DR. NISSEN: You know, this is difficult. Obviously, this is one of those examples where there are very few people that doubt that there is class effect here. Having said that, I think this trial was very well run. There are a few things

that I would have done differently and I would have given investigators a list of approved ACE inhibitors that would include those ACE inhibitors for which there was some reasonable data to support their use in chronic heart failure. That would have given plenty of choices so we wouldn't be strong-arming people, you know, beyond any reasonable belief. Having said that, they really mostly used ACE inhibitors that are approved. It doesn't detract hugely from the trial. But if I were somebody sitting here, listening to this, designing a trial I would take that out of the equation. I would try to take it out so nobody could criticize me for using an unapproved ACE inhibitor. And, there are enough ACE inhibitors out there that have some trial evidence--have trial evidence that they work in heart failure that you probably could have easily limited to that. It is not, in my view, an issue of approvability but it is an issue in terms of what is an optimal design. Anybody else?

The next question is how does one pick the

target regimen for the ACE inhibitors? You always ask tough questions, you know.

DR. TEMPLE: It is all Norman's doing!

DR. NISSEN: Since nobody else is speaking--you know, my motto is frequently wrong; never in doubt! But the cleanest possible design of a study like this which, in fact was not impossible--we heard all the reasons why it wasn't done but it would have been to take an ACE inhibitor--if you were doing a study like this tomorrow, right, enalapril is generic; you can get it very easily; you can over-encapsulate it and you can come up with a strategy where everybody gets enalapril, a drug we know a lot about; gets it titrated up to effective "adequate" therapy and then gets randomized, and it is just a whole lot cleaner. In my view, the perfect design here is to take a drug in a class that is approved for that indication, for which there is lots of data on what an effective dose is, and use that agent and demonstrate that you are using it at doses that we know to be fully effective. That would be ideal.

DR. TEERLINK: And given that you had already said that in future trials you would also do the same, would you do the same for beta-blockers so that now we have a two-phase run-in up-titration trial?

DR. NISSEN: I would sure try. That is the cleanest experiment you can possibly run. The real life is tougher. As somebody who does clinical trials, I mean, I know that you can't always achieve the optimal but if I were a regulator and I wanted to see a perfect application that would just leave me no questions, that is what I would expect to see.

DR. TEMPLE: Of course, it presumes that they are all the same, which they probably are--

DR. NISSEN: They probably are, yes.

DR. TEMPLE: --but you don't really necessarily always know that.

DR. NISSEN: Other people?

[No response.]

Number three, the CHARM-Added protocol recommended that subjects be treated on

individualized optimum doses of ACE inhibitor based on tolerability and "recommended target doses." What is known about the relationship between dose of ACE inhibitor and clinical benefits and risks in heart failure?

DR. TEMPLE: Well, there is one high/low study that barely maybe showed a difference at the borderline. That was sort of high/medium versus really, really low. So, I think everyone agreed that we don't know much about pushing it, although we saw the results of a trial where I guess the pushed dose did work.

DR. PICKERING: The enalapril 20 versus 60 but there was no difference. It was the ATLAS trial where you had an inadequate dose of lisinopril of 2.5-5 versus--what was it?--32.5 where there was a difference.

DR. TEMPLE: The 20 versus 60 showed no difference--

DR. PICKERING: Right.

DR. TEMPLE: --but my dim recollection is that the higher dose was slightly worse. So, it

doesn't encourage you to think there is a real benefit.

DR. CARABELLO: Right, but within some brackets of dose what is high for one patient may be low for another, and vice versa. If you say you have to push everybody to a given number of milligrams you will have some people falling over from hypotension. Obviously, 1.25 mg of enalapril is probably not an effective dose. That is why I think that you can't get away from titration on a case-by-case basis. I don't think that you could ever come up with a recommended number of milligrams.

DR. TEERLINK: That being said, the ATLAS trial, which is the one that really compared the low dose to actually a pretty high dose, was a 3000-plus patient trial and it ended up getting patients at the end of dose titration to 33.2 mg of lisinopril. So, they were able to get 1500-plus patients on a mean dose of 33.2. I think they have shown that you can actually titrate it up to that point, and the low dose ended up being 4.5 mg. So,

you know, it is a lower dose than we have talked about before.

DR. TEMPLE: But even that didn't show a huge difference.

DR. TEERLINK: Yes, I guess it was an 8 percent decrease in all-cause mortality with a p value of 0.13.

DR. NISSEN: This is a weakness of what is known about an awful lot of drugs. It is a really interesting problem for us because if you look at some of the clinical trials that are done with fixed doses of drugs, and you have some massive clinical trial with, you know, metoprolol in post myocardial infarction and you pick a fixed dose and you give everybody the same dose, and you know that dose works but you don't know that more wouldn't work better or less wouldn't work as well. This is another example where we don't know as much as we would like to know about the dose-response curve. I would argue that Blase is probably right here, that with an enzyme inhibitor--

DR. CARABELLO: Gee, thanks a lot!

DR. NISSEN: It has to happen once!

DR. TEMPLE: We should break for lunch after that!

DR. NISSEN: We should break for lunch, but with an enzyme inhibitor, when you know that the background of activity of that enzyme system varies over an extraordinary range--you know, the amount of activation of the renin-angiotensin system in heart failure has been studied and I am sure there are probably people out there in the audience who know a hundred times more about this than I do but, in fact, the more geared up the system is, usually the sicker the patient is. So, when you have a biological system that is deranged and that can be real deranged or can be only moderately deranged, it is not surprising that the optimal dose of an inhibitor of that system might vary over a fairly broad range.

So, I would like to believe that there are people in whom a 2.5 mg or 5 mg dose of enalapril is all they will tolerate and all that they will need, and that there are other people that you

really want to get to 40 mg or maybe more to get the same kind of benefit. So, if you say, well, we tried to do an individualized and optimal dose and if an effort was made to do that, that seems reasonable and that is not an irrational approach, to the background therapy. Am I making any sense?

DR. TEMPLE: Well, you know, we have quite good data on blood pressure responses--

DR. NISSEN: Yes.

DR. TEMPLE: --you know, in hypertension studies the curves tend to be, over the range you are looking at--you know, we are not going up by orders of magnitude like Ray would have asked, but within the limits of the doses that are used the curves tend to be fairly flat toward the upper part of the dose so you don't really think you are getting much.

I guess the other pitch I would make is there actually are ways of looking at individual dose-response curves. A method developed by Lou Shiner actually can be used that way, and they never are. So, I just want to make my usual pitch.

Proper analysis of titration designs can actually identify people who are much more responsive and much less responsive, and those methods are just never used. You have to give more than one dose to people to do that.

DR. NISSEN: Yes. You know, one of the problems that exists in a program like this is you have this global trial going on in a whole bunch of countries and, you know, these very elegant dose titration sorts of effects are very hard to explore in this kind of a large, multi-country, multi-center trial. So, I don't think you are going to see a lot of examples where people are going to do this in real life. It is just hard to pull off; hard to pull off in a big study, for sure. Other comments?

[No response.]

Were the choices of ACE inhibitor in CHARM-Added reasonable? Anybody?

[A chorus of yeses.]

Is there anybody who disagrees with that? No disagreement.

Were the target regimens in CHARM-Added reasonable? I am not sure what the difference is here.

DR. D'AGOSTINO: The answer is yes though.

[Laughter.]

DR. TEMPLE: Well, one is about which drugs, the other is about the regimens.

DR. NISSEN: I see. Okay. So, one is about the regimens. Were they reasonable?

[A chorus of yeses.]

Anybody think they weren't?

[No response.]

What features of the CHARM-Added ensured ACE inhibitor optimization? That speaks to Norman's challenge earlier.

DR. TEERLINK: I think this is kind of like shipping packages with FedEx or something like that where it is insured but not necessarily guarantied.

[Laughter.]

So, I think they did very reasonable techniques to try to ensure that they were in terms

of giving specific guidance in the protocol and having the investigators--

DR. STOCKBRIDGE: What specific guidance are you talking about?

DR. TEERLINK: The specific guidance in terms of the slide, whatever it is, saying these patients have to be on these things, and I didn't get to finish--

DR. STOCKBRIDGE: That sentence says you should try really hard.

DR. TEERLINK: Yes.

DR. STOCKBRIDGE: That is it.

DR. TEERLINK: And that is the same thing--

DR. STOCKBRIDGE: There are no procedures--

DR. TEERLINK: Well, if you would have let me finish--

[Laughter.]

--in addition, the investigator had to put their nickel down and say yes, I really tried. So, there you are going to be impugning the virtue of

the investigator, saying they are lying if they don't do that, which is possible. Then, in addition, the thing that adds additional kind of comfort to me is that, in fact, post hoc it turned out that they actually did get what we believe to be reasonable doses.

DR. NISSEN: That wasn't the question.

DR. TEERLINK: Then, the other thing that I had added earlier in terms of having a clinical response form saying, you know, this is why we couldn't get any higher would also have been reasonable.

DR. NISSEN: You know, I think that we have all said we thought they got adequate doses, but they got there in spite of the fact that they didn't necessarily build it into the protocol in the way you are suggesting. So, I would opine that additional assurances could have been provided.

Let me talk about reality here. Who do you think checks off the box? The research nurse or the investigator? Somebody there says, you know, we did our best. In fact, to be able to have

a document and have data that says why didn't you go higher on the ACE inhibitor, because, (a), the patient's blood pressure was too low or, (b), they were coughing or, (c), whatever the reason might be, would have amplified our ability to be comfortable here and would have enhanced the submission.

So, part of what we always do here, we try to tell people who are out there, who are maybe planning follow-on trials what can you learn from CHARM that somebody else might be able to do just a little bit better. I think, Norman, there are some things that could have been done. Not everything that could have been done was done. Now, gratefully, for the study, you know, they got to very reasonable doses but not every possible thing. I personally would have liked the forced titration design. I would have liked a design that really was a forced titration design on the background ACE inhibitor. That would have been incredibly compelling, if that had been done and that could have been done. It wasn't the design that was

chosen and we have to live with what they did but more could have been done. Anybody else?

[No response.]

3.5, was optimized usage of ACE inhibitors realized? How do you know?

DR. SACKNER-BERNSTEIN: I don't think there is a way to know because we don't have the kind of information gathered that we would like to and so we are forced to go back to the data that we do have about the doses that were employed and how those doses compared to other trials which, fortunately for the sake of the applicant, really fell within the range that I think we all believe are appropriate doses, or adequately optimized or whatever, but we don't actually know that.

DR. TEMPLE: Norman is going to become famous for that phrase.

DR. NISSEN: Adequately optimized, yes. We call this FDA double-talk!

DR. D'AGOSTINO: I think the response to 4, 5 and 6--we are very uncomfortable with it, but they did start off and had in the protocol that

they were going to attempt to sort of have the optimal--adequate optimal dose and we don't really have any verification of it.

DR. NISSEN: Yes. I mean, what we have is what we have and we know what the mean doses were. We don't have a lot of individualized data on what happened. For example, you know, how often was the ACE inhibitor down-titrated temporarily or permanently? You know, when you look at exposure data and you have some snapshots in time it doesn't always tell you actually what was going on in the meantime. There may have been some people who, for example, temporarily had lower doses of ACE inhibitors in order to tolerate the candesartan and then later they got up-titrated again. I mean, that is always possible. And, that degree of transparency in a trial, a big trial, is really hard to achieve. The more you can achieve it, the more you can actually look at the area under the curve, if you will, for exposure the more robust information you have.

The reason it is not so germane here is

that we just don't have a huge amount of information that suggests that the endpoint is that sensitive to it. You know, a few milligrams more or less of the ACE inhibitor, is it really likely to make a big difference? The clinical data suggests that it is probably not. But if this were a lipid-lowering trial, if you were going to use an add-on therapy and as you added on therapy you were down-titrating or up-titrating the background therapy, there might be a lot of discomfort. You know, we have a lot of information that suggests that it really does matter a lot exactly how much LDL reduction you get. Here we don't have that background information.

DR. SACKNER-BERNSTEIN: I think we actually do have a pretty good sense of what happened to ACE inhibitor therapy and the background over time. The sponsor's document on page 96 gives us a very nice snapshot. I think that we discussed that. There are issues in trying to figure out how to interpret that as a post randomization phenomenon. Intuitively, as I look

at the numbers it looks like they are a little bit different but it doesn't seem like there is a whole heck of a lot of difference. I don't think there is a statistical test you can use. But I think you do see that there is some difference and they do provide that data at each visit for the percent of patients at the recommended doses, the maximal doses, the means normalized to the maximum doses. They really do a very nice job of presenting all this data. So, it is there. I think it is pretty transparent.

DR. PORTMAN: In summary, it was inadequately optimized because the methods were inadequate to get there but they actually did get there.

DR. NISSEN: What is really interesting to ask ourselves theoretically is how would we feel about this application if between the start of the trial and the end of the trial the ACE inhibitor dose fell by 30 percent, or if you went from an average of 17 mg of enalapril to 12 mg of enalapril? What would we think if that had

happened? And the answer is there would be some trouble here today if that had happened. So, the fact that we have enough information to be comfortable is good, and it is germane, very germane to this question that we are asking.

DR. TEMPLE: Some of the subanalyses though of people who were on high doses would also contribute.

DR. SACKNER-BERNSTEIN: So, another point here that could be used for future trials is that a protocol like this where there is overlap in mechanism perhaps should spell out very explicitly the first three things you do when you have an increase in creatinine, cut back the study medication in half, then cut it back to a quarter, then cut it back and then worry about the background therapy. Maybe things like that, perhaps not that extreme, should be considered as part of future protocols to make sure there is not too much dropout. But here it doesn't seem like it makes much of a difference.

DR. NISSEN: You know, when I was

answering 3.7.1, is this a potential problem, the answer is absolutely yes I think. Was it an actual problem? The answer is no. Any more discussion on number 3? Have you, guys, got what you need there?

A second possible claim would be that candesartan has effects one could not achieve with ACE inhibitors, regardless of dose. What evidence does CHARM-Added provide that candesartan has benefits in patients with full ACE inhibition?

4.1, in analyses of CHARM-Added that factored into ACE inhibitor dose, does it matter that subjects were not randomized to ACE inhibitor dose? I am not sure I completely understand what you are asking.

DR. TEMPLE: Well, what dose you were on is the baseline characteristic.

DR. NISSEN: I see.

DR. TEMPLE: People were randomized to where they got the sartan or not but they weren't randomized to the ACE inhibitor dose.

DR. NISSEN: I see.

DR. TEMPLE: The question is does that

matter. It is not easy to think of how the study would be done if you did want to randomize the ACE inhibitor dose. I guess you could do a full factorial which would be very interesting for next time.

DR. NISSEN: And unethical.

DR. TEMPLE: Why would it be unethical?

DR. NISSEN: Full factorial? You would have to have--

DR. TEMPLE: Combination versus each single.

DR. NISSEN: Oh, but nobody would get placebo?

DR. TEMPLE: No, that would be unethical.

DR. NISSEN: You said full factorial. I interpret that one way, Bob.

DR. TEMPLE: You don't always have to have a placebo.

DR. NISSEN: It actually would be a very interesting design.

DR. HIATT: The problem with an ACE inhibitor, as we talked a lot about earlier, is

that I am not sure the same milligrams means the same thing in every patient. So, I would have a hard time knowing what to do with that because I think it is the clinical pharmacodynamic effect in that patient that matters, so you would sort of have to randomize then to hypotension or just before hypotension, hyperkalemia or not.

DR. TEMPLE: Or a dose and then you pull back.

DR. NISSEN: The approach that I was suggesting earlier to me makes a whole lot more sense, which is to pick an agent that we know works and do a forced titration with certain parameters to guide, you know, when you stop, and then add. That is I think fine in terms of design.

DR. TEMPLE: It still doesn't tell you whether the ACE inhibitor helps.

DR. NISSEN: Do you have any doubts about that?

DR. TEMPLE: Sure. If you put someone on an A2B, do they still need the ACE inhibitor? How would one know that?

DR. NISSEN: I see.

DR. TEMPLE: You don't know that for any therapy you add to.

DR. NISSEN: I see.

DR. TEMPLE: We are stuck with it. I don't know of anything to do if they are not toxic. If they were toxic you would test their elimination but you are just not going to know that.

DR. NISSEN: Fair enough. Any other discussion of 4.1?

[No response.]

Compared with full ACE inhibition, what loss of effect with candesartan has been excluded by these analyses?

DR. STOCKBRIDGE: What you saw was a series of comparisons of the effect of candesartan depending on sort of how close to target you were by various measures. The question is those things didn't appear to be alarming and, in fact, they don't appear to have any consistent relationship in terms of sort of the background ACE level. But there are wide confidence limits around all of

those things and so the question was how reassuring was that?

DR. NISSEN: Comments?

DR. TEERLINK: I think to directly answer the question that is here, since 4.1, for me, is that yes, it does matter that they weren't randomized and weren't pushed to full dose, then the question in number 4.2 which is saying, you know, how can we interpret it, I don't know because we don't have the data to actually look at the effect of candesartan on top of full dose ACE inhibitor. I think we have data to look at perhaps an inadequately optimized dose of ACE inhibitor.

DR. D'AGOSTINO: When you look at the subgroup analysis, and there is a big danger in doing so, I think sort of the legitimate subgroup analysis that you want to do is recommended dose, yes and no. They did that analysis and when it is yes you actually see a better effect for candesartan. This is on Table 59. When you look at the maximum dose with the two different analyses, again, when they are yes you see a better

effect. Now, I don't know how much we should make of it but, certainly, it doesn't destroy the effect. If it went the other way and sort of lost the effect it would be very disturbing.

DR. TEERLINK: The only challenge with that is that the patients in the lower dose, you don't know what would have happened to them had--

DR. D'AGOSTINO: Absolutely, yes. I agree 100 percent. It is very uncomfortable. My stomach is jumping, talking about these analyses given that they are so after the fact, and what-have-you but they aren't disturbing in terms of their results and I think it is, you know, sort of a very sensible analysis to look at.

DR. NISSEN: As reassuring as it is, you know, you asked the question what loss of effect has been excluded and the answer is we don't know. I mean, we really can't answer that. We can tell you that we are not worried about it; that all of us saw exactly the same thing Ralph saw. Again, you know, we might ask ourselves what kind of votes we would be taking today if those patients who had

gotten the highest doses of ACE inhibitors had no benefit. If that had happened, if that had been the result of CHARM, then you and I and all of us would be having a really big battle here around this table.

DR. TEMPLE: You wouldn't have seen it.

[Laughter.]

DR. NISSEN: You would have flushed it before we ever got to it. Let me tell you why that is a really important issue. If you are out there and you are going to design another trial, maybe you don't make yourself vulnerable and maybe you would do the forced titration so you can absolutely assure the agency and the committee that you got to the maximum tolerated dose before you added the other therapy and you protect yourself. If we think there is no effect, then the way to guaranty trouble is not to make this analysis, you know, that subgroup which could have really caused a lot of trouble if there was a lower effect size or no effect size.

Do the results of CHARM-Added support a

claim that candesartan has clinical benefits unachievable with ACE inhibitors?

You asked this question ten different ways to us, which is good.

DR. TEMPLE: But this is the real one.

DR. NISSEN: And we are going to have to vote on this one, by the way. This is a voting question. So, discussion first.

DR. SACKNER-BERNSTEIN: I will start out by looking at the word unachievable. I would put forth that that is quite a selection. Unachieved might be something that is more relevant to the way clinical guidelines are written and clinical practice evolves and clinical trials are performed. If you are asking unachievable by saying is it possible in any scenario ever that we could add more ACE inhibitor to get this effect, well, yes, it is possible but we have no data to say that that is a clinical likelihood.

DR. TEMPLE: But if somebody asks you that question about can you get effects with an ACE inhibitor that you couldn't get with a diuretic

alone, you would have no problem answering that question. There are dozens of studies that have shown that a diuretic takes you up to a certain point and then you need a different modality. Probably a lot of people would find the same argument convincing on beta-blockers where people were on pretty good doses. So, we are just asking the question here. It is the same question we have been asking over and over again. If these people have pretty much had it with ACE inhibitors, have you now added something to it?

DR. STOCKBRIDGE: But the unachieved question is number 5. We are not there yet. This is the unachievable.

DR. SACKNER-BERNSTEIN: So, can we say it is unachievable based on a population? Because anybody who sees patients knows there are occasionally patient responders.

DR. TEMPLE: I must say, I think it is the same question. If you think people were on pretty much optimal--you know, details to be discussed--pretty much optimal ACE inhibition, then

you would say, well, this added something so ACE inhibitors didn't achieve that. As Norm says, there is another one. Maybe for practical reasons they couldn't get to the optimal ACE inhibitor. That is a different argument but what everybody has said repeatedly is they think they got pretty close to the optimal. So, if you believe that, if you do--

DR. TEERLINK: Given my previous answers to 4.1 and 4.2 when I said I don't know in terms of what the effects are on full dose ACE inhibitor because that wasn't tested in this study, and given that I my sense is that you are asking should we have a claim that candesartan adds something to full dose ACE inhibition on the basis of this study, I would have to say no, the results don't support it because it wasn't a hypothesis that was tested by this trial design or any other trial design, for that matter.

DR. TEMPLE: And the subanalyses in which they looked at people who pretty much were on high doses--

DR. TEERLINK: Those help in addressing question 5 but, given that I don't know what happened to the patients who were on low dose, whom they didn't force to go up to higher dose--maybe those patients on low dose when they got into high dose would have diluted any beneficial effect of the candesartan. Since they didn't force titrate the low dose people up they are now removed from that group of high dose ACE inhibitors. If they had been moved up to a high dose group and treated and now were included in the high dose group, perhaps candesartan would have had no beneficial effect in that overall group of full titration patients. I think it probably would have--

DR. TEMPLE: But no drug has to work in everybody.

DR. TEERLINK: I know, but they weren't forced to go up to high.

DR. HIATT: I agree with you, John. There is a margin of uncertainty here with this question. I think the population achieved adequate doses; the individuals may not have and I think that is what

we are wrestling with a little bit so I think there remains some uncertainty here about individual cases. Truly, they could have achieved all the benefit from just pushing their ACE dose and for some reason they hadn't. But the question in my mind is really whether that is really an individual patient kind of question or if it is a population question. Population-wise, they got close enough.

DR. NISSEN: Yes, I am willing to be a little more generous here than I guess some of my colleagues are. You know, as you point out you never know about an individual patient. That is just too difficult to know because the optimal dose of an ACE inhibitor for Bob Temple might be 80 mg of lisinopril, for all I know. That is something one can never know. So, I think that if you weigh all of the evidence here, particularly when you look at the subgroup that did get high doses, and you see, if anything, the result is a little more robust, you know, my comfort level that these results could not have been achieved by up-titrating the ACE inhibitor is very high.

Now, you know, it is all a matter of your comfort level. Is it 100 percent certainty? Would I bet my life that another trial couldn't show this? No, but I think it is very, very probable that these are unachievable by increasing ACE inhibitor.

DR. SACKNER-BERNSTEIN: You said that you were persuaded by the point estimate of the effect at the best treated--

DR. NISSEN: Influenced by, yes.

DR. TEMPLE: Well, then it doesn't go away.

DR. NISSEN: Yes.

DR. SACKNER-BERNSTEIN: So, that sort of gets back to the 4.2 question of how convincing was that really. It has now taken more import in your interpretation than just being fairly reassuring. You are banking quite a bit on that point estimate.

DR. NISSEN: Yes, I guess there is more involved here than this. I mean, I guess I am also recognizing that we know a fair amount about the dose-response curve to ACE inhibitors. I think

that Bob has pointed out, and others have pointed out, that it does tend to flatten out at the higher doses. You know, we have a body of evidence here that suggests that you are unlikely to get a lot more bang by increasing the ACE inhibitor dose. The hypotension stuff seems to show it. There is not really any secure evidence from the heart failure literature. You have the data from this trial that at high doses of ACE inhibitors there was still a benefit when you added candesartan. So, I am trying to weigh the body of evidence here that suggests that there is much of a chance that pushing up the ACE inhibitor would have achieved the same results, and I just don't think there is.

DR. TEERLINK: To try to clarify this issue, if you had a choice between saying that you would recommend this for approval as additional therapy on top of full dose ACE inhibitor, that it has been shown to have benefit on top of full dose ACE inhibition versus approvable on the basis of having beneficial effects on top of optimized ACE inhibition, which of those would you pick? Isn't

that the question you are getting at?

DR. NISSEN: Yes, and I think we all agree that what was used here was optimized or adequately optimized.

DR. CARABELLO: But what is full dose? If the guy can't stand up or his creatinine is 7, that is not full dose for him.

DR. TEERLINK: But that wasn't ever tested in this trial. The hypothesis of whether candesartan can add beneficial effect to full dose force-titrated ACE inhibitor was not tested in this. If you are asking my belief system, I have certain beliefs but in terms of what actually has been proven and what should go into labeling and those kind of things from a regulatory standpoint, I would have to say I don't know based on this data.

DR. TEMPLE: And you don't find the subset analyses convincing on that point?

DR. TEERLINK: No, because as actually in every point of the subset analyses Dr. U mentioned, he says, you know, of all the caveats of subset

analyses the number one is that these were not randomized, not force-titrated doses. So, we just don't know.

DR. TEMPLE: But some of them were at the largest approved doses of those drugs.

DR. TEERLINK: Some of them were, but we are splitting up populations so this is a self-selected population of those who could tolerate. Maybe the people who could tolerate high doses of ACE inhibitors really have no effect from ACE inhibitors because they are getting more ACE escape. Therefore, they would get better benefit for the A2. So, I think there are too many confounders and I can come up with all sorts of interesting scenarios for how you could explain a balanced effect in the groups but that is pure conjecture based on some interesting hypotheses. So, on the basis of this data--and just so nobody over there is concerned, obviously number 5 will look much better from my standpoint but, for number 4, I have a hard time saying that it really adds to full dose ACE inhibitor therapy because we don't

know.

DR. D'AGOSTINO: I was going to support that. I think the way we looked at the high dose previously, because it showed an effect and seemed to be consistent we were very comforted by that, but do we then take the other flip that, therefore, we don't worry about the randomization and all these other matters that should go into a randomized clinical trial? I think that is a big jump.

DR. NISSEN: Let's vote on this. Let's this time start with Ralph.

DR. D'AGOSTINO: No.

DR. SACKNER-BERNSTEIN: No.

DR. KASKEL: No.

DR. NISSEN: You, guys, have convinced me. No.

DR. TEERLINK: No.

DR. PORTMAN: No.

DR. PICKERING: No.

DR. HIATT: No.

DR. CUNNINGHAM: No.

DR. CARABELLO: No.

DR. NISSEN: It is unanimous. If CHARM-Added supports use of candesartan by virtue of effects unachievable with an ACE inhibitor, skip to question 7. We are not there yet.

A third possible claim might result if one could not achieve a full effect on a system by one drug, perhaps because of system-independent tolerance problems, but one could achieve a larger effect with the addition of a second agent, does one need to establish that the original, poorly tolerated therapy is still needed in such a trial? A really interesting question. This speaks to what Bob really wants to see somebody do. Reminds me of your Cox ALLHAT study.

DR. TEMPLE: I don't know, people are lining up.

DR. NISSEN: You know, it really cannot be answered. I mean, I just don't think we have sufficient data, and it would be wonderful to know that. I mean, what you are really suggesting by this question is that in those people that either

didn't tolerate very well the ACE inhibitors and, therefore, maybe were suboptimally treated, you could have put them on candesartan and taken away the ACE inhibitor and gotten the same event reduction. I guess the only way you find that out is by doing your non-full factorial design where some people get started with one and get the other added. So, you would start with ARB and add ACE in some people. Is that what you are looking for?

DR. TEMPLE: I am not sure, but I do want to point out one nuance here. If you are talking about blood pressure lowering, you could assess whether a person was getting full desired effect or not. In this case we are talking about something different. You have no idea whether they are getting the full effect. So, it may or may not be the full dose of an ACE inhibitor but it is sort of the best dose you can manage. That is what this question is about.

DR. TEERLINK: So, in that perspective, I think CHARM-Added really does address this hypothesis. The hypothesis was, okay, we told the

investigators to push as best they could. They did their best. They checked the box and said they did, or the study coordinator did. And, in that context then, candesartan did demonstrate beneficial effects on top of that. So, if that is the question that you are asking, then it seems reasonable.

DR. SACKNER-BERNSTEIN: The only thing about this question, since it is starting out as a hypothetical and then moving into this particular application, is that we just need to be clear. I mean, I don't think the background therapy is one that should be labeled or considered poorly tolerated in this particular case. ACE inhibitors are not poorly tolerated therapies.

DR. CARABELLO: Not only are they not poorly tolerated, but they are the foundation of the therapy for heart failure.

DR. NISSEN: But there is a study design that would be possible here. I am not saying that it should be done and I am not even sure that IRBs would agree to do it, but what could happen is you

could take people, you know, optimize them on an ACE inhibitor and then you could add in candesartan, and if you got to the full dose of candesartan then you could randomize them to have the ACE inhibitor withdrawn, and you could then compare outcomes in a group. In other words, you are really asking the question a different way.

DR. TEMPLE: You could take the study as it was planned and as it was done and after six months randomly take the ACE inhibitor away.

DR. NISSEN: Yes.

DR. CARABELLO: You could do it now because candesartan was just approved for the therapy of heart failure but three days ago you couldn't have done that.

DR. TEMPLE: Well, I think it would be a very had study to do now. You are taking a drug that isn't very toxic and taking it away to see if people are going to die, and I think very few IRBs--

DR. NISSEN: That is why I said I don't think any IRBs--

DR. TEMPLE: --it is not like stopping tamoxifen after five years because tamoxifen has toxicity.

DR. NISSEN: Yes, I think we are not going to know the answer to that.

What would be required to obtain such a claim? I think we have sort of discussed that.

Does CHARM-Added have these design features? Does anybody think that they do? No? Okay.

This is now a voting question, 5.4, did the results of CHARM-Added support a claim that candesartan should be used in patients unable to take a full dose of ACE inhibitor?

DR. HIATT: We just don't know that. We don't know that so how can we vote on that?

DR. NISSEN: Well, if you don't know the answer, then the answer is no, the study does not support such a claim. I think the spirit of this is that this would be something that one could discern if you did a forced titration study and you took those people in whom you were simply unable to

up-titrate to a full dose of ACE inhibitor and you asked the question in advance, prespecified, whether those people got additional benefits. That would be the design that would answer that question and that was not the design that was used here.

DR. CARABELLO: Yes, but the physicians involved in taking care of these patients pushed the ACE inhibitor to the maximum dose that they thought they could. They have said that.

DR. NISSEN: Yes, Blase, I think it is different though from a forced titration study. I mean, I think there is a design element here that the FDA's question is really asking us to comment on, and that is, this was not a forced titration study.

DR. STOCKBRIDGE: Well, this is your invitation to say I think people got the highest dose they could reasonably be expected to get to on their ACE inhibitor, and the drug clearly has an effect in that setting.

DR. TEMPLE: And in many cases that dose was the highest labeled dose.

DR. STOCKBRIDGE: Right, it was sometimes that.

DR. TEMPLE: But those are not people unable to take a full dose of ACE inhibitor.

DR. NISSEN: That is right.

DR. STOCKBRIDGE. Right, fine. That is true.

DR. NISSEN: I am reading this question very literally, which is do we know that those people who simply couldn't tolerate a full dose of ACE inhibitor--

DR. STOCKBRIDGE: No, that is not really the intent here. This really is poorly worded in that respect.

DR. NISSEN: I mean, we have all said we think they got to very reasonable clinically important, generally accepted doses. We have all said that many times here. So, that answer is obviously somewhat different.

DR. HIATT: I also think that this whole dose question makes me wonder if the forced titration experiment, which we are not going to

see, versus the data we are seeing now--the margin of uncertainty here, I mean quantitatively, has got to be small, not large. So, it would be, you know, a 100,000-patient trial to really prove that there was some meaningful clinical difference between forced titrated, can't take anymore, and then we add candesartan versus what we are getting today. I mean, that margin of uncertainty I just don't think is big enough to matter.

DR. NISSEN: And what you are doing in answering that question is you are integrating everything we know about the dose-response curve of a patient's ACE inhibitor and how well tolerated--

DR. HIATT: With the flat dose-response curve individuals don't exactly give you the information you need.

DR. NISSEN: So, you are integrating everything we know and saying, you know, I just don't think that we would learn very much by doing a forced titration because I don't think you are going to get very much more out of it, and I think that may be the spirit of what you are asking.

DR. TEMPLE: The real question is--I mean, from what I hear everybody saying they all think that the study showed something.

DR. NISSEN: Yes.

DR. TEMPLE: Though there is a general feeing that people got a pretty reasonable dose, even if it wasn't the optimal dose in every case. So, the question sort of is if you think all that how would you describe the population the stuff should be used in? Who are they? The question here is unable to take full dose of ACE inhibitor. I don't think that is right so there must be something else that can characterize this population.

DR. NISSEN: I think that would be a real important discussion to have because it does speak to what the label ought to look like. So, how would the committee advise the agency to describe the population in which this therapy would be beneficial?

DR. SACKNER-BERNSTEIN: Not to pick on the diction before but I think it basically falls into

this idea of adequately optimized background therapy with ACE inhibitors in patients with low ejection fraction.

DR. TEMPLE: So would it be recommended for addition in people on adequately optimized therapy?

[Laughter.]

We will find another word--on an appropriate, or whatever, dose of ACE inhibitor. That is who it would be for?

DR. NISSEN: Yes.

DR. SACKNER-BERNSTEIN: You could say maximally tolerated.

DR. NISSEN: But that is not what was studied.

DR. TEMPLE: We will obviously have to think about it but you could use words like recommended dose of an ACE inhibitor.

DR. HIATT: Yes, heart failure doses.

DR. NISSEN: I like the idea of saying on recommended or usual or typical--

DR. TEMPLE: Usual is often well below

what is recommended.

DR. NISSEN: All right, let's say of effective doses.

DR. TEMPLE: Okay, we will think about that.

DR. NISSEN: Words like that, to me, imply that the agent has been proven to work on top of what are considered clinically meaningful therapeutic doses of the agent that they are being added onto.

DR. HIATT: I don't know if you want to go this far but you could actually use the doses they achieved here and actually put in that mean or some range around what you all think really is a heart failure dose for each of these drugs.

DR. NISSEN: The problem is there are so many ACE inhibitors.

DR. TEERLINK: And I wouldn't necessarily say what dose they were on, but I would include--you know, basically you live and die by the protocol you write and you get the label for what you did. So, what they did was they suggested

that physicians optimize the dose of ACE inhibitor according to a table that is shown here, with the blurb that was shown. I would be tempted to put in that table and say these were the doses of ACE inhibitors that were the target doses, and in patients who achieved those target doses candesartan showed blah, blah, blah.

DR. TEMPLE: And the description could even say what fraction of patients achieved those doses.

DR. NISSEN: I guess what we are really saying, and we said this several times, is that we think that they achieved the doses that are used in the treatment of heart failure, commonly used, known to be effective doses. I mean, there are lots of ways to say it. But we do not think that they used inadequate doses; we think they used adequate doses. I think the spirit of that should come through.

DR. KASKEL: We currently have an NIH trial for treatment of focal segmental glomerulosclerosis in patients up to 35 years of

age, and there is a template in that trial that just began in January with a chart showing how to titrate these patients that are randomized, with enalapril over a course of six weeks, getting their blood pressure under control, checking for hyperkalemia. If they can't tolerate the drug, they can then take losartan. So, there is a template that is going on in a 500-patient trial now that was well thought out over the course of about two years. So, that can be used as recommendations for this.

DR. NISSEN: Blase?

DR. CARABELLO: So we don't vitiate the entire proceedings here, haven't we delayed this till one o'clock for the opportunity for the public to speak?

DR. NISSEN: Oh, my goodness, thank you. Yes.

DR. CARABELLO: We don't want to vote on question 8 and then find out that there is difficulty--

DR. NISSEN: Yes, I have been very remiss

here. If there is anyone that would like to speak at the open public hearing, now is the time. Oh, I have to read the statement. Of course. I don't want to miss that.

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[No response.]

DR. NISSEN: Great. You wanted to vote on 5.4 so we really are going to vote, but you really changed the question. Would you rephrase it for the committee?

DR. STOCKBRIDGE: The real problem is the full dose part of that. That seems to be where people have a problem. And, 5.4 really was intended to establish whether or not people thought whether it supported a claim. You may be ready to vote on whether or not it alone is adequate to support a claim, which is 8.

DR. NISSEN: I think we can go on. You have heard a lot of discussion about this.

DR. TEMPLE: Well, we will listen and figure out what you think who it is for.

DR. NISSEN: So, we are not going to vote.

Is there another possible claim resulting from CHARM-Added? Anybody want to offer up any other claims?

DR. TEERLINK: There is one issue that is of concern to me. It is actually not so much what other claim results from it but I want to ensure against a certain claim being made, and that is, having heard that candesartan was approved for heart failure, I actually am concerned--and I know the FDA mandate is not to tell physicians what to use, when and to look mostly to efficacy and safety--but I would want to urge caution in writing a label that suggests that candesartan should be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors. I don't know if that is even germane to this, but this seemed to be the forum to at least bring that up.

DR. NISSEN: Is that label already written?

DR. TEMPLE: Well, we are not telling anybody to take somebody off something they are doing well on. But CHARM-Alternative has been

taken as making the case that if you are going to pick a drug you could pick candesartan as well as one of the ACE inhibitors. We didn't do that for valsartan because it was based on a 300-patient subanalysis and we didn't feel that was quite the level of data that was needed. So, it is labeled only for people who can't tolerate an ACE inhibitor. But we have several thousand patients studied; it is about as good as the other studies, so we didn't make that distinction.

DR. TEERLINK: The only distinction that I am concerned about here is that you are leaving the door open for potential marketing and other forces to have people withdrawn from ACE inhibitors and switched to ARBs. That, to me, on the basis of problematic trials but even the RESOLVe trial and OPTIMAL have troubles with them. I admit those. But certainly there is no evidence to say that they are better than, and there is some trend towards saying they may be worse in terms of survival. If this were a blood pressure thing purely--I mean, this is not just a symptom endpoint. You are

potentially withdrawing people from a life-saving therapy, a therapy that has been demonstrated to save lives in multiple tens of thousands patient trials, and substituting on the basis of one trial an agent that we think does have benefit, but I am not sure that it preserves all of the survival advantage of an ACE inhibitor. And, I am just a bit concerned by the proposed labeling that I have seen. It seems to leave that door open, and once a door like that is opened it is going to be their job to walk through it and encourage people.

DR. TEMPLE: Do you have suggested language?

DR. TEERLINK: I would continue it to be in intolerant patients.

DR. NISSEN: The difficulty, of course, is the distinction between practice guidelines and regulatory--

DR. TEERLINK: And I understand that.

DR. NISSEN: I think there will be a need for the practice guidelines that we write for the management of heart failure to address the issue of

is candesartan a first-line alternative to starting an ACE inhibitor? I mean, that is a very interesting practice question.

DR. TEMPLE: There is now a trial more or less equivalent to the individual trials of ACE inhibitors, many of which are supported by just a single trial in heart failure.

DR. TEERLINK: And if we didn't have ELETE-II and if we didn't have OPTIMAl and if we didn't have RESOLVe, then I might feel more sanguine about that. But these other trials do show, if anything, a turn in the wrong direction in terms of mortality. I guess there are things that the FDA can do and these are things that, okay, if we are going to say that we don't want to have the sponsor walk through that door, then through educational activities and postmarketing requirements of the sponsor and certain prohibitions in terms of marketing in certain manners, are in the purview of the FDA, or you can tell them to do a trial, a head-to-head comparison and show that it is better.

DR. SACKNER-BERNSTEIN: Even before a trial, I think a point that you made about there being a slight trend, an apparent signal that an ARB, or at least the ones tested, compared to some ACEs are probably not quite as good are of a magnitude that is going to be difficult to detect comparing the result in the CHARM-Alternative trial to the historical ACE inhibitor trials, and the CHARM-Alternative trial was an alternative in patients who were intolerant, or at least should be thought of as CHARM-intolerant, that should be the name of it not CHARM-Alternative because it wasn't an alternative; it was an intolerant.

DR. TEMPLE: No, I know. We thought being intolerant to an ACE inhibitor doesn't predict how you are going to respond to another drug. It does mean you need another drug but we concluded that it represents essentially a regular population, indistinguishable from any other population and now in a trial of substantial size, that was about as big as trials of individual ACE inhibitors at least.

DR. TEERLINK: As long as you are comfortable potentially recommending to the physicians to substitute a drug that hasn't been shown to preserve all the survival advantage of an ACE inhibitor--

DR. TEMPLE: And vice versa.

DR. TEERLINK: --then that sounds right, and vice versa.

DR. NISSEN: See, the problem, John, we don't know.

DR. TEERLINK: And the group that was studied in the CHARM-Alternative study is a select subset. If you open up that subset by the labeling, saying anybody with or without an ACE inhibitor--

DR. TEMPLE: Right, we did not think it was a subset. I mean, the fact that you have an adverse effect on a particular drug doesn't usually say anything to whether the drug is going to work in you. Why would it? There are people who coughed or who had angioedema. That doesn't really go--or at least we didn't think it did--to whether

the drug works or not. So, we thought the conclusion that it works is more generalizable.

DR. NISSEN: The other thing about this just to be very, very careful about is that if you want to look at this with historical vision, a lot of the ACE inhibitor trials are before beta-blockers. So, it is a completely different experiment.

DR. TEMPLE: Right, and everybody was on a lipid-lowering drug.

DR. NISSEN: Exactly. So, the experiment is completely different and if you look at this from a regulatory point of view, you had to answer the question did they make the case that candesartan reduced morbidity and mortality in heart failure in people not on an ACE inhibitor? And, you concluded that it did, and that you didn't need our advice to conclude that. Would I hope that somebody would do a candesartan versus full dose of ACE inhibitor comparative trial, that would now be justified. Such a trial would be very, very easily justified and would be potentially useful.

It would be, however, very large.

DR. TEMPLE: So, you don't think most people are going to read these results by saying you should probably be on both?

DR. NISSEN: Yes, they will, and if you can't take an ACE candesartan is a great alternative.

DR. TEERLINK: But I think direct to marketing, which is going to be allowed, to the consumer is going to say candesartan is a great drug for you for heart failure. Ask your doctor why aren't you on candesartan.

DR. TEMPLE: No doubt. No, I think we contemplated that that would happen. As far as we were concerned, the data looked similar. Obviously the data for each ACE inhibitor isn't exactly the same either.

DR. NISSEN: Yes. You really have difficulty in this situation when your trials of the other class of agents are completely different era. It is very, very hard to know. And that is where I think people writing guidelines for heart

failure will have to really chew on this pretty hard.

DR. TEMPLE: We also don't know how the beta-blockers compare and there are concerns that they might not be comparable. I mean, it is very hard to know when drugs work and the differences are small. You have to tease those out. That is what ALLHAT sort of tells you. It is very hard to sort out differences.

DR. NISSEN: Yes. Obviously, your concerns are on the record.

DR. TEMPLE: That is helpful.

DR. NISSEN: Can we go to 7?

DR. STOCKBRIDGE: For question 7 you have to think about whether you want to ask it at all. It walks through the strength of evidence, you know, components, if you believe you already know what you want to do with 8.

DR. NISSEN: I think we probably do. I did want to make a couple of comments here that I do think are relevant. This has come up several times on the committee. That is, you know, do we

place any weight on ValHeFT? The answer is yes. When there is prior evidence of another drug in this class that has some similarities, producing similar benefits, to me, it has an effect on my thinking. It suggests to me that from a mechanistic point of view the hypothesis that a dual inhibition of the renin-angiotensin system might be better than inhibiting only the ACE mechanism.

DR. TEMPLE: Of course, we found ValHeFT unpersuasive on that point.

DR. NISSEN: Yes, but if you remember--

DR. TEMPLE: We could debate that.

DR. NISSEN: If you remember, I happen to be one of the four people that voted in favor, for what it is worth. I didn't win that argument but I thought that they made a good case because I thought that the beta-blocker data was likely spurious and it didn't influence me as much as it influenced other people.

DR. TEMPLE: But even leaving that aside, what we mostly found was that the dose was really

not adequate of the ACE inhibitor, and that there appeared to be improved response the lower the dose got.

DR. NISSEN: Yes.

DR. TEMPLE: Which itself is not so surprising.

DR. NISSEN: Yes. Having said that, if the result of ValHeFT had gone the other way--I am trying to say is that it is relevant and the fact that it went in the right direction, to me, allows--this hypothesis has been tested before. We know something about that, and it tends to lower the bar. Now, it turns out that the CHARM trial did very, very well, but what if the p values had been somewhat more marginal? We did this once before, if you remember, with RENAL and IDNT and we ultimately said, well, we got these two trials with two different ARBs and neither of them was necessarily a slam-dunk but if you take the two of them together it probably means something. I guess I am saying we are not rejecting that as irrelevant; it is relevant and I do think it is

supportive. I don't know if anybody else has any other comments about that.

DR. CARABELLO: No, in those trials we even allowed the fact that ACE inhibitors were helpful in reducing the progression to renal failure. So, we took the totality of the information.

DR. NISSEN: Yes. You know, every time you get more information it adds to a database of what you know and, you know, we know something from ValHeFT and we know more now from CHARM.

DR. TEMPLE: So, we should probably see if we want to have you take another look at ValHeFT.

DR. NISSEN: Maybe.

DR. TEMPLE: I see mixed reactions.

DR. NISSEN: People want more work.

DR. TEMPLE: We will think about it.

DR. NISSEN: All right. Anybody else want to comment on anything that is in 7? Any of this that has any impact?

[No response.]

So, we come to a question that may be of

some importance to the sponsor.

[Laughter.]

Should candesartan be approved for use with an ACE inhibitor in the treatment of heart failure? Discussion and then voting.

DR. CUNNINGHAM: I want to make one comment, and that is, if this gets approved, one of the things that we really don't have is data on African Americans in the percentage in which they are represented in the American population. I know we are only one of many countries but I would like to encourage the sponsor, if they want approval in this country, to think about having representation of major ethnic groups in the same population as exists in the country.

DR. TEMPLE: Could they do it?

DR. CUNNINGHAM: It would be a good goal.

DR. TEMPLE: How would somebody feel about doing, say, the same trial with the results you now have? Would that be okay?

DR. CUNNINGHAM: I wasn't talking about going backwards; I was talking about going

forwards.

DR. TEERLINK: Are you talking about a CHARM?

DR. TEMPLE: Yes, something like that. I mean, it is perfectly true that the participation of blacks was very modest, sort of leaning the right way, but now that you have a survival plus hospitalization effect in the overall population convincing enough--well, we will see, you haven't voted yet but I am just guessing--how would you feel about a placebo-controlled trial in a black population in this setting? I guess I think that would be a very difficult thing to support.

DR. CUNNINGHAM: I am trying to push going forwards. So, I am trying to make a point so that people in the future, when they are thinking about designing their trials, think about having a representative population.

DR. TEMPLE: Oh, I totally agree.

DR. TEERLINK: I think your point is well taken. The challenge is they are going to get--also using foresight--probably approval for this now not

having done that. So, there is no stick here. We continually mention these things; we say they have to have better representation of minorities.

DR. TEMPLE: The other part of the problem, as I just read about in today's paper, is that offshore is in and it is very hard for us to stop when you are talking about large trials. All the trials we have seen recently are multinational and most nationals don't have a large black population. That doesn't mean people couldn't go out of their way to try to find people even in those countries, and they should.

DR. NISSEN: What Susanna is saying is it is a very desirable thing to have information that tells us about how minority populations respond since we know that in this class of drugs there may be differences, so it is very relevant. I thought that in ALLHAT it was very helpful to have that information and, to me, it actually changed my practice to some extent.

DR. STOCKBRIDGE: The only thing I would add to or amend what she suggested is that if you

really cared about that as a fundamental issue you wouldn't target having representation that was consistent with the U.S. population. You would, in fact, try to get more.

DR. PICKERING: Maybe I could comment. To do an NIH study you wouldn't be allowed to do a study like this with under-representation of minorities, and I don't see any reason why the FDA shouldn't make similar type of requirements of studies.

DR. NISSEN: Well, they can't do that.

DR. TEMPLE: Well, it is not clear we can. In a limited way we can. The labeling has to provide adequate directions for us for the people who are going to use it. The difficulty for us is we are seeing large numbers of very desirable international trials and it is a real problem to have them be representative of the U.S. population.

What I can answer for you is whether if people made a major effort in Europe and elsewhere where there are minorities, after all, they could actually succeed in doing that if they really

tried. These are helpful comments.

DR. PORTMAN: Just remember in pediatric studies we have a burden that 40-60 percent of the population have to be African Americans.

DR. TEMPLE: In cooperative studies in the U.S.

DR. PORTMAN: Right.

DR. TEMPLE: Well, NIH clearly has requirements for funding that are--

DR. PORTMAN: That is the FDA's requirement. That is your requirement.

DR. TEMPLE: Oh, for the pediatric exclusivity, yes, there we can be bossy.

DR. PICKERING: But the design of this study, I think we heard, was reviewed with FDA and I don't know whether anything was said about minority representation in the original study design.

DR. TEMPLE: Well, we will look further. We have accepted the inevitability, maybe too quickly, that if you do--I don't know what it was--75, 80 percent of your trial outside the U.S.

you are going to have a population that is not going to be typical of the U.S. Maybe we have been insufficiently attentive to that.

DR. NISSEN: Bob, what would you do if you got a study which was done 100 percent outside of the U.S. for a regulatory claim?

DR. TEMPLE: Which happened. That is not uncommon.

DR. NISSEN: What do you do with it? You just treat it exactly the same way?

DR. TEMPLE: Yes. We inspect various sites. We have to make a decision whether we think it is relevant to our population. So, it depends on whether the condition is one that you think is similarly treated, all of those things. This is all discussed actually in an ICH guideline called E5. If we are nervous enough about it, we might ask for a domestic study. There are certain categories where we might. We are very nervous about depression. We have seen some examples of entirely foreign studies with the impression that they were successful and they utterly failed when

they came to the U.S.--one case, not making more out of it than it deserves. So, it is on everybody's mind but the reality is that a lot of studies are being carried out abroad.

DR. NISSEN: All right.

DR. SACKNER-BERNSTEIN: At the risk of getting into a political aspect of this as opposed to where we are headed, if the discussion is going to go into the direction of trying to get sponsors to do studies where minorities are recruited, as an important part it also needs to be done with genetic analysis at the same time. There is a fair amount of literature that shows that African Americans and African blacks, blacks from various parts of the globe, have a tremendous amount of differences in terms of the ACE gene polymorphisms, with some areas of Africa being more akin to white Norwegians than other parts of Africa. So, to merely create a document or a set of guidelines based on skin color would be an inappropriate application of the science that we have at hand currently.

DR. TEMPLE: This has come up in discussions. We don't know what genetics to look for. If we did, ho-ho! But at the moment we don't. If there were a characteristic that was a good predictor everybody would be beating a path to it, but so far there are relatively few characteristics that are well characterized that way.

DR. KASKEL: There are two clinical trials now that involve taking bloods, urines and other specimens at particular time points and having them stored in the NIH biorepositories because no one in those trials knows what genes to study right now either.

DR. TEMPLE: Well, we know that drug companies keep lots of samples around and there will be things to look for. There is a lot of thinking. We are working with somebody to try to look at serum in people who have torsade to see if you can characterize them. The NIDDK is looking at people who have adverse reactions to hepatotoxins. Why do some people have it and others not? So,

there is tremendous interest in this, as you can imagine, but it would be hard to say we would know what to look for yet.

DR. NISSEN: Yes, the era of pharmacogenomics is not yet fully developed.

DR. TEMPLE: Yes, but there is a lot of interesting stuff.

DR. NISSEN: Interesting stuff, yes. I think this is perhaps a little bit of a tangent so let's come back. I want more discussion on 8, if there is any, and if we are ready to vote, we are ready to vote. So, let's start with Blase.

DR. CARABELLO: I vote yes. I am convinced that the investigators did their best to up-titrate the drugs. The final doses of ACE inhibitor achieved were quite substantial and in line with other trials of ACE inhibitors, and the subset analysis of patients on very, very high dose ACE inhibitors all go in the same direction.

DR. CUNNINGHAM: Yes, I am convinced by the investigators' data.

DR. HIATT: I vote yes too, and I think we

have emphasized the need to provide data on what those doses mean that were achieved so that we don't fall off that target.

DR. PICKERING: Yes.

DR. PORTMAN: Yes.

DR. TEERLINK: Yes, with the definition of the optimal therapy as per protocol, which is given on page 26.

DR. CARABELLO: Excuse me, just to add to my answer, yes, with the obvious caveat we are talking about, patients with low ejection fraction. That is not in the question.

DR. NISSEN: My answer is yes as well. With all the nit-picking aside about optimal strategies, I have to say I think it was a very professionally run trial. You know, you can pick apart any trial and find things you might want to see done differently but I think they executed this trial well and I think the idea of having three trials together that would actually answer questions, separating out the Preserve, the low EF Added and the Alternative was very informative. It

gave us a lot of information in a single trial, much more than we would ever hope for, and it gave the investigators a lot of manuscripts, which they really liked--

[Laughter.]

--but in all seriousness, I do think this was a very well done study, which doesn't mean we can't learn something from it about how to do the next one even a little bit better. But I think the case is convincing and I think this does, in fact, add to the opportunity for patients to benefit with heart failure, and I think it is going to be good for patients and I vote yes.

DR. KASKEL: Yes.

DR. SACKNER-BERNSTEIN: Yes.

DR. D'AGOSTINO: Yes.

DR. NISSEN: If there are no further comments, I think we can declare the meeting closed. Thank you.

[Whereupon, at 1:32 p.m., the meeting concluded.]