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ADVISORY COMMITTEE

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Two Montgomery Village Avenue
Gaithersburg, Maryland

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Cathy Groupe, RN, BSN, Executive Secretary

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Susanna L. Cunningham, Ph.D., Consumer Representative
William R. Hiatt, M.D.
Frederick J. Kaskel, M.D., Ph.D.
Thomas Pickering, M.D., Ph.D.
Ronald Portman, M.D.
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Jonathan Sackner-Bernstein, M.D.
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FDA

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

C O N T E N T S

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 am going to call us to order. We have got a long day's work ahead of us, and so if everybody could take their seats.

Let's begin with some introductions. Perhaps we can go around the table and everybody can introduce themselves and tell us who you represent or what discipline you represent.

DR. McCLESKEY: Charles McCleskey. I am the Industry Representative on this committee, on loan from the Anesthesia Committee for reasons that I am unclear about, but nevertheless, I am actually an anesthesiologist, work for Abbott Laboratories in a therapeutic area different from the one being discussed.

DR. CARABELLO: I am Blase Carabello, cardiologist, from Houston, Texas.

DR. CUNNINGHAM: I am Susanna Cunningham. I am the Consumer Representative on the committee, and I am Professor in the School of Nursing at the University of Washington in Seattle.

DR. HIATT: I am Bill Hiatt, a vascular medicine specialist in the University of Colorado.

DR. PICKERING: Tom Pickering. My specialty is hypertension, and I am at Columbia University Medical School in New York.

DR. PORTMAN: I am Ron Portman, specialist in pediatric nephrology and hypertension from the University of Texas in Houston.

DR. KASKEL: Rick Kaskel, also a pediatric nephrologist and hypertension at Albert Einstein College of Medicine and Montefiore in the Bronx.

DR. KNAPKA: I am Joe Knapka and the Patient Representative. I am retired after 28 years at NIH. I have been retired about 10 years. Thank you.

DR. NISSEN: I am Steve Nissen. I am a cardiologist from the Cleveland Clinic.

LT GROUPE: I am Cathy Groupe, FDA, the Executive Secretary for the committee.

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

DR. TEERLINK: John Teerlink, University of California/San Francisco, and San Francisco VA Medical Center, with a specialty in heart failure and echo.

DR. BLACK: I am Henry Black at Rush in Chicago. I am a hypertension trialist.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

DR. PROSCHAN: I am Mike Proschan. I am a statistician from NIH, from the National Heart, Lung, and Blood Institute.

DR. STOCKBRIDGE: I am Norman Stockbridge. I am the Acting Director of the Division of Cardio-Renal Drug Products at FDA.

DR. TEMPLE: Bob Temple. I am the Director of ODE I.

DR. NISSEN: Let me just make a couple of other introductory comments. We have got a lot of work to do today, so I would like to ask all of our speakers to do their best to stay on time, and we will have to be very efficient to get through this very long list of questions and a lot of

discussion. So, let's all try to be disciplined, otherwise, we will be here late into the night, which I am sure some of you would rather not do.

I am going to turn it over to Cathy Groupe, who is going to do 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 a part of the record to preclude even the appearance of such.

Based on the agenda, it has been determined that the topics of today's meeting are issues of broad applicability and there are no products being approved. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions. All special government employees have been screened for their financial interests as they may apply to the general topics at hand.

To determine if any conflict of interest

existed, the agency has reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food and Drug Administration has granted general matters waivers to the special government employees participating in this meeting who require a waiver under Title 18, United States Code Section 208.

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.

Because general topics impact so many entities, it is not practical to recite all potential conflicts of interest as they apply to each member, consultant, or guest speaker. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

In addition, we would like to note that Dr. Stephen MacMahon, FDA's invited guest speaker, is participating as a representative of the George

Institute of International Health. He has no financial interest in, or professional relationship with, any of the products or firms that could be affected by the committee's discussion.

Dr. Jay Cohn is also an FDA invited guest speaker. He is participating as a representative of the University of Minnesota. He has not financial interest in, or professional relationship with, any of the products or firms that could be affected by the committee's discussion.

With respect to FDA's invited Industrial Representative, we would like to disclose the Dr. Charles McCleskey is participating in this meeting as an Acting Industry Representative acting on behalf of regulated industry. Dr. McCleskey is employed by Abbott Laboratories.

In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participants have a financial interest, the participants involved and their exclusion will be noted for the record.

With respect to all other participants, we

ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. NISSEN: Thank you, Cathy.

For what it is worth, to ensure maximum transparency, even though the regulations don't require it, I have a more detailed conflict of interest disclosure. If anybody is interested, I would be happy to give it to you, or you can e-mail me and I would be happy to respond.

Norman, I think you wanted to say a few things.

Welcome

DR. STOCKBRIDGE: Yes. Good morning. I wanted to thank committee members and consultants and guest speakers for their participation in today's meeting.

I would also like to acknowledge the four members of the Cardio-Renal Advisory Committee as their terms are expiring this week. I am going to

ask Ms. LeSane to pass out a little token of our appreciation to the retiring members: Dr. Blase Carabello, Susanna Cunningham, Beverly Lorell, who is not seated here today, and Dr. Steve Nissen.

I especially want to express our appreciation for Dr. Nissen's service over the last year as chairman of the committee. On behalf of the Cardio-Renal Drug Division and the Food and Drug Administration, I want to thank all four of you for your years of public service.

Thank you.

[Applause.]

DR. STOCKBRIDGE: If I could make a couple of other comments. Today's meeting has been under discussion for at least as long as I have been with the Cardio-Renal Division. That is some 14 years. Now I understand why we never did this.

It is going to be very interesting to see what we come up with as a sort of consensus. This is going to be a very different meeting from ones where we often wrestle with some controversial issue and try to figure out how to resolve those

issues.

I think we will find some controversies today. I just don't think we are going to be able to resolve any of them. In that respect, this is more like--this is more like what goes on in the ICH process. It's a meeting to try to figure out what the lowest common denominator is, areas in which are most confident and then can reasonably be expected to act in making some broad changes to the labels.

So, again, I want to thank everybody for their participation and a special thanks for those of you who traveled long distances to participate in this.

Thank you.

DR. NISSEN: Bob, you wanted to make some comments?

FDA Review Division Presentation

Introduction

DR. TEMPLE: Only very briefly. It is true we have been thinking of this for a long time. It is worth saying why we have been thinking of it.

We have been conscious for at least the period of time Norm is talking about of the unsatisfactory nature of the treatment of hypertension.

One possible reason is that not everybody seems to know what the more sophisticated people know, which is that have it, whether it's systolic or diastolic, is not good for you.

So, this is perhaps our contribution to putting stuff in labeling that says it is worthwhile treating this condition, you should really understand it now, how far to go, how much to say about goals, all of those things are difficult and complicated, how to deal with the different amounts of information available on each drug and each drug class is a thorny problem, and all of those things very difficult, as Norm says, and how much we can agree on remains to be seen.

But it really is sort of stunning that one of the first things we knew how to do to save people's lives in cardiology isn't reflected in any of their labeling, so we, as rapidly as we can, are trying to fix that. Fourteen years is about as

rapidly as we can, it turns out.

DR. NISSEN: Thank you, Bob, and again it is a very daunting challenge, and we will try to work our way through this in an efficient fashion.

One of the questions I guess we have is we can have each of these talks and then save the discussion for later, or we could have some specific discussion after each talk. Is your pleasure, Norman, you want to let everybody go straight on through and maybe discuss afterwards?

DR. STOCKBRIDGE: I think it is really your call. I think that is a perfectly reasonable approach to this, but at least one of your participant speakers is going to have to leave before the end of the day.

DR. NISSEN: So, we probably want to move right along.

DR. STOCKBRIDGE: You might want to do that.

DR. NISSEN: That is what we will do then.

Let's then begin with Steve MacMahon who has come a long way to be with us, from Australia,

and we appreciate your coming, Steve. He is going to talk about applicable outcomes claims for antihypertensive drugs.

Applicable Outcomes Claims for

Antihypertensive Drugs

DR. MacMAHON: Thank you very much. It is my pleasure to contribute to this meeting of the Cardiovascular and Renal Drugs Advisory Committee.

I have been asked to speak about two issues, the first, the claims that may be generally applicable to antihypertensive, and then secondly, to discuss the issue of whether or not different claims may be applicable to different classes of blood pressure lowering agents.

What I am going to do in the first presentation is, first of all, remind you what the effects of blood pressure are on the risks of various vascular diseases using epidemiologic data, prospective observational studies, and then I will specifically talk about evidence from randomized trials of antihypertensive treatment.

I have broken this into sort of two time

periods, the first through to 1994, and then the last decade.

First, just a summary of what does blood pressure do vascular disease, and we have a tremendous amount of evidence available to us now. This is a collaboration that has been conducted over the past decade of so, involves 60 different cohort studies around the world, around a million people, almost 13 million person years, a follow-up, and a very, very large number of outcome events, 56,000 deaths.

We published the results of this in the Lancet in 2002. These data demonstrated very clearly, and not entirely surprisingly, that there were continuous relationships, both systolic and diastolic blood pressure, to the risks of a variety of vascular outcomes.

Plotted here is stroke, mortality, and you can see that at all ages, from 40 to 89, there is clear evidence of a continuous relationship of blood pressure to the risk of death from stroke. You can also observe that the relationship appears

to be considerably steeper in young people than in older people.

You can see, for example, that a 20-millimeter difference in blood pressure at age 40 to 49 is associated with a 64 percent difference in risk, and by the age of 80 to 89, the difference is reduced to 33 percent, but nevertheless, you can see very clear relationships at all ages.

This just shows in a different format, the association with different types of stroke. Here, we are plotting the hazard ratio associated with a 20-millimeter difference in systolic blood pressure, and you can see clear associations with subarachnoid hemorrhage, cerebral hemorrhage, cerebral ischemic stroke, and other strokes of unknown type.

You can see once again clear evidence that there are bigger associations, smaller hazard ratios associated with this blood pressure difference at younger ages.

Coronary heart disease, very similar observation, continuous relationships at all ages,

right down, so you can see a systolic blood pressure of 115, reinforcing this idea that an arbitrary definition of hypertension at 140 is, of course, truly arbitrary. The lowest risks of both coronary heart disease and stroke are seen among individuals with a systolic blood pressure of 115 mm of mercury.

We look at all other vascular mortality, about 10,000 deaths from these causes. Once again, identical relationships. If we look by cause, you can see clear effects of blood pressure on heart failure, deaths from aortic aneurysm, not surprisingly hypertensive heart disease, atherosclerosis, sudden death, and even diseases, such as inflammatory heart disease, rheumatic heart disease, and even pulmonary embolism.

So, blood pressure really contributing in a major way, at all ages, to virtually all major types of vascular disease.

If we look at the totality of cardiovascular mortality, you see here very clear effects, once again strongly age dependent with the

biggest relevance of blood pressure to all outcomes being in the youngest people.

So, that is a summary of the epidemiological rationale really for expecting blood pressure lowering drugs to confer benefits in terms of reduced morbidity and mortality. What do the trials say?

Well, these were data that we published back in 1990 just prior to Norman's appointment I guess to the FDA, and as you can see here, these were data from about just less than 40,000 individuals in all of the randomized trials of antihypertensive drug therapy.

At that time, the trials had achieved on average of only about a 5 to 6 mm reduction in diastolic pressure, for an average of about five years of follow-up, but you could see here clear evidence, highly statistically significant evidence of a reduction in stroke risk of about 38 percent, a clear reduction in coronary heart disease risk of about 16 percent, a reduction in total vascular deaths, and no apparent effect on non-vascular

mortality. So, that was the state of the evidence in 1990.

Most of these trials comprised treatment with a stepped care approach, largely based on treatment with diuretics. Some of the trials involved treatment with beta blockers, but in the vast majority of studies, they utilized drugs from many other classes, as well.

We updated this a few years later in 1994 when there were just under 50,000 patients in trials, 10 to 12 mm reduction in systolic pressure, 5 to 6 mm reduction in diastolic pressure, and you can see here in some of the studies individually, and certainly collectively in all studies, a very clear reduction in the risk of stroke.

If we look at the same thing for coronary heart disease, there has been some uncertainty with some of the individual studies, when we looked at all of the studies in combination, clear evidence that lowering blood pressure was producing some benefit for major coronary events.

Now, since 1995, we have been involved

with a collaboration that has involved essentially all of the investigators from large-scale trials of blood pressure lowering treatments.

We have been the secretariat for that in Sydney, and this has been an initiative that the principal sponsor has been the National Health and Medical Research Council of Australia.

It comprises a prospectively planned series of overview or meta-analyses which have prespecified hypotheses, prespecified study inclusion criteria and outcomes, and all of these were prespecified in 1995.

We published the first results in 2000, and the second cycle of analyses were published in 2003, and that is mostly what I am going to speak about today. It involves data from 29 trials, 160,000 patients, and more than 700,000 patient years of follow-up.

These were the primary outcomes that we prespecified - stroke, coronary heart disease, heart failure, and I will just emphasize fatal or hospitalized heart failure, total cardiovascular

events, cardiovascular mortality and total mortality, and I will just focus on the first four of these in the interests of time.

There were three sorts of treatment comparisons that we made. We looked at trials comparing an active regimen versus some sort of inactive or less active control. We looked at angiotensin receptor blockers versus other regimens, and we also looked at versus active comparisons looking at ACE inhibitors, calcium antagonists.

In this first part of the talk, I will just talk about these two comparisons. I am going to show a number of plots, all of which look like this. It tells you the blood pressure difference between the two treatment groups, the active treatment and, in this case, the control group, and then plots the relative risk associated with the treatment to the left.

You can se here. This is ACE inhibitor versus placebo. There was a 5 mm systolic blood pressure reduction, 2 mm diastolic blood pressure

reduction. This was the estimate of the effect on stroke, a relative risk of 0.72, suggesting a 28 percent reduction in the risk of stroke in the trials of ACE inhibitors compared with placebo.

If we look at calcium antagonists, similar effects, slightly larger, but wide confidence limits, about 38 percent reduction, and if we look at more versus less, so this was more intensive blood pressure lowering versus less intensive blood pressure lowering. Once again, clear evidence of a greater reduction in stroke risk among patients receiving more intensive treatment.

So, these data extend the data that I showed earlier, which had indicated that the older drugs, diuretics and beta blockers, were associated with a reduction in stroke risk. These data show that ACE inhibitor, calcium antagonists also confer similar sorts of benefits, and, indeed, the more intensive the regimen, the bigger the reduction in risk.

For coronary diastolic, somewhat similar picture for ACE inhibitors, 20 percent reduction in

risk, calcium antagonists about the same, so again, extending the evidence to the newer agents for protection against coronary heart disease, although no clear evidence in this instance that more intensive blood pressure lowering necessarily conferred any additional benefits, but very wide confidence limits and moderate benefits couldn't be excluded.

If we look at heart failure, and the earlier trials I don't think collected nearly as good data on heart failure as the older studies have done, but here we see clear evidence of benefit with ACE inhibitors and 18 percent reduction in the risk of heart failure; with calcium antagonists, no clear reduction, trend towards an excess, but not statistically significant, similarly for more intensive blood pressure lowering, trend towards a lower risk, but not statistically significant.

If we look at the composite, then, of all major cardiovascular events in these trials of active versus control, then, unquestionably,

benefits of ACE inhibitor based therapy, about 22 percent reduction in the risk of any major vascular event, similar reduction with calcium antagonist based therapy, and also a clear 15 percent reduction in the risk of any major event with more intensive blood pressure lowering.

Now, this is a separate analysis that we conducted looking an angiotensin receptor blockers versus others. It was conducted separately because the nature of the trials were quite different to those of other agents insofar as many of the studies neither fitted the description of being comparison of active treatments or comparison of treatment and control.

They were essentially trials which compared treatments based on angiotensin receptor blockers with other sorts of therapy, which tended to be less intensive. As you can see here, there was as bigger blood pressure reduction in the angiotensin receptor blocker assigned patients than there were in patients assigned to a variety of other regimens.

Nevertheless, notwithstanding that, there were clear reductions in stroke risk with ARB-based therapy. There was no clear reduction in coronary heart disease. There was a clear reduction in heart failure and the clear reduction in major cardiovascular events.

So, based on this, which is essentially the totality of the available evidence, one might propose that the outcome claims that are generally applicable would be that regimens based on either older or newer classes of drugs have been shown to reduce the risks of stroke, or coronary heart disease, and of a composite of all major cardiovascular events that would included cardiovascular death, stroke, myocardial infarction, and heart failure.

These benefits are observed across a very broad range of patient groups, and I haven't really been able to go into this in any detail because of time constraints, but we see benefits in Caucasian populations, Asian populations, African-American, among the middle-aged and the elderly, in those

with hypertension and those with diabetes, and those with a history cardiovascular disease, and without any consistent evidence of heterogeneity in the size of the treatment effects in different patient populations.

I would just like to emphasize that the benefits of blood pressure lowering drugs are not restricted to patients with hypertension, which is a common myth in many respects.

This is results from a trial in patients with cerebrovascular disease, the PROGRESS study, a large study of blood pressure lowering for the secondary prevention of stroke, and you can see clear benefits in terms of prevention of stroke among hypertensive patients, a 32 percent reduction, but you can also see clear benefits in the non-hypertensives, in fact, not all dissimilar magnitude for both stroke and for the totality of major vascular events.

Other potential claims. in some trials, there have been reports of reduced incidence of heart failure, as you saw in the trials of ACE

inhibitors, in other trials evidence of reduced progression of renal disease, in other trials evidence of reduced incidence of new onset diabetes, but I think it is probably a reasonable conclusion that the evidence is insufficient to claim any of these as being generally applicable to all drug classes.

That is the end of my first presentation. Do you want me to go straight on, Steve?

DR. NISSEN: We are actually somewhat ahead of schedule. Perhaps if there is a burning question or two, I think, Tom, you may want to ask something.

DR. FLEMING: Steve, thank you very much. I found the manuscript that corresponds to your presentation extremely insightful.

One of the things that was of interest is the slide on the ARBs. I don't know if you could flash that slide up again for a moment, where it appears that what you are indicating is that in the trials, there is somewhat better blood pressure control.

DR. MacMAHON: Yes.

DR. FLEMING: That analysis predates value, is that correct?

DR. MacMAHON: Correct.

DR. FLEMING: What is your assessment when you incorporate value?

DR. MacMAHON: In the next presentation, I am going to talk specifically about how the new trials impact on the interpretation of treatment effects of specific classes, so if you don't mind, I might leave it until then.

DR. NISSEN: Bob, you had a question.

DR. TEMPLE: The effect on, let's say, coronary artery disease related events, in early trials was always lower than the effect on stroke. It didn't quite roll back the epidemiologically predicted effect.

I have always attributed that to hypokalemia from the doses of diuretics that were used. Do you see any difference between the earlier studies using 100 or thereabouts and the later studies using either lower doses or

protecting against hypokalemia with triamterene or something like that, because my impression that the effect size gets larger when you do that, so that is probably an important consideration than what we are talking about.

DR. MacMAHON: Certainly, it was true that in the early analyses around 1990, the 16 percent reduction in coronary risk was, one, less than the reduction in stroke risk although the epidemiology would, of course, predict that you would get lesser relative risk reductions, however, as you say, it appeared that there wasn't as complete protection as one might have hoped for, and there was great discussion at the time about adverse metabolic effects, not only of diuretics, but of beta blockers.

I think probably those concerns have dissipated somewhat as new data have indicated somewhat larger reductions in risk. Whether those differences are really the play of chance, or whether they are specific to some difference in the treatments in the early studies and the later

studies, I think it is hard to necessarily interpret.

But it is worth thinking about this in respect to other interventions for the prevention of coronary heart disease, because even lipid lowering therapy, which we unequivocally know to be of great value in terms of primary and secondary prevention, you don't see entire reversal of the full epidemiologically expected effects of cholesterol reduction within the first few years of treatment.

You are still seeing on average about two-thirds of the full benefit in the cholesterol lowering trials, so that is not dissimilar to the sorts of proportional benefits one is seeing with blood pressure lowering, so it could be just a more chronic process than stroke reversal.

DR. NISSEN: This is both in answer to you, Bob, and a question for Steve. I have always attributed it to the way we define the events. You know, myocardial infarction, you know, particularly if you go back a few years, had a definition that

required one to have the classical, sort of transmural infarct.

Now, a lot of the events that we see, contemporary events, are these softer events, you know, patients get admitted to CCU for ACS, they have a little troponin leak, maybe they go on and have revascularization.

So, my question is, do you have any information you can bring to bear about, you know, because these are obviously very undesirable events for patients, you know, having an admission to the hospital and getting an interventionalist to go put a stent in you is an adverse outcome, and the question is if you add those events in, do you learn anything, or can you? I mean do you have that information?

DR. MacMAHON: In general, we haven't consistently collected data on revascularization, for example, in this project, but if you look at major individual studies, in general, one sees similar sorts of effects on revascularization rates as coronary death, or major myocardial infarctions,

so there is a similarity of treatment apparently.

DR. TEMPLE: But the disparity applied to coronary mortality, too, which is not just getting into a hospital. I was always struck by the--I don't remember if it was Mister Fit, or which one of them--one of the NIH trials had to stop its chlorthalidone-100 arm, because of excess mortality. Oh, we know that must have been hypokalemia, I mean it is hard to think what else it could be.

I guess I was also struck that when SHEP finally got around to using the right dose of diuretic, you would have the expected 30-plus percent reduction in coronary mortality, so maybe that is not the explanation, I don't know. I have got slides saying it is.

DR. BLACK: I think there is one other way to look at it, Bob, and, Steve, as well. If you look at the trials of isolated systolic hypertension, like SHEP, which didn't only have diuretics in them, then, the epidemiological predictions for MI are very similar to what you

would expect, so the populations may be different, as well as the drugs, and I am not sure we can really say.

DR. NISSEN: You had a question, Bill?

DR. HIATT: Just somewhat of a broad question, but it relates to the population studied, and never is needed to treat, we talk about primary and secondary prevention quite a bit.

Would you just comment a bit on these numbers and the effect sizes in terms of absolute risk reduction versus relative risk reduction?

DR. MacMAHON: First of all, the relative risk reductions are broadly comparable, so it was difficult to find evidence that the size of the relative risk reduction varied by patient group, but the absolute benefits vary enormously, absolutely enormously.

So, at one extreme, for example, among patients who have got a history of cardiovascular disease, for example, in the PROGRESS study, in whom all patients had cerebrovascular disease, then, you are preventing an event in half a dozen

patients treated for five years, whereas, at the other extreme, when you are looking at very modestly elevated blood pressure in patients otherwise without pre-existing disease and frequently without other cardiovascular risk factors, you can be talking about treating hundreds of patients for the same period of time to prevent an event, so there are a huge range of absolute treatment effects that appear to be entirely driven by the background level of risk.

So, you know, you are reducing stroke risk by, say, 30 to 40 percent at all levels of absolute risk, but that is clinically meaningful in some groups and much less so in others.

DR. HIATT: Steve, I would like to suggest that that concept be retained throughout the day in terms of these labeling discussions.

DR. NISSEN: It is interesting because I had very similar thoughts. You know, with lipids, the intensity of therapy is determined, not so much by what the cholesterol level is, but by the level of risk, whereas, in hypertension, we say, well,

here is your goal with the exception of, say, diabetes, and this concept is not as well developed in the hypertension world, but it is a very important one that I hope we get back to discuss.

I think we had better not get hung up here. I could ask a thousand more questions of Steve, who spent quite a long time looking at these data, really terrific.

Steve, do you want to go on and give your second presentation?

Differences in Outcomes Claims for Different Drug Classes

DR. MacMAHON: The second topic concerns the question of whether there is evidence to justify different claims for different drug classes.

Once again I am going to focus predominantly on data from the Blood Pressure Lowering Treating Trialists' Collaboration. I am going to focus also predominantly on the second cycle, although I am going to show some unpublished data which is really only going to be released this

week, in fact, tomorrow in Milan at the European Society of Hypertension meeting, which really updates effectively a third cycle of analysis.

I have showed you results for the comparison active versus control, and ARB versus other regimens. I am now going to focus on the evidence of treatment differences comparing different active regimens, so ACE inhibitor versus diuretic or beta blocker, calcium antagonist versus diuretic or beta blocker, and ACE inhibitor versus calcium antagonist.

One of the issues that these comparisons raise is should we be really be putting diuretics and beta blockers together as the control condition. I think that is a reasonable question to raise.

Unfortunately, because this was prespecified hypothesis and prespecified protocol, this is what we said we would do, so fundamentally, this is what we have done. However, we have done sensitivity analyses in which we have taken out all the beta blocker trials, the ones which were beta

blocker was the principal control condition, and none of the conclusions that I will show you would change.

Fundamentally, very few of the trials were based on a beta blocker as the number one drug, so mostly what you are seeing here is evidence comparing a newer agent with a diuretic-based regimen.

In all these comparisons, most of the trials compared regimens rather than single drugs, so we are not looking at necessarily drug A versus drug B, but a regimen based on drug A versus a regimen based on drug B.

In almost all the studies, there was the capacity to add additional therapy where it was required for blood pressure control.

We have quite a lot of data now from these trials comparing different agents, 47,000 patients in trials comparing ACE inhibitor with diuretic or beta blocker based therapy, and you can see there are the component studies, 6,000 major events in these trials. Calcium antagonists versus diuretic

or beta blocker, 68,000 patients, 7,000 events, and ACE inhibitor versus calcium antagonists, 26,000 patients, 4,000 events.

So, looking at the results, first of all, if we look at stroke, ACE inhibitor based therapy versus diuretic or beta blocker. The ACE inhibitor based therapy was less effective in lowering blood pressure, so there was a 2 mm higher blood pressure in ACE inhibitor treated patients than in those receiving the diuretic based therapy.

There was also a borderline significant treatment advantage for the diuretic, about a 10 percent greater reduction in stroke risk.

If we look at calcium antagonist versus diuretic or beta blockers, once again, a slight advantage to the calcium antagonist in terms of the size of the blood pressure reduction, only 1 mm though, and this time borderline significant evidence of greater reduction in risk with calcium antagonist based regimen, about a 7 percent greater reduction in risk.

Not surprisingly, therefore, when you

compare ACE inhibitors and calcium antagonists, a slight advantage to the calcium antagonists in terms of the blood pressure reduction and about 12 percent greater reduction in stroke risk.

So, some evidence here that there may be differences between agents in their effects on stroke risk, but pretty wide confidence limits, all of them tending towards one, so hard to say whether or not these treatment differences, on the one hand, are real, and if they are real, how large are they in reality.

For coronary heart disease, really no evidence of any difference between the regimens, ACE inhibitor, diuretic, calcium antagonists versus diuretic, or ACE inhibitor versus calcium antagonist in their effects on major coronary disease.

Heart failure, probably the clearest evidence of differences between regimens. No clear evidence of a difference between ACE inhibitor and diuretic or beta blocker, but very clear evidence of the difference between calcium antagonists and

diuretics and beta blockers with a markedly greater reduction in risk with the diuretic and beta blocker based therapy.

Similarly, when we compare ACE inhibitors versus calcium antagonists, once again, a much larger reduction with the ACE inhibitor.

However, if we look at the composite of all cardiovascular events, then these core-specific differences were largely balanced out, so overall you can see here no clear difference between groups in their effects on the composite of all major cardiovascular events.

One area where there has been great controversy is whether or not specific drugs have particular benefits for patients with diabetes, so I just show here a paper which is coming out I think this month, in the Archives of Internal Medicine, where we have looked at separate treatment effects on these outcomes in patients with and without diabetes, and overall you can see that there is really no clear difference in the benefits of these agents in diabetic patients

compared with non-diabetic patients.

We have also done the same for the angiotensin receptor based regimens, and once again you see a very similar finding, that the treatment effects in the relative sense are similar in diabetics and non-diabetics, although to come back to the issue that was raised earlier, diabetics are at higher absolute risk and therefore stand to benefit more from the same size relative risk reduction.

So, conclusions then based on this second round of analyses might be that calcium antagonists and diuretic/beta blocker based regimens may be more effective than ACE inhibitor-based therapies for stroke prevention. ACE inhibitors and diuretic-based regimens appear to be more effective for heart failure prevention, and there were no clear differences between regimens in their effects on coronary heart disease.

For total cardiovascular events, however, there were very similar effects of ACE inhibitor, calcium antagonists, and diuretic/beta

blocker-based regimens. There was also, as I pointed out earlier, clear evidence that angiotensin receptor blocker-based therapies also reduce cardiovascular risk and that these effects for all the drug classes appear to be similar in diabetic and non-diabetic patients.

So, the question then of independent drug effects, do these analyses necessarily rule out the potential for there being independent drug benefits? This has been, as many of you will know, the primary focus of debate in the blood pressure and hypertension community for at least a decade, and I think as was pointed out in the introductory remarks, this has been an area where there has been really no consensus as to whether or not there are effects which are independent of blood pressure lowering.

One of the major hypotheses has concerned the potential advantage of agents that inhibit the renin-angiotensin system. Therefore, we have undertaken as part of the Blood Pressure Trialist Collaboration some analyses which looked

specifically at the question of whether ACE inhibitors and angiotensin receptor blockers confer benefits that are greater than that which would be expected on the basis of the blood pressure reductions achieved alone.

So, specifically, what we have done is we have looked in trials of active versus active agents, as you know, and we have seen no clear advantage of ACE inhibitor-based regimens in those head-to-head comparisons, but it is important to point out that there were moderate differences between the regimens and their blood pressure lowering effects, and there could have been some masking therefore of potential independent benefit.

In the trials of the ARB-based regimens, we have seen clear evidence of benefits, but there is uncertainty as to whether or not those benefits are greater than might have been predicted by the reduction in blood pressure alone.

So, in these new analyses, we have looked at the effects of ACE inhibitors and ARB-based regimens, and to follow up Tom Fleming's point,

these now include all of the most recent trial data including the VALUE study.

We have stratified these treatment effects by blood pressure differences between randomized groups, and we have looked at three cause-specific outcomes: stroke, coronary heart disease, and heart failure.

I would just point out that because of the clear difference between calcium antagonists and other agents, and their effects on heart failure, we have taken out the calcium antagonists from the heart failure analyses where calcium antagonists was the control group.

It doesn't really make a huge difference, but given the clear difference of a differential effect, it didn't seem appropriate to include those trials in which calcium antagonists were the controls.

This is a very complex looking slide, but this is basically the difference in achieved blood pressure reduction between the randomized treatments, and this is the odds ratio.

What you see here for the ACE inhibitor in the black and the black circles, it shows that the bigger the reduction in blood pressure, the bigger the prevention, the reduction in the stroke risk.

For the ARB, you see almost exactly the same thing. Importantly, if you look at this intercept at zero mm of mercury difference between the two groups, both these regression lines are pretty much going through this intercept, suggesting that there is no protection against stroke when there is no blood pressure reduction, and this would suggest that most of the differences that we have seen at least with ACE inhibitors and ARBs can be explained by the size of the blood pressure reduction.

Now, when we look at coronary heart disease, we see something different. Here is the result for angiotensin receptor blockers, once again suggesting the bigger the reduction in blood pressure, the bigger the prevent of coronary disease, but largely going through the origin here, but if we look at ACE inhibitors, you can see that

the results for ACE inhibitors are set about 10 percent below the results for angiotensin receptor blockers, suggesting--and this is highly statistically significant, and the difference between ACE inhibitors and ARBs is also itself highly statistically significant--suggesting, as you can see here at zero mm of mercury difference between treatment and control condition, that you are seeing about 10 percent protection against coronary heart disease.

So, this is perhaps the first--I hesitantly use the word "clear"--but the first evidence that suggests that there may well be something specific about some drug classes which are offering some protection beyond blood pressure reduction.

It is interesting that we see here, we don't see the same results for ARBs, which suggests that it is not something that is necessarily specific to inhibition of the renin-angiotensin system, rather, something that appears to be specific to ACE inhibitors.

Heart failure. Really, no evidence with the ACE inhibitors that there is any protection against heart failure when there is no reduction in blood pressure, perhaps not quite what would be expected for ARBs, although they are shift away from the origin here, the confidence limits are very wide and there is no significant evidence with ACE inhibitors or ARBs that we are seeing any protection beyond that which could be explained by blood pressure lowering alone.

You can see that for essentially all of these outcomes, the principal observation that is common to them all is that the bigger the blood pressure reduction, the greater the protection against all of these core-specific cardiovascular outcomes.

That indeed might be the principal conclusion that for all regimens, irrespective of drug class, it is the same of the blood pressure reduction that appears to be primarily driving the size of the risk reduction.

However, for coronary heart disease, we

appear to see about a blood pressure independent effect of ACE inhibitor-based regimens of about 10 percent.

For stroke and for heart failure, there is no clear evidence of blood pressure-independent effects of either ACE inhibitors or ARB-based regimens.

This, of course, suggests that the observation in the direct comparisons, the trials that compared ACE inhibitors with other outcomes, this apparently independent effect of ACE inhibitors was obscured by the fact that they are less effective at lowering blood pressure. So, what we saw in those trials was a similarity of treatment effect in terms of the outcome, but with lesser blood pressure reduction.

Now, obviously, because of that practical limitation, one might ask whether or not there really is any therapeutic relevance given that the net effect is no different. Nevertheless, it does suggest the perhaps combination therapy with an ACE inhibitor, which might give you this 10 percent

independent protection,and other agents, which would extend that size of the blood pressure reduction would offer the greatest production.

In closing, I would just like to acknowledge the people who really do all this work: Fiona Turnbull, Bruce Neal, Charles Algert back at the coordinating center in Sydney.

Thank you very much.

[Applause.]

DR. NISSEN: We are doing very well on time, so if there are some burning questions, let's ask them.

DR. PICKERING: I have two questions related to the stroke prevention. The first is the recently published MOSES study that showed that recurrent stroke appeared to be prevented by an ARB more than calcium channel blocker, and they said it was independent of blood pressure. You probably didn't include that in your analysis.

DR. MacMAHON: I don't think that was included in this analysis. I think once again if you look at the totality of the evidence, it is

hard to see that there is much convincing evidence that there is a major difference between these two groups of therapies or between any of the treatment regimens really that are independent of blood pressure lowering, but there will be occasional studies that suggest the converse, but I think it is only when you look at the totality of the evidence that you can rule out, you know, small differences, the results of play of chance.

DR. NISSEN: Steve, you obviously have been looking at this for a long, long time. Would you agree with the statement that any drug class or drug-specific effects could largely be overcome with, say, an extra millimeter or two mercury blood pressure reduction?

In other words, if you tried to compare two regimens, even if you had a drug that was better on one endpoint than another, you pick up an extra couple of millimeters, and those all go away?

DR. MacMAHON: Yes, that is exactly right, yes.

DR. PORTMAN: It is hard to have a

discussion about antihypertensives and their effects on the different classes without including issues related to the kidney, and the progression of renal disease, end-stage disease, doubling of serum creatinine, and the like.

These are wonderful analyses and I was wondering whether you had something similar related to progression of renal disease.

DR. MacMAHON: Well, we are right in the middle of that now. I would like to be able to show you results, but we haven't gotten them yet. We are collecting data on progression of renal disease from all the trials, and we realize that that is the major outstanding issue, and also specifically with respect to diabetic and non-diabetic patients, that although there is no clear advantage of any regimen for the prevention of vascular or microvascular events, whether there is differential effects from microvascular events is another matter.

DR. PORTMAN: A follow-up, if I might. The other thing, in looking at the combination, we

have looked at diuretic and beta blocker, but really, the combination that is being used at least in practice more commonly now is the ACE inhibitor and a diuretic, or the ARB and a diuretic.

Have you been able to address any of those studies, or are they still pending?

DR. MacMAHON: I think, in reality, there are no specific studies which have looked at particular combinations. I mean I guess the ASCOT trial aside, which looked at the combination of calcium antagonists and an ACE inhibitor versus a diuretic and a beta blocker, but most of the others, there was a relatively free use of add-on therapy, so it is a little hard to talk specifically about particular combinations, but certainly ongoing are large-scale trials looking specifically at the issue of ACE inhibitors/diuretic combinations in particular patient groups like diabetics.

DR. PICKERING: A couple of years ago we approved losartan for drug prevention on the basis of the LIFE study, and there was debate at that

review as to whether it was because the ARB was better or the atenolol was worse, and since then, there was a paper in Lancet that appeared suggesting that atenolol lowers blood pressure, but does not lower risk.

Could you comment on that?

DR. MacMAHON: Yes. In our analysis of all the ARB trials, there is no evidence that the protection against stroke is any greater than would be expected by the size of the blood pressure reductions achieved, and that includes the LIFE trial.

I don't think we have adequate data to comment on whether or not beta blockers per se are less effective, because as I said, although beta blockers were used in some of these trial, for the most part, the comparisons in this group are diuretic based.

DR. NISSEN: I had one more question, and maybe this is a rhetorical question, but pharmacokinetic effects are very different amongst drugs, and we know that obviously, blood pressure

can potentially have an effect 24 hours a day on endpoints.

So, I assume that almost all these trials, the data you had available was a casual blood pressure taken in the clinic. This comes up frequently. For example, take a trial like HOPE, where the drug was given in the evening, and then the blood pressure is measured the next day at trough, so it looks like there is not much blood pressure difference, but the blood pressure difference at night in a smaller ambulatory blood pressure study was much, much larger.

So, is it possible that some of these potential differences you are seeing are really related to the pharmacokinetic properties, and not actually to any differences between the drugs themselves?

DR. MacMAHON: That's a good question, and certainly we are aware of the issues relating to the HOPE study in particular and how that might impact on these analyses.

When we take HOPE out, you see exactly the

same thing, so that 10 percent advantage, which is specific to coronary disease, still seems to be there. There is a sense, of course, in which that if we were seeing anything that was masking a blood pressure specific effect, you would see it more for stroke that you would for coronary disease, so the coronary disease results seem to be robust even when you took HOPE out and looked at the trials, where I don't think there is the same degree of concern as to whether or not you are really seeing a lesser picture of the blood pressure reduction.

DR. HIATT: I have on general question, as well.

You have shown us that the different classes probably don't differ much in terms of benefit, but the question I have is one of harm, do calcium channel blockers cause harm, and specifically, there are trials comparing ACE to calcium channel blockers that suggest an increase of non-fatal MI, at least in the ABCD trials, and the question about heart failure.

Would you just address that?

DR. MacMAHON: Once again, these data don't provide any evidence that would suggest that calcium antagonists, ACE inhibitors, or diuretics confer different effects on coronary heart disease per se.

Although there have been reports in observational studies and in a few small trials, when you look at the totality of the evidence for coronary disease, the effects of all the agents appear to be very similar.

That's, of course, also confirmed now by placebo-controlled trials of calcium antagonists where there is a 20 percent reduction in coronary risk, which is statistically significant.

So, I think some of those concerns that there have been about the safety of calcium antagonists for coronary disease are largely, if not entirely, allayed by the recent results. However, for heart failure, it is a different matter, and here we do see, I think, unequivocal evidence of the difference between regimens in their effects on heart failure, and the calcium

antagonists appear to be clearly less effective than the others.

In the placebo-controlled trials, there is no significant excess of heart failure, but there is a trend in the wrong direction, there is no clear evidence of a reduction, and the head-to-head comparisons always favor the non-calcium antagonists regimens.

There are lots of questions about to what degree the peripheral edema caused by calcium antagonists are clouding the issue of whether this is real heart failure or not. It is almost impossible to avoid that if it is a real bias.

What we have tried to do here is standardize the definition of heart failure in all these trials, and what I have shown you only includes death from heart failure or hospitalization from heart failure.

Now, of course, it is quite possible that deaths and hospitalizations from conditions other than heart failure, that appear with peripheral edema, might be called heart failure incorrectly,

but at least what we are seeing here is definitely hospitalizations and deaths.

DR. HIATT: So, my question is harm.

DR. MacMAHON: Yes.

DR. HIATT: So, you are interpreting the data as neutral in heart failure, not causing excess heart failure.

DR. MacMAHON: I think there are two issues. One is that other regimens are clearly more effective in preventing heart failure. In terms of whether or not calcium antagonists cause heart failure, the only way you can really assess that is from the placebo-controlled trials, because otherwise you don't know whether it's the harm of one or benefit of the other, or both.

The placebo-controlled trials don't show any significant excess of heart failure. The confidence limits are wide, the point estimate is on the wrong side of the line, so these results are not inconsistent with an increase in heart failure, but they are also consistent with no effect or even a modest benefit.

So, I think the only conclusion that is really rock solid is that they are less effective.

DR. NISSEN: John Teerlink was next.

DR. TEERLINK: Given that stroke and coronary artery disease are both vascular diseases, I was always interested, the difference between stroke and coronary artery disease.

One of the hypotheses I have been interested in hearing more about is whether calcium channel blockers or the reducing blood pressure effect relates more to preventing early stroke, whereas, if you looked at sort of a time-dependent analysis, ACE inhibitors and ARBs may be better at preventing development of risk of stroke later down the line.

From your data, is there any suggestion that that may be at play?

DR. MacMAHON: No, really, we haven't got at the moment analyses which would allow us to look at time-specific effects, which I guess is what you are saying, is it possible that there are differential effects of different agents at

different time points. No, we don't have that data unfortunately.

DR. NISSEN: Bob, you are next.

DR. TEMPLE: One of the distortions that is inevitable in these comparative trials is that you introduce artificiality into the regimen. So, in ALLHAT, you know, if lisinopril didn't work, you weren't allowed to take a diuretic, because that was one of the test drugs. Well, no one would behave that way, they would always add a diuretic.

So, my question goes to the calcium channel blockers. One question might be should you start with one, and maybe the heart failure data says that's not as smart as some other choices, but a bigger question, especially since most people don't get controlled is, is there a potential adverse consequence of adding it.

So, can you say anything about whether the worse finding on heart failure continues to show up in the presence of a diuretic or in the presence of one or another renin active drugs as opposed to when you use it alone?

DR. MacMAHON: Well, certainly in the VALUE study, that's probably the greatest single experience of the use of the calcium antagonists in combination with a diuretic, because in that study, which compared valsartan and amlodipine, the second line therapy for all patients was a diuretic. I can't quite remember what it was, but it was a diuretic, and a large proportion of both groups received that.

In that study, there was no significant difference in heart failure between the ARB-treated patients and the calcium antagonists-treated patients. There was some non-significant divergence in favor of the ARB in the second half of the trial. You can ask Tom, he and I were on the DSMV, I don't think that we thought that this was convincing evidence that there was a difference in that particular trial where you have a lot of background use of diuretic.

DR. TEMPLE: So, that goes to the question of whether the heart failure difference is harm or failure to benefit, or might go to that, which is

really quite important, because we are going to be talking about multi-dose regimens for the most part.

I was struck in ALLHAT, the ACE inhibitor didn't look very good, and what I was reminded of was that 100 percent of all the ACE inhibitor heart failure trials are in people on diuretics. Well, not in ALLHAT you are not. So, you wonder what the role of that is in the finding.

DR. MacMAHON: One of the issues I guess in thinking about harm is also I think while it's important to look at core-specific outcomes, it is obviously net harm that really is the issue, that although there may be differences between agents in the core-specific effects, it is really in terms of the net effects on, if you like, the totality of the cardiovascular disease burden that is most important. I mean I just think that has to be kept in mind.

DR. NISSEN: Just one comment. We are going to go for about five more minutes, and then I am going to keep us on time. But, of course,

sometimes we have clues as to which outcomes a patient is most susceptible to, and when we do, we can use that information in making selections of drugs.

I think we are going to come back to that, Bob, maybe later, because we sometimes know that certain populations are more vulnerable to certain adverse outcomes for a number of reasons, and that may impact on the best choice of drugs.

I think, Henry, you were next. We are going to do Henry and then Tom, and is there anybody else?

DR. CARABELLO: Yes.

DR. NISSEN: And Jonathan. Everybody has got questions. Unfortunately, we are going to get behind here, and I am going to go until 9:15 exactly, and I apologize if everybody doesn't get to ask their question. Just write it down and we will come back to it during the discussion period, but we are going to lose Henry, so that is a problem.

DR. BLACK: Thanks. I just want to make a

couple of comments. I always enjoy hearing Steve's analyses and live off them, for the most part.

One thing I think he hid in some of what he said, was to lump ACEs and ARBs together. They have different effects on outcomes. ARBs look good for strokes, ACEs don't look good for strokes. There is a difference in coronary disease, as well, and it can't be the renin-angiotensin system blockade because they both do that, it may be the other effects that ACEs have, and maybe we ought to start thinking about them differently. That is one thing.

I also want you to comment a little bit on nondihydropyridines and dihydropyridines. Once again, we lump together those as both calcium antagonists. In the CONVINCE study, which wasn't exactly a comparison of a nondihydropyridine against a diuretic or beta blocker, and the others, we saw no real differences. Atenolol was the beta blocker that was used in more than half the patients as their first drug. Hydrochlorothiazide was added to both.

We saw really no differences between what you did, but it didn't change the conclusions in the Lancet paper, which we hoped it might, so I think there is a lot we need to understand.

DR. MacMAHON: In terms of dihydropyridine versus nondihydropyridine, certainly in some of the early analyses, the first round, we looked at this specifically and saw fundamentally the same sort of outcomes for both.

In the second round, we didn't really focus on that, but I have asked them to rerun those, and once again the overall findings that we saw for calcium antagonists appeared to apply equally to dihydropyridine and non-, but the very latest results that I have put up there, we obviously haven't yet looked at that split.

DR. NISSEN: Tom.

DR. FLEMING: Let me see if I can do this in a minute, Steve. Can you put up one of your last slides on heart failure, the relationship with heart failure risk, and while you are doing that, I want to follow up on what Tom Pickering was saying,

given that we spent an entire day on January 6, 2003, talking about this issue of the LIFE trial.

It did strike me in that study that Losartan against atenolol, there was a 25 percent relative difference in stroke reduction, only a 1.15 mm difference mercury in blood pressure.

Is that just an oddity in that trial that doesn't, in fact, show up in the entirety of the data? You seem to dismiss it as, in fact, not reflecting potential effects on stroke beyond blood pressure lowering.

DR. MacMAHON: I think once again what we are trying to do is rather than interpret any one trial by itself, look at the totality of the evidence and see whether or not there is a consistent pattern, because, you know, as you are fully aware, when you have dozens of trials like this, you are going to bet by the play of chance some things that look extreme and others that don't.

DR. FLEMING: That is what I am getting at. So, you would say, in fact, it is inconsistent

with the totality of the data, the totality that would not suggest this.

DR. MacMAHON: I think that's correct, but I would balance that by saying this data set does not provide good evidence about whether or not beta blocker themselves are inferior treatments because so few of these trials used beta blockers as the primary outcome.

So, it is not impossible that--

DR. FLEMING: Doesn't this slide here actually suggest, maybe in small data, that for ARBs, that it is not blood pressure and heart failure?

DR. MacMAHON: Well, it does, but if you look at these confidence limits, 12,000 percent is a pretty high upper confidence limit.

DR. NISSEN: I think Jonathan was next. I want to make this the last question. I apologize for the rest of you. You will have plenty of chances to talk later, so let's do this, one more.

DR. SACKNER-BERNSTEIN: Thanks, Steve.

I enjoyed the presentation. I think the

idea of lumping together the classes is something that we need to pay ongoing attention to, and these analyses are one example of that.

If you look at the paper that Tom mentioned before from Lancet, looking at the atenolol meta-analysis, it really shows no effect on clinical outcomes except potentially that on stroke risk, despite remarkable blood pressure reductions, and I say potentially stoke risk because of the four studies comparing atenolol to control, one was open label. That's really the only one that made it have an effect overall the meta-analysis, that carried the meta-analysis to say stroke reduction.

The other three, which were blinded, looked like atenolol has no effect on stroke despite blood pressure reduction. So, it ties into the point that you raised, Tom, about the LIFE trial. I think that as we go forward, that is something we have to be sensitive to, that if we are using a control that has been shown by meta-analysis not to have clinical benefits despite

blood pressure lowering, that we need to take that into account, as you have the differences between ACE and ARBs that you showed in that one slide.

DR. MacMAHON: I think the only comment that I will make about that is that we have looked, I mean we have done sensitivity analyses taking out all the beta blocker trials, so what we have seen here for differences between agents appear to be independent of any beta blocker-specific, if you like, deficit.

What the data don't provide, though, is very good evidence about what magnitude of the fact beta blocker themselves have, because that hasn't been our focus.

DR. SACKNER-BERNSTEIN: Except that those studies almost all used atenolol. Hardly any studies used other beta blockers, relatively speaking, in terms of patient numbers and patient exposure, if I understand correctly.

DR. MacMAHON: Well, metoprolol was also used in some of these trials, but I mean once again we have taken out all the beta blocker trials from

some analyses to see whether or not the difference that we see, or the lack of differences that we observe, were dependent on the beta blocker inclusion, and it doesn't appear to be the case. When we take them all out, we still see the same result.

DR. NISSEN: We are going to move on and I do apologize, but we will have a whole day to talk, so you will get your questions in later.

Jay Cohn is next. Jay, you have the floor.

Deciding Whom to Treat for Hypertension

DR. COHN: Thanks very much, Steve, Bob, Norm, members of the committee. I really appreciate the invitation here today to talk on the topic that I have been interested in for more than 14 years, and I would like to present to you this morning a concept that has grown over quite a few years.

I believe that we are approaching the tipping point with this concept, and the fact that I have been at this for so many years, I think is a

tribute to my patients and that there will be another discussion tomorrow, which probably addresses my patients over the years, and this concepts gaining widespread acceptance.

How should one decide whom to treat for hypertension?

I have been focused on this issue for a long time, and Steve has provided some background that will make my job easier at the beginning here, because he has already covered some of these things.

Obviously, from what he and others have shown, there is a clear relationship between CV mortality risk and blood pressure going all the way down to pressures of 115/75, and these kind of data have been used over the years to stress the importance of blood pressure control.

But you have to recognize that these data are flawed because, first of all, they don't correct for age, and we know that blood pressure tends to rise with age, so you are going to have more and more older people as you go up in blood

pressure.

Now, this is a slide that Steve already has shown, and it just emphasizes now you can break this down by age, and, in fact, there is a striking linear relationship between systolic blood pressure on the left, and diastolic blood pressure on the right, at all age levels, once again showing what is at least identified as the role of blood pressure in increasing risk.

Now, first of all, this is a risk for an event over a given period of time, and obviously, if you are 60, 70, or 80 years old, let's look at the top list, which is 80 to 89, you are obviously at a much higher risk for an event whether your blood pressure is 120 or 180.

Therefore, perhaps we should be more interested in lifetime risk rather than 10-year risk. We should keep in mind that the older you are, the less time you have to live at least that is what people tell me, I am working on that.

Of course, if you are 49 years old with a blood pressure of 180, your risk is still lower

over the next interval than if you are 60 years old and have a blood pressure of 120. So, you have to integrate all of these factors in to try to make sense out of kind of risk slides like this, but these are the kinds of data that have led to the concept, if you will, that blood pressure itself is a very high risk for events.

Well, I think there is another hypothesis, an alternate hypothesis that could be put forward to sort of challenge that simple view.

That is, that the apparent linear relationship between blood pressure and ischemic disease events--and mostly we are talking about ischemic disease events--as well as age and ischemic disease events does not necessarily mean that age or blood pressure cause events, but that both markers capture a progressively higher proportion of people with early disease.

So, if your blood pressure is over 140/90, it isn't necessarily that the blood pressure is the cause of your likelihood of having an event, but that by using that cut point for blood pressure,

you have a larger proportion of people in that category who have early vascular disease, therefore, yes, blood pressure is an excellent marker for risk, but maybe it's not the cause.

Well, what is the relationship between blood pressure and likelihood of disease? Now, here is a very simplistic diagram which plots systolic blood pressure on the horizontal access and the frequency in the population.

The current idea is that if your blood pressure is below, say, 115 and 120, your risk for events is very low, and I put No Disease in that category, and that may involve 50 or 60 percent of the population. Let's set them aside. They are at that point when you measure them probably without significant vascular disease, probably not completely true, but at least a useful marker.

The JNC VII identified a group of people that had pre-hypertension and used a cut point of 120/80. All right, it's arbitrary. We don't know what blood pressure is anyway, it varies every day and every hour in every patient, so to give a

specific number to identify a patient's blood pressure, we all know is fallacious.

But I have put in here a blood pressure, a systolic blood pressure from somewhere around 115 or 120 up to about 160 as a group of people that clearly incorporate people with a higher risk, probably because they have vascular disease, everyone within that group does not have vascular disease, but some do, and therefore, that is a group we could call "possible" disease.

Then, you get above that, and in our experience, if your systolic pressure is over 160 or 170, you almost inevitably have vascular disease, and we call that "likely" disease, and of course, that involves a smaller percentage of the population.

So, this is sort of a global simplistic view of how blood pressure relates to disease, not necessarily that it's the blood pressure, but that identifies the patient with risk.

Now, Steve has already shown this sort of data, which relates the fall in blood pressure in

response to therapy to cardiovascular disease mortality, and these are data published by Jon Staessen, and once again sort of suggesting that it is the blood pressure reduction which accounts for the benefit on outcome, and Steve has already provided an elegant review of that evidence.

Of course, the p value is highly significant, and that has led to this sort of view that systolic blood pressure reductions as little a 2 mm mercury reduced the risk of cardiovascular events by up to 10 percent. So, a 2 mm mercury decrease in blood pressure reduces the risk of ischemic heart disease mortality by 7 percent, stroke mortality by 10 percent, and this has led to the widespread recommendation get blood pressure down. That is your challenge, blood pressure reduction, monstrous benefit of 2 mm mercury.

JNC VII has said if we could just get the whole population's blood pressure down 2 mm mercury by changing diet, we would reduce the risk of events by umpteen number in our society.

The HOT study has been used as further

evidence for the benefit of intensive blood pressure reduction. The achieved diastolic blood pressure in the HOT study, the greater the achieved diastolic blood pressure, the fewer the number of MI's.

It was not a very highly significant outcome, but it has been used as further support for the greater the blood pressure reduction, the greater the reduction of events, and Steve has again reiterated that this morning.

I think there is an alternate hypothesis. That hypothesis is that the apparent linear relationship between the magnitude of drug-induced blood pressure fall and the reduction or morbid events does not necessarily indicate that blood pressure reduction prevents events, but that the drugs protect the arteries and heart while also lowering blood pressure.

All the drugs that we have used have had benefits, and as Steve has pointed out, it is hard to distinguish one drug from another in terms of benefit. Does that mean that it is the blood

pressure fall which accounts for the benefit?

It is sort of like the investigator who wanted to find out why people got drunk. So, he gave one group a Scotch and water, one group bourbon and water, and one group gin and water, and everybody got drunk, so we concluded that water was, in fact, the cause of the drunkenness.

Now, there is a corollary to this hypothesis, and that is, that the greater the blood pressure reduction from a drug, the less the vascular disease, that is, blood pressure fall identifies a low-risk population.

I believe that is a very powerful hypothesis, and it is very difficult to tease that out in the kinds of studies that we do looking at large-scale trials. We are looking at blood pressure as outcome, when, in fact, blood pressure reduction may be a manifestation of a low risk.

Building on what Steve MacMahon has already talked to us about, this is my simplistic, non-rigorous review of what we have learned from clinical trials about drug effects.

I think drug effects have to be looked at separately on what they do in the vasculature and what they do in the heart. These are antihypertensive drugs that I believe have been shown to slow disease progression in known doses, and it is striking that in the discussion so far today of class, we left doses out, and it is the dose of a drug which exerts the benefit that we measure, and to translate that into a class effect without having identified the dose of the individual drug, I think can be very misleading, and this is not a list that identifies class because these are individual drugs.

I think on the vasculature, we have pretty good evidence that ramipril and perindopril and maybe some other ACE inhibitors, and that amlodipine, that probably valsartan and losartan, and that hydrochlorothiazide all, in fact, slow progression of vascular disease, both pre-clinical and clinical data.

On the cardiac side, I think the data are more powerful because we have had a better way to

monitor the slowing of disease progression, and I think enalapril and captopril and carvedilol and metoprolol and bucindolol and valsartan and candesartan, spironolactone, eplerenone, and the combination of isosorbate dinitrite and hydralazine all slow progression of cardiac disease.

When we lump everything together, of course, we get kind of fruit salad, and we don't separate out what these drugs are doing to the vasculature and what they are doing to the heart.

Now, the old paradigm, the one that we have operated on for a long time, and probably still is, in fact, the model that the FDA relates to, is that blood pressure elevation is a disease and that treatment is aimed at reducing that blood pressure to normal.

We have on the--I don't know whether can see all this anyway, since it's hard to see the screen from the back--but whether you set the level here or you set it down here for where you call normal and what the target should be, the concept is if your blood pressure is high, you have

disease, treatment is aimed at lowering disease.

The same thing is true with cholesterol. If your cholesterol is high, I guess that is disease. The goal is to lower cholesterol below some arbitrary limit that we call normal, and the goal therefore of therapy is the target response.

I think this is over with, this concept is no longer tenable.

The current paradigm is one that I think has been widely now accepted, and that is, the disease, if it is present, needs to be treated, and we treat both the blood pressure and the cholesterol because there is disease, and the treatment is aimed, yes, probably still at the target response, that is, the reduction of blood pressure and the reduction of cholesterol, but we have complete changer our targets and, in fact, now I guess the lipidologists would say the target for lipid reduction is to an LDL of 70.

I mean we can just throw numbers around and say that is our target, and it has, frankly, confused the practicing physician community, and I

would suggest to you that one of the reasons why adherence to guidelines is so poor from blood pressure and cholesterol, is that we have confused the hell out of the doctor.

He or she doesn't quite know any longer what exactly to do, because we have a target response in which the blood pressure target or the cholesterol target is below the range that we consider normal, and they aren't exactly sure how to handle it.

Well, the cardiovascular continuum that we now are talking about a lot, that is, this progressive process of vascular and heart disease has a pathophysiology to it, and I don't want to burden you with this, but just place in your heads the idea that there are genetic determinants and there are environmental determinants, and these genetic and environmental factors obviously impact on the blood vessel and the heart, and that the vascular and cardiac disease we now know progresses by structural remodeling, and that remodeling process is a vicious circle in which the more the

remodeling, the worse the blood vessel and the heart disease, and the ultimate outcome of that remodeling process is coronary disease and cerebrovascular disease, heart failure, renal failure, peripheral vascular disease, dementia, all of the manifestations of progressive vascular disease.

We now know that there are a number of factors that seem to be involved in this progression - excess angiotensin, deficiency of nitric oxide, perhaps aldosterone, norepinephrine, cytokines, anti-oxidative stress. All of these play a role here, and we now have therapies which impact upon some of these putative mechanisms.

So, we are gaining some insight into this disease process in which we have to get beyond just simply looking at blood pressure as a target for therapy.

Now, to place this in a slightly different perspective, how do genes, ethnicity, diet, exercise, smoking, obesity, and lipids play their role?

They appear to have an effect initially on early endothelial dysfunction, which is predominantly manifested in the small arteries and may, in fact, lead to a raise in blood pressure, but not necessarily.

It may influence plasma norepinephrine level and angiotensin-II levels, but not necessarily, so you may see none of the usual overt manifestations of that endothelial dysfunction, but if left untreated, these same factors at the top begin to impact on arterial structural abnormalities, and as those structural abnormalities develop, you often get microalbumin in the urine, you get an increase in intermedial thickness of the large arteries like the carotid.

You get retinal vasculopathy which you can visualize. You get a reduction of large artery elasticity. Your blood pressure begins to go up dramatically during exercise, which we usually don't assess, and then your resting blood pressure may rise, too. It may stay within the normal limits, but it may rise from what it otherwise had

been.

As the disease progresses, you begin to get cardiac abnormalities in which the left ventricular mass goes up, there is a rise in BNP as a biomarker for left ventricular dysfunction, and you may get abnormalities in the electrocardiogram.

Well, somewhere along this sequence of events we begin to say ah, this is a disease that needs to be treated. Where you place the line in this sequence is somewhat arbitrary, but I have just put a line here and said this now is disease, and this needs to be treated.

What is the drug therapy for this disease? Well, it is multiple. It is perhaps inhibition of the renin-angiotensin-aldosterone system, and that can be discussed later on, because there is pros and cons whether that is a selective target.

There is certainly statin therapy, which we know is remarkably effective. There is nitric oxide-enhancing therapy, which we will be talking about tomorrow, which is another mechanism of slowing progression, antihypertensive drugs in

general, for sure, antioxidants, well, maybe, we haven't found the right one. Maybe anti-inflammatories, possible, and a host of other potential things which we have to pay attention to.

So, it's not just blood pressure, it is progressive disease.

Well, the American Society of Hypertension has embarked upon a new definition of hypertension. This is the initial product of this ASH Writing Group. This is the proposed new definition of hypertension:

Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated etiologies--I don't know what that means. Early markers of the syndrome are often present before blood pressure elevation is sustained, therefore, hypertension cannot be classified solely by discrete blood pressure thresholds.

Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys,

brain, vasculature and other organs and lead to premature morbidity and death.

Now, that is a very new definition. How do you come to grips with that?

Now, this Writing Group has also provided a new classification of hypertension which may undergo considerable revisions. This hasn't yet been published, but it is in review for publication.

What is says is, well, you are normal if your blood pressure is for the most part normal, maybe occasionally it goes up, but you have no identifiable cardiovascular disease. Your risk factors are few, early disease markers, that I will show you in a moment, are not present, and there is no target organ disease. You are normal. Good luck. Don't do anything.

Stage I hypertension by this new classification is a patient who has occasional or intermittent blood pressure elevations, but maybe won't even show them, or early cardiovascular disease, often risk factors are present, and

disease markers are present, and I will show you those in a moment.

Stage II hypertension, the blood pressure may well be elevated on occasions, but there is clear evidence of progressive cardiovascular disease, the markers are present, and often you have early target organ damage, and Stage II hypertension, everything has become abnormal including sustained blood pressure elevation.

What are these early markers for hypertensive vascular disease? Well, with blood pressure, in addition to resting blood pressure, there is an exaggerated blood pressure response to exercise, and there is often a widened pulse pressure indicating stiffening of the large artery.

On the vascular side, there is reduction of small artery elasticity and large artery elasticity. They get stiffer. There is endothelial dysfunction. There may be an increase in pulsewave velocity if you measure that. There is an increase in carotid intima-medial thickness. There is retinal vascular changes, which you can

photograph, and there is microalbuminuria.

From the cardiac standpoint, you get increased left ventricular wall thickness and mass, your B natriuretic peptide levels go up, there is an increase often in LV volume over time, and an abnormal electrocardiogram.

These are all markers for the structural disease that we believe tells you this patient needs treatment, and blood pressure is only a small part of it.

We have been practicing this for a number of years in our center, center called the Rasmussen Center for Cardiovascular Disease Prevention.

Everybody who comes through the center and here is what they get measured in one hour, in one room, all these tests are done. There is a vascular evaluation, the large artery and small artery elasticity is measured by pulse contour analysis, which is a simple device.

Blood pressure is measured at rest and 3 minutes on a treadmill at 5 mets exercise level, a remarkably sensitive measure for people who have

vascular disease, who didn't know their blood pressure was elevated, but who get on the treadmill and it rises. I will show you examples in a moment.

We get a digital photograph of the retina to look at the vasculature. We collect spot urine for microalbumin/creatinine ratio, and we do an ultrasound of the carotid artery for intimal-medial thickness.

We do an electrocardiogram. We do a cardiac ultrasound for left ventricular internal dimension and wall thickness in mass, and we take a blood sample for B-type naturated peptide.

We also make all these obligatory measurements of modifiable disease contributors, which can be targets for therapy, lipids, blood sugar, and homocysteine.

Now, what we do in this center is screen so-called healthy people, who don't know that they are sick, but are worried. Each of these tests, if I go back to these, each of these tests are given a score. If you are normal, the score is zero, if

you are borderline abnormal, you get 1, if you are abnormal, you get 2.

So, there are 10 tests. There are 7 here, and there are 3 here. So, if all 10 tests are abnormal, your score is 20. If all tests are normal, your score is zero. We think this is a marker for early disease.

Well, in the first about 1,000 patients that we have studied in the center, this is the distribution of scores in a so-called healthy Twin Cities population.

A third of them are very low risk, we think, because their scores are zero, 1, or 2, and think a zero, 1, or 2 exhibits pretty normal cardiovascular system.

Another third of them have what we consider modest risk, because their scores are 3, 4, and 5, which we think is already exhibiting enough disease to be somewhat concerned about, and we usually recommend lifestyle alterations in those patients.

About a third of the patients have

remarkably high risk that is for the most part unrecognized, because their scores, as you see, are above 6, and we think manifest considerable disease.

Let me show you 3 examples of why I think blood pressure is not the marker for disease. this was a 60-year-old registered nurse that we saw in our center. Her past history was entirely negative except she had been told her cholesterol was elevated. Both of her parents had smoked, she did not, but there was no significant family history of cardiovascular disease.

She was 5 feet 4 inches tall, she weighed 126 pounds. Her resting blood pressure is 132/66, and she is a nurse, so she checked her blood pressure periodically, it is always normal.

Screening results: Her large and small arteries are very stiff. Her exercise blood pressure when she got on the treadmill rose to 173, which is, in our hand, very abnormal. Her retinal photo showed A:V nicking, quite surprising. She had microalbumin. Here LV ultrasound showed an

increase in mass, and her Rasmussen score was 12 points. She needs treatment, blood pressure notwithstanding.

Her LDL was 187, her HDL was 70. We interpreted this as advanced disease, and we recommended treatment with antihypertensive drugs and statins.

Here is another example. This is a 62-year-old female florist, asymptomatic, plays tennis and golf. She has an elevated cholesterol and she was taking Atorvastatin 10 mg.

Family history: entirely negative.

Blood pressure 140/80. She is 5 feet 5, weighs 128 pounds, and she has got very stiff, small arteries, 1.2, which is remarkable stiff, means endothelial dysfunction. Her exercise blood pressure went to 182. Her retinal vasculature was abnormal. She had striking microalbuminuria. Her Rasmussen score is 90.

Her LDL is 137, her HDL is 129. I suspect that no primary care doctor is going to treat that cholesterol. They think she is protected by that

HDL. Her CRP is slightly elevated. She has advancing disease. We think she needs an ACE or an ARB blood pressure control, and we need to increase her Atorvastatin from 10 mg.

So, we have learned something here, I believe, from this.

Now, here is another example of a 49-year-old male executive, who was overweight. He has been told his blood pressure is elevated. He has no symptoms, is on no therapy. He has a family history of hypertension and coronary disease, so immediately your antennae go up.

He is 5 feet 8 inches tall, he weighs 240 pounds. his blood pressure is 144/84. Now, I think most physicians would probably say this man needs to be treated.

His screening is remarkably normal. His exercise blood pressure is only 154/74, despite his obesity and his resting blood pressure, which is borderline high. His Rasmussen score is only 2 points, and the only 2 points he gets is because of his blood pressure. No evidence of vascular

disease.

His LDL is 172 and his HDL is 38, which you might think would mandate therapy. His blood sugar is 108, so he is approaching metabolic syndrome, if you will, and yet he has no evidence of vascular disease.

Well, he needs diet and maybe he should be given a statin or maybe you would say why don't you come back in 5 years or 3 years or a year and let's see whether you are developing any vascular disease because there is really no obvious disease that this man needs to be treated for other than his high cholesterol, and high cholesterol is not the disease, it's only a potential risk factor that one could modify.

Well, then, what is the strategy to treat patients? How do you decide who to treat? Well, the goal of primary prevention is to treat everybody, and there is a Polypill in UK that Steve knows I guess well about, that says everybody over 55 should be treated with this mixture of drugs which will favorably affect outcome.

There is a problem here, it's impractical, it's inefficient, and we haven't tested the benefit-risk ratio of treating a whole population.

Primary prevention, which is more targeted, is aimed at risk factor identification and treatment targets the risk factor. Now, the patients I showed you are certainly examples where risk factor targeting would not have identified the disease or perhaps appropriately treated it.

Early secondary prevention, which I have emphasized, is to detect the markers for early disease and treat the disease, not the risk factor. Obviously, we need to identify the sensitivity and specificity of our markers, the benefit-risk ratio of treatment.

We have to demonstrate that we can prolong event-free survival and reduce healthcare costs, and this is a challenge I think for the next generation.

Late secondary prevention, which is now being practiced widely, is to take patients who already have symptomatic disease, they have had an

MI, they have had a stroke, and try to treat them aggressively to prevent subsequent events.

That seems to be effective, but, of course, it increases the burden of healthcare costs, because we are keeping people alive who have disease and who are expensive.

Well, how do we put all of this together? Well, I think the biomarkers that we use to identify risk, like cholesterol and maybe even blood pressure, and then intervene with primary prevention, maybe, in fact, be effective in preventing the structural and vascular abnormalities, but these markers don't identify necessarily the patients who need to be treated.

If we wait for non-fatal morbid events to occur to initiate treatment, a lot of people will already die and be lost from the system, and if we can identify the structural abnormalities and intervene with secondary prevention early, we can perhaps prevent progression and, of course, identify people who are likely to die before the event takes place.

So, who treat with antihypertensives? Pressure orientation, well, you can use pressure, and that has been the traditional view. Systolic pressure over 160, treat everybody. One greater than 140, most of the time treat it. Greater than 130, if you have vascular cardiac disease or diabetes, yeah, that is the guidelines.

Systolic pressure greater than 130 with evidence for vascular or cardiac functional structural abnormalities, that is still a question mark, but the goal in this pressure orientation has been to lower blood pressure.

I think we have reached the tipping point that no longer is an adequate approach.

What is the pathophysiologic orientation? Anyone with symptomatic atherosclerotic vascular or cardiac disease needs to be treated, blood pressure, cholesterol, everything.

I suggest that perhaps anyone with vascular or cardiac functional structural abnormalities and blood pressure over 120/80 may need to be treated.

What is the goal for treatment? The goal is slow disease progression, not targets.

In fact, what is therefore the future paradigm? Early disease treated, statins, RAAS blockade, antihypertensives, nitric oxide donor/enhancer, and other innovative therapies.

The goal, slow progression, the goal then is target dose, not target response. In fact, the success in treating heart failure in the last decade, and we have been very successful, is because we haven't confused the practitioner.

We have said here is the drug you give, here is the dose you give. We have fortunate up until now in that we did not have a target, we didn't have a blood pressure, we didn't have a cholesterol, we had no target for therapy, therefore, the drugs were developed for their dosing to slow progression of disease, and now you go out to the practicing community and say here is what you give rather than a target response, it is a target dose.

So, I hope I have stimulated you with some

new thoughts, new approaches to this complicated disease. It has become very simple in my mind, the challenge is to bring you along in the thought process that now I believe is going to be the 21st century paradigm, and I will stop here. Thanks.

[Applause.]

DR. NISSEN: In order to stay on time, we have about four minutes for questions. If anybody has any burning ones, let's ask them and then we are going to move on. Keep in mind we will have lots of opportunities. Jay, you are going to say with us today?

DR. COHN: Yes, I will be here.

DR. NISSEN: We can come back with questions to you a little bit later.

Bob, you wanted to ask something.

DR. TEMPLE: Well, it seems to me, Jay, that most of the information on risk factors is at least sometimes looked at for the influence of that risk factor with everything else held constant, so that for hypertension, you can show, and we just saw, for different age groups, that is one risk

factor, there is a benefit across all of those.

You could undoubtedly do the same thing for people at any given cholesterol level or name some other risk factors that you want.

Doesn't that suggest that the simple minded idea that lowering blood pressure is generally good, but will, of course, depend on the wide variety of other characteristics the person has to influence them?

Why do we need to change that view, which is sort of what you are advocating? I don't quite seek it.

Part of that question is my assumption is that when you encounter a blood pressure at the level you want to see treated, dose of drugs aside, you will get it down. You will keep adding drugs until you get it down, right? So, aren't you doing the same thing, the same mindless thing that everybody else is doing?

DR. COHN: Well, you are in part right, but I think incomplete. It is certainly true that at the moment, the drugs that seem to have had a

favorable effect have all reduced blood pressure, so is it wrong to use blood pressure as a marker for the response of drugs? No, I don't think it is wrong given the drugs that we use today.

I fully believe that we will have yet, in fact, statins which have a dramatic benefit on outcome do not lower blood pressure, and you can give a statin at any level of cholesterol, you don't have to have a high cholesterol to demonstrate the benefit of statin. It is true across the whole range of statin therapy, and it is also true across the whole range of blood pressures.

So, yes, if you are 136, and you drop blood pressure to 125, you do, in fact, apparently reduce the risk of progression of disease. Is it the blood pressure that fell to 125, or is it the drug that you have given, and if you view this continuum, and Steve has I think been the major proponent of looking at this blood pressure as a continuum all the way from low to high levels, then, I think you are correct.

The trouble is that physicians in general don't look at it as a continuum, they look at it as a threshold, and the threshold gets you into trouble because the fall seems to not matter where you start.

DR. TEMPLE: But one of the points Dr. MacMahon made is that it really doesn't matter what drug you use, everything from a diuretic, reserpine, calcium for most things, calcium channel blocker, something that works, the renin-angiotensin system, I mean they can't all have exactly the same effect on the vasculature, and we know they don't. Some work in the arteries, some work in the veins, and they all seem to have about the same effect.

The only constant is that is seems to relate on how much change of blood pressure.

DR. COHN: Well, because all these drugs that we have now been working on, and this is true of structural remodeling, all those factors that lead to structural remodeling also lead to blood pressure rise.

All the drugs that we currently have in our armamentarium, that slow structural remodeling also lower blood pressure. I fully believe that in the future, we will find drugs which influence the structural remodeling process without lowering blood pressure, and then we will be forced into a new paradigm.

Right this minute I think you are correct that there is, in fact, congruence between lowering blood pressure unless you get into drugs like statins, which, of course, have a very favorable effect without lowering blood pressure.

DR. TEMPLE: Right, but everything you look at shows that the effect of statins and the effect of blood pressure lowering behave independently. They both have the desired effect that you are talking about, but at constant cholesterol, blood pressure lowering is good. At constant blood pressure, cholesterol lowering is good. That screens independent functioning.

Undoubtedly, there are a bunch of things we are not smart enough to know about yet, family

history. Some of the cases you made, why is that first woman sick, or why is she well, or why is she sick, you can't tell. That just means there is probably some HDL fraction that Steve is going to pin down, that is more important than those other things we haven't been smart enough to figure them out yet, but that doesn't mean still, what you are sort of challenging is whether what have been thought of as independent risk factors, like blood pressure, really are independent risk factors.

I guess I didn't hear anything that says they are not even though they don't account for everything, which is undoubtedly true.

DR. COHN: I think you are correct in that from the operational standpoint, if we continue to focus on blood pressure, as long as we don't try to claim that that gives us insight into the process, we are okay, but the confusion to the practicing community is that we have set thresholds for treatment, and that, in fact, does get us into trouble, and the moment we eliminate the thresholds, we have to become a little more

sophisticated about what it is we are actually doing.

We are not lowering blood pressure to a target, we are using drugs which favorable affect progression, and, yes, by the way, when you use those drugs properly, the blood pressure will tend to fall.

DR. NISSEN: We are going to continue this debate, I think, after the talks, but I want to keep on time.

Michael, you didn't get a chance to ask a question the last round, so I am going to give you the final question here, and, Tom, we will come back to you later.

DR. PROSCHAN: Thank you.

In evaluating the merits of your argument, it seems to me that one thing you have to take into consideration is whether there is some physics reason that lowering blood pressure should reduce strokes, for example.

Is there the science that explains why lowering blood pressure would, from the physics

standpoint, would reduce stroke, for example?

DR. COHN: Well, of course, stroke and myocardial infarction and plaque rupture are pressure dependent. I think the fallacy that has confused physicians is this idea that a 1- to 2-mm mercury reduction has a profound benefit on outcome, because we all recognize how much blood pressure fluctuates.

You put a patient on a treadmill and their blood pressure, which may represent a very modest activity, represents probably what they are doing every day, most of the day, the blood pressure rise is quite dramatic.

Now, if you say you are going to reduce resting blood pressure by 2 mm mercury, and yet every day you are walking around, your pressure is going up by 30 or 40 mm of mercury, it is sort of strains credulity to know how the 2 mm of mercury reduces stroke rate, when you are walking, your pressures are 160 and 170, and that's normal.

So, I think it is the confusion about this tiny blood pressure effect and the magnitude of its

benefit which has confused doctors, which makes them unwilling to treat people who walk in their office and whose pressures are 150/80, and the patient says I have had a very bad morning, I have been stressed out, my boss yelled at me, and they write it off because they are focusing on the pressure.

If they recognize, if they can identify disease, then, it doesn't matter what their pressure is, they need to be treated. I think in the long run, it is going to help management strategies even if it doesn't necessarily alter the paradigm, which as Bob has pointed out, is still valid.

That is, blood pressure reduction, yes, that is a manifestation of a beneficial effect, but it isn't that small decrement in blood pressure which probably accounts for the benefit.

DR. NISSEN: We are going to have lots of time to talk about this. Rather than weigh in, I am going to pass the microphone to Henry Black, and, Henry, you are going to talk about when do we

initiate successive antihypertensive drugs.

When to Initiate Successive Antihypertensive Drugs

DR. BLACK: Thanks very much. I am really happy to be here. Jay and I have had many, many arguments about what he has had to say for many, many years, I think, and I won't go into it either.

I want to talk about when to initiate successive antihypertensive drug therapy, but I want to begin by reminding people that even before Norman was interested in blood pressure, there were others who were, and sometimes they got it wrong.

This is Paul Dudley White. I think you all know who he was. He was Eisenhower's cardiologist. He was one of the six people who founded the American Heart Association, and back in 1937, I guess when he was worrying about pathophysiology more than numbers, he said, "The treatment of hypertension itself is a difficult and almost hopeless task in the present state of knowledge, and in fact for aught we know...the hypertension may be an important compensation mechanism what we shouldn't tamper with, even if we

were certain that we could control it."

I think when you see what he had to work with, it is not a great surprise.

The drugs available or the methods to treat in 1930 weren't quite as good as what we have now. I don't really know what liver extract did. I know that lumbar sympathectomy was a somewhat aggressive therapy for what we were dealing with.

Watermelon extract, I am not sure how that worked, and I can't really figure out how mistletoe will lower blood pressure, it's much easier to figure out how it might raise it. I don't think radiation turned out to be a great idea either.

So, we have made a lot of progress over the years, and it is also good to review these a little bit.

In the 1940s, we had drugs that did lower blood pressure. They were effective all right, but they weren't terribly well tolerated, like ganglionic blockers. We had some drugs back then that we still use in some way or another, like reserpine, and like hydralazine.

The vasodilators or I should say the agents we only use as additional therapy are in purple. Then, in 1957, thiazides were introduced, and that really revolutionized things. We could now begin to think about treating people who weren't necessarily ill with a drug that was safe and effective.

We had to work on the dose, we had to work on what else to use, and then in the 1960s, we got central alpha agonists, like aldomet, we got nondihydropyridines, particularly verapamil, and we got the first beta blockers back at that point, and those are drugs that are in yellow that we still use as initial therapy under current recommendations.

In 1979, we saw captopril right after teprotide, alpha blockers that we may use as second or third drugs or may, in some situations, first drugs, and nondihydropyridines angiotensin receptor blockers, and somewhat later we got drugs that were focusing on systolic pressure. Whether we will ever see them, it is hard to know.

We also have been in the combination therapy business for a lot longer, fixed dose combination, that is. Back in the 1950s, we had a series of drugs. I would defy anyone here to admit that they had used them, but in the 1960s, a three-drug, fixed dose combination was the most popular agent at that time. That was Ser-Ap-Es. It had a syntachylytic and a diuretic.

We had aldomet and thiazides coming out together. They were followed very shortly thereafter by fixed dose combinations including a potassium-sparing diuretic, so the issue of that wasn't a question, beta blockers and thiazides, clonidine and thiazides, finally, ACE inhibitors and thiazides in the 1980s, one of which is still approved for first line therapy, but never really marketed much, and then we have got additions of ACE inhibitors and calcium antagonists. We have four so of those, low doses of beta blockers and thiazides, and so on.

So, the questions that I thought I was asked to address, I could really break down into

two, one of which I think is fairly straightforward, and one of which is a little more interesting as we think about what to do.

How and when should we titrate or add additional agents? When should we consider starting with more than one drug?

When to add additional agents, I think is a somewhat simpler question. Any schedule for dose is going to be arbitrary, and it is going to be based on the pharmacodynamics and the pharmacokinetics of the particular drugs that we are using.

We would generally recommend titrating somewhat slowly for people who are not having urgent or emergent complications, you know, 1- to 4-week period, once again depending on the drugs, and adding drugs to patients who are not at goal.

I am a strong believer in goals rather than targets or rather than something vague, because I think our problem with practicing physicians is we haven't given them a goal. We are pretty goal oriented. I will talk about that a

little later.

The speed with which this is undertaken really depends on the stage of blood pressure, which is an example of relative risk, Stage 3, 2, 1 doesn't take into account absolute risk. It is, in fact, looked at by the staging we had and the further stratification. So, that, in fact, determines what we do.

When we look at a few regimens, for example, and I am going to pick on ALLHAT and VALUE, because I am going to talk about those somewhat later, we talk about ALLHAT as a diuretic or calcium antagonist or an ACE inhibitor, or we talk about it as an alpha blocker if we realized that that was part of it, as well, but it was a lot more than that.

We titrate it up to what was considered full doses, took about 3 months, then, if we weren't at goals, we added a second drug and titrating that, and if we still weren't there, we added a third drug. So, this took about 8 to 10 months if you followed the protocol precisely as

written. Now, clinical judgment could always override that if you thought you needed it.

It's a little easier to see in the VALUE study, which both Steve and Tom and were on the DSMB which was an interesting experience for all of us, as I will show you.

People were mostly previously treated. This turns out to be an important issue. In fact, 92 percent had been on therapy. Here, the schedule was rather aggressive.

It began with what was considered the starting dose per package insert of amlodipine at 5 or valsartan at 80, and then in a month, if you weren't at goal, you doubled the dose, and then you added a diuretic to both arms, and then you increased the diuretic dose, and then you could add other things until you reach drugs, and could keep on going.

So, this took about 6 months to get where you wanted to go beginning in a fairly stepwise fashion as recommended by most committees.

So, I think the question I want to address

is when we should start with more than one drug.

In addition to being a trialist, I am also a guideline writer, which to some degree I am very proud of, and to some degree I have to defend myself from everybody as we go along.

I had a role in JNC VI and JNC VII and I want to point out a couple of things. We did coin the term "goal." We coined it because prior to that, we said "control," and we said goals because goals are something that even though they are sort of silly, the dichotomists, you know, 139 is really not that different on an individual patient level from 141, but we wanted to give our practitioners something that they could shoot for.

Michael Jordan's goal I think was to hit every shot, he wasn't planning to ever miss. He didn't get there. Ted Williams wanted to get a hit every time. The best he could ever do was about 40 percent, but that doesn't mean he didn't have that goal.

If you set the goals too high, nobody gets there, so that is not going to be any good, and if

you set them too low, you get a false sense of security that you are doing something. So, we very clearly set that out to not confuse practitioners.

We thought control was confusing, something vague was confusing. Sure, you are not going to get there every time, but that was the idea.

This algorithm appears to say that you start with one drug and then you add, substitute or add, but, in fact, we had learned some things before we actually did that.

This is Barry Materson's work from the VA study, a very modest goal, below 95 at a year, and it was clear that whether you used a calcium antagonist, in this case, diltiazem, or pravacin [ph], or beta blockers or diuretics, whatever it was, you weren't going to have the majority of the people in that study selected, getting their medicines for nothing at goal at a year very often.

So, in fact, we snuck in--no one really has seen this--low dose combinations may be appropriate. This is very different from starting

with one and stepping up, but it is in there, so we could introduce people to this concept later on.

Now, in the interim between JNC VI and JNC VII, much more data became available as to the lack of getting to goals or getting controlled or whatever you want to call it with a single agent, and as has been pointed out by Steve before, no regimen, no trial is about one drug, no long-term trial anyway.

So, George Bakris and Barry Brenner and Ed Louis, and others, have shown that in order to get to goals, you needed multiple drugs, whether they be renal goals or blood pressure goals or diabetes goals, you are not going to get there with one agent.

The HOT study, which you have heard about earlier, has some other facets that I think are worth discussing. This was about 19,000 volunteers, about 6,000 of whom were already on treatment when they enrolled. That is the group I want to look at.

Sixty percent of those on treatment were

on one drug, 40 percent were on more than one drug. This isn't necessarily fixed dose combinations. This was a regimen where you started with a calcium antagonist at its first dose, then, you added an ACE inhibitor or beta blocker as the second dose, and then you went to the full dose of the calcium antagonist, then, the full dose of the second drug, and then finally to the diuretic. It wasn't what we usually do, but it is instructive.

So, the people who entered this study had diastolic goals, and by being more aggressive, they went from 161/98 to 142/83, and if they had the less than 80 goal, which was the most aggressive, too bad this wasn't a systolic study, but that is another story, they got to 140/81, and now three-quarters required more than one drug.

It took about 3 months for all of that group to get under that diastolic of 90 on average, I am talking about average. It is rather similar for systolic pressures although they are higher.

There was a benefit in the highest risk group, the group with the most absolute risk, 1,501

diabetics. In the diabetics, there was a clear reduction as you were more aggressive, the high-risk group, the higher absolute risk group for sure.

In PROGRESS, the study that Steve did, there are some other aspects of PROGRESS that I think are very important for us to understand. There were 6,105 people in this. They all had had strokes before. The physicians were given their choice of starting with a single agent, in this case, perindopril and ACE inhibitor, or two drugs, either perindopril plus indapamide, or once again compared to placebo.

So, one would assume that the people who were at highest risk got the two drugs. I guess that is why those choices were made. For strokes, all of the benefit, and there was benefit of 38 percent was in the people who got both drugs.

People who got a single drug with a fairly dramatic lowering of blood pressure didn't have any protection against a second stroke, nor did they have protection against major vascular events,

which included MI.

So, here is an example of even though blood pressure went down with an ACE inhibitor, it didn't prevent either strokes or MI's or vascular events, a fairly dramatic reduction, as Steve showed you earlier, in the non-hypertensives, as well as the hypertensives using our conventional definitions.

Now, ALLHAT, of course, is the elephant in the room. It's the largest study. You are all I am sure familiar with it and have talked about it a lot. I want to talk about some other aspects of ALLHAT, then, it's final answer.

First of all, let's look at the blood pressure distribution. ALLHAT, as I said, had a similar protocol where you stepped up within 3 drugs, 3 dose titrations of each. It took about 8 to 10 months to get there.

At baseline, a 31 percent less than 140, 14 percent were even greater than 160. Overall, 27 percent of this group was at under 140/90. That is in orange. So, here was the distribution of blood

pressures.

At 3 years, it was a dramatic reduction as you see in blue. This is systolic, the diastolics are the same. To do that, you needed to use more and more drugs, beginning with 27 percent, under 140 and under 90, ending with 66 percent under 140 and under 90, and there was a progressive increase in the number of drugs used.

Diastolic pressure was not difficult, 92 percent reached it, and, in fact, two-thirds of the people reached systolic goals. So, I think those goals are quite reasonable. If you had 100 percent of goal, that would be much too low. If nobody was at goal, that was much too hard, and we do the same thing.

In our clinic, we did the same thing in CONVINCE and pretty much the same in VALUE and LIFE, as well.

I want to look at some other aspects of ALLHAT to talk about another factor. There was I think as you all are aware, a 10 percent increase in combined cardiovascular disease events, and that

includes heart failure and stroke, in the group that was initially begun on the ACE inhibitor lisinopril compared to chlorthalidone, but I want you to see where this began.

We are talking about huge sample sizes now, or huge cohorts. This is especially clear for stroke. In that first 6 months, very early on, when the titration is still going on, there is a separation for stroke that continues throughout, a 15 percent increase overall, and it is primarily in African-Americans, a prespecified hypothesis, where, in fact, as I will show you, blood pressure was not lowered nearly as well at the beginning, 40 percent increase.

No one would argue that that was important. You didn't see anything at all with amlodipine compared to chlorthalidone, and, in fact, there was no evidence at this point of any protection in diabetics when you are looking at strokes, things we have seen from Steve.

Now, what was different during those first 6 months or first year? Let's focus on where that

arrow is. All of the initial systolics and diastolics are about the same, but the drop with chlorthalidone over those first few months was substantially better or greater than the drop seen with amlodipine, in turquoise, or the drop seen with lisinopril, in orange.

This was particularly the case in African-Americans where the stroke risk was higher. These things evened out later on as the additional drugs were being added.

So, we guideline writers were aware of this, and we are not embarrassed to say goal, we think that was a good idea, because we think people can follow that, so we did talk about two drug combinations as initial therapy, understanding that there wasn't real evidence that this was better, understanding that this group hasn't blested as yet, but sometimes we feel we have to do what we have to do.

So, two drug combinations were recommended for anybody who was 20/10 over goal when we started the treatment, because it was very unlikely we are

going to get where we want to be with a single agent.

We also said it was a possibility that you could do this, as well. We took the most time I think in all of our deliberations was how to say this. Should we recommend diuretics for everybody or unless contraindicated, the way ALLHAT said? Well, no, because we didn't study anybody under 55.

Should we say the majority? Well, that would have been interpreted as 50.1 percent, and that is really not what we meant either. Should we say the overwhelming majority? That would have meant 99 percent. We didn't mean that either.

So, we took that very precise word "most," which I am sure everybody knows exactly what that means, and for compelling indications, as well, once again focusing on goals, optimizing doses, adding additional drugs, and not talking at all about sequential monotherapy any longer.

Now, this has been I think confirmed from another source, namely, the VALUE study, which is, as I say, the three of us were very intimate with

and had some fun discussions over time.

If you look at strokes again, between the two drugs, at the end of the study, they weren't quite significant, but every other data point along the way, they were, especially right at that beginning. In fact, if you look at the first three months, there was about a 4 mm difference in systolic pressure and a highly significant increase in risk, no arguments about this.

Why didn't we stop the study? Well, by the time we knew this, everybody was down here, and the curves were pretty much parallel as you went along.

What was different then? Well, the same thing that was different in ALLHAT. About a 4- or 4-mm difference during that first three months in high-risk people that we felt was important, and this became balanced out as additional drugs were added.

Now, in a somewhat unusual attempt to try to understand this better, the VALUE investigators who didn't like the overall answer went ahead and

drilled down into the data in a non-randomized admitted fashion to look at how fast people responded.

They defined "immediate responders" as untreated people, and that was only about 8 percent who had a 10-mm drop in systolic during the first month, and people who were previously treated who had a drop in blood pressure, and everybody else was a non-responder.

What they found, immediate responders did better than non-responders. It is not a real big surprise, but that first month is a bit of a surprise. If they looked at 6 months, as well, pooled the treatment groups, didn't matter what drug you got, if you were at goal you did better than if you weren't at goal.

It seemed sort of obvious, but that was very interesting, and it didn't matter here which regimen you used, whether it was calcium antagonist regimen first, or the ARB regimen first, getting people to goal in a fairly rapid fashion prevented cardiac events, strokes, mortality, and heart

failure hospitalizations, as well, for both drugs.

ASCOT also says the same thing, and I have to borrow slides, because this isn't published, and borrow presentations, but I think there is some of the same idea.

So, they were looking at non-fatal and fatal MI, comparing two regimens, one that began with a beta blocker to which a diuretic was added, one that began with calcium antagonist to which an ACE inhibitor was added.

At the end of three years, 27 percent were on a single drug, most people were on more than one drug, and here, too, this study was stopped early even though the primary endpoint wasn't reached. In every case, the combination therapy with a calcium antagonist and ACE inhibitor did better than atenolol plus a diuretic.

What they have said in their presentation, but I haven't seen this and maybe others have, is that there were early differences in blood pressure between the two groups. I am guessing, maybe someone has seen this data since, and there were

modest differences, but very comparable to what was seen in HOPE and what was seen in ALLHAT and what was seen in VALUE.

So, to close, I am going to show you slides you have seen already, so that makes it a little easier for me.

This impacts the small differences in blood pressure, and we are not talking about a patient here, we are talking about a population. So, 2 mm times 250 million people is a lot of millimeters. I am sure a doctor can't tell a difference, but to us who, in my view, translational biology or translational research is not going from the lab to the bedside, but from the patient to the population, and we have got to make that work, and a very large increase in stroke mortality.

It has always kind of amused that we, in the hypertension business, apologized about 15 years ago for only preventing strokes, not doing as well for coronary disease. Now, I have yet to meet a person who, if you knew you were going to have

one or the other, and were going to survive, would prefer to have a stroke. We should not have apologized for that.

On meta-regression shows the same thing, small differences in systolic pressure, large differences in outcomes using all the trial data you see, and then Steve's really outstanding work from the Trialist Group showing the same thing, drops in stroke, modest differences to a physician, big differences to a population scientist, big differences in outcomes.

So, I think if we are looking at a single overriding communications objective for JNC VI, you know, what you say on CNN with the 8 seconds you have, it was go for goal and don't settle for less.

I think in JNC VII, it's not beyond blood pressure, it is the blood pressure.

I think if we ever have a JNC VIII or whatever it looks like, it may also be not only that it's the blood pressure, but, in fact, how fast you get there.

Thank you.

[Applause.]

DR. NISSEN: Now, we are beyond our break, but we are going to lose Henry, so I thought maybe we ought to have a few questions before he goes. Does anybody want to ask anything of Henry? Jonathan, thank you.

DR. BLACK: I have got at least an hour.

DR. SACKNER-BERNSTEIN: I think it won't take that long. I am hoping you might be able to clarify something about the ALLHAT operations that may make it easier certainly for me to understand how to apply a lot of the data that has come out because I haven't been able to figure this out from the publications.

I know that patients were enrolled in ALLHAT if they were treated with antihypertensives in advance, and it appears, including from some of the bibliographic references we have been given by the agency, that the use of diuretics was a common background therapy.

I am having difficulty understanding how to interpret the effect on blood pressure and the

effect on clinical outcomes when you are starting out with a large proportion of the patients who are on a diuretic and apparently went through a step-down phase or withdrawal phase according to the way the protocol is written as posted on the internet through the NIH.

So, I am trying to understand were patients withdrawn from their diuretics before they entered, how many of the patient who were on diuretics to start with prior to entry ended up staying on diuretics, is this a partially withdrawal study, and have the data been looked at for those subsets of patients?

DR. BLACK: The easiest thing is it was not a withdrawal study, it was, in fact, a switch study with the exception of the people on beta blockers who we felt it wasn't safe to just stop, and they were tapered.

VALUE was the same thing. LIFE was not, LIFE, there was a withdrawal of a month, and a substantial number of people, maybe as many as 10 percent, never got in the trial, because their

blood pressure was either too high or too low, but ALLHAT was a switch study at randomization.

How many were on diuretics, I am not exactly sure. We had 35 percent African-Americans, presumably of the treated ones, and that was 90 percent. Many were on diuretics, but I am not certain that that data has been looked at yet or is fully analyzable.

The dose isn't necessarily known, which diuretic was this isn't necessarily known, what else they had isn't necessarily known. We wanted people to be on no more than two drugs when they entered, because we wanted them hopefully controllable with one drug at the same level the blood pressure.

DR. SACKNER-BERNSTEIN: So, just to play the role of the skeptic along those lines, I know all that has been discussed by the agency previously, and a lot certainly in the literature, but perhaps then we would be potentially drawing many conclusions from a secondary endpoint, which in part was addressed as a question of what is the

influence of continuing someone on a diuretic versus giving them another agent when the overall primary endpoint wasn't positive.

I find that it is very difficult to understand how to interpret it when data such as these with background therapies still aren't published in the literature.

DR. BLACK: The primary endpoint, I think if I understand where you are coming from, the primary endpoint was designed to show that the other drugs were better, not that they were equivalent.

DR. SACKNER-BERNSTEIN: Right, for coronary risk, though.

DR. BLACK: For coronary risk first because of the issue that Bob brought up, and I mentioned as well, we didn't think we did as well at preventing coronary disease as we did for stroke, because most of our studies had diuretics in them and we had to see whether that was the case.

So, we were powered and planned to show

that with the comparison of chlorthalidone, which was the SHEP drug, that calcium antagonists were better for coronary disease prevention, or that ACE inhibitors were better, or that alpha blockers were better.

Now, they weren't better, so we, in fact, demonstrated the primary endpoint as being true, but in opposite direction from what it was planned to be, or what some people thought it would be.

DR. NISSEN: Tom, you wanted to say something?

DR. PICKERING: I have on quick question. Your colleague, Bill Elliott, has tried to make the case that chlorthalidone and hydrochlorothiazide are not interchangeable. Would you like to comment on that?

DR. BLACK: Well, I agree, but exactly how to dose substitute them is very hard to tell. We just, in fact, just this week, a little study we did in our clinic, we took a series of patients who were not at goal on a full dose of hydrochlorothiazide, up to 25 mg is our definition

of a full dose, and switched them to chlorthalidone at the same dose, got an additional 10/5 mm drop.

Now, there has been really nothing done, to my knowledge, since the early or late '70s really comparing these two drugs with respect to their blood pressure lowering effects or maybe other effects on some of the things Jay brought up, that could well be different, so we really don't know exactly how much to use or whether there are pleotrophic effects that these drugs have that are wildly different. It is just that there is nothing around with chlorthalidone other than in NHLBI studies.

DR. NISSEN: Bill.

DR. HIATT: It's attractive to think that some of these differences in drug classes may be due to their absolute benefit as single agents on controlled blood pressure, and then as you add more agents, blood pressure becomes better controlled, and the group differences start to come together, correct?

DR. BLACK: Yes.

DR. HIATT: My question is there is a different paradigm where that may be true, that is, in an acute thrombotic event, the rapidity with which you resolve that matters, but in a situation where your absolute risk at any given day or an event is extremely low for most of these populations.

Why would another month or two at an absolute risk of 0.00-something, low, low, low risk, on any given day, matter to the rapidity with which you control blood pressure over a very long interval?

DR. BLACK: We have a difficult task, I think, in treating for the most part healthy people to prevent an event that may never happen and to figure out the best way to do it, so we have to extrapolate from all the studies we have, many of whom have not been done on the people we want to prevent their vasculature from getting abnormal, and try to figure out the best way to do that.

Here, I think it comes to harm. If you are going to take someone who is Stage 2, as we

called it, or who is a higher risk individual based on comorbidity, and lower their blood pressure not rapidly, but more quickly than we used to, so within 3 to 6 months, say, are we going to hurt them.

I think the harm question is really what I am more interested in. If I could set a goal really for interhypertensive therapy, it would be to the lowest blood pressure that you can sustain when you can mentate and urinate. That is probably where our blood pressure ought to be.

That is very hard to do as you would be adding more and more drugs, and more and more elastone modifications to get there. That is unreasonable, but there is a big difference between nifedipine gets for rapidity and something that you get to go within 3 to 6 months.

DR. HIATT: That is kind of it, but not exactly. I mean sure, the calcium channel blocker is more effective, more quickly, and you are using that, and you are looking at these early time points as explaining late event risk, and that the

group differences were explained more by not so much the drug class, but the rapidity with which control--

DR. BLACK: No, in fact, the drug class that was most rapidly effective was chlorthalidone, and compared to valsartan, at probably two low doses, it was the calcium antagonist. There was no diuretic arm in VALUE. It would be nice if there had been.

DR. NISSEN: Bill, let me see if I can answer your's and Jonathan's question. I think there may be several hazards that are overlapping. One is the hazard, the instantaneous effect of what your blood pressure is, and the other is the effect of lowering blood pressure on the progression of vascular disease over time.

So, what you are seeing is the intersection of the instantaneous effects with the effects on the progression of the underlying disease, and at any given point in time, there may be some blending of that.

To answer Jonathan's question, you know,

many people have thought that it is very difficult to interpret ALLHAT because of the heart failure data, because you take people who are on diuretics, you pull them off diuretics and put them on another class, are you then going to unmask heart failure because of the switch?

So, this is what makes it very, very confounded and very difficult to handle.

Bob.

DR. TEMPLE: I don't think Henry was showing you the late effects of earlier control at all. What he is showing you is that a difference emerges early, and then persists. These curves are not diverging. He is not showing that at all, but there is over any given 3, 6, or whatever month period, a certain risk of stroke, and that is what he is showing there, and it separates early because you are not controlling as well early, and then it stays constant or moves closer together.

So, it is not at all really that you pay a price later for this event. You pay a price early while the blood pressure is up.

DR. BLACK: It's in that monotherapy phase when blood pressure is not controlled that you see this excess risk that, in fact, does come together. That is why we were able to let value go on because the damage, if there was any, was over by the time we had a chance to do this.

Steve, as far as the heart failure data from ALLHAT, those curves are absolutely superimposable until 3 years, and then they begin to diverge. That is not the case with doxazosin, that is much earlier, so the calcium antagonist, ACE inhibitor, and diuretic are inseparable until about three years, long past the time this happens.

DR. NISSEN: Norman.

DR. STOCKBRIDGE: One of the problems I have in trying to think about translating the controlled clinical trials into advice about goals and instructions for use, is that in the trials, you measure the blood pressure multiple times on a single visit, the visits are all, you know, there are instructions about resting people in advance of the measurements, and so forth, and then you are

making measurements over a several week period before you sort of make decisions about where you are going.

I don't have the impression that's the way people practice medicine, and it is part of the reason why it makes me nervous to think about people who see patients much less frequently than the titration interval in trials, and then making decisions based on the goals that are proposed.

Do you have comments about that?

DR. BLACK: I agree, and it reminds me, and I have a slide of this which I didn't bring, of what Winston Churchill said about democracy. He said, "It's a terrible system, but it's the best we have so far," and I think in some ways when we decide how to advise people, and I think that is really our responsibility.

We have to use trials which aren't like real life, they don't enroll people who are the same necessarily as you see. We don't evaluate them or measure things is the same as we see, but I think it's the best way as flawed as they are until

we think of a better way.

One of the reasons I didn't mind showing the VALUE data, which is non-randomized to ASSURE, is I think it does give us some insight, and we shouldn't ignore it just because it wasn't necessarily part of what we do.

DR. PROSCHAN: One thing about the fact that congestive heart failure was a secondary outcome in ALLHAT, the fact that it came out so significant, so an issue is multiplicity, but even if you multiple that p value by the mass of the earth, which is 6-6 trillion tons, it still comes out significant, so I think the fact that it was a secondary outcome, the multiplicity issue there is not of real concern.

As far as the masking, several analyses were done to suggest that that is not really a big problem in ALLHAT. One thing they did was they compared baseline characteristics of the patients who had been diagnosed with CHF in different arms, and if there were this masking issue, you would expect there to be a difference in those baseline

characteristics, and that was not, in fact, seen.

Also, if you look at the case fatality rate, it was very high among those people who were diagnosed with CHF, and it was similar in the different arms. So, I think there were analyses done that showed that that is not as big an issue as people seem to think.

DR. BLACK: If I could comment on that, as well, we were certainly disturbed by that answer. It was sort of assumed that ACE inhibitors would be good in this case, but as Bob pointed out, there were virtually no trials since maybe SOLVE, where your diuretics were not part of what you did, or they were always there.

So, I think what we went through, which were analyses by two different groups plus a lot of things that Mike talked about to show that these really were heart failure cases, it wasn't just edema, probably is what everybody should do in the future when they analyze their heart failure cases.

It's a touch endpoint to sometimes be sure about.

DR. NISSEN: I would like to get a break in here now, so how about is we take no more than 15 minutes, get back here promptly. We are running a little bit late. I knew we would, but we are not as late as we could have been, so we are going to be okay.

[Break.]

DR. NISSEN: We are getting close to a quorum here and even if we are not, we are going to move on. We are missing Blase, we have Bob. Okay.

Next on the agenda, we have a presentation from two representatives from Pfizer. First up is Dr. Lance Berman, so, Lance, you have the floor.

Can One Evaluate an Outcomes Claim Based on an Active Controlled Study?

Introduction

DR. BERMAN: Good morning, Dr. Nissen, members of the Advisory Panel, Dr. Temple, Dr. Stockbridge, members of the FDA, members of the public.

The purpose of the presentation today by Pfizer is to address the question you can see on

the screen, can one evaluate an outcomes claim based on an active controlled trial.

My name is Lance Berman and I am part of the Cardiovascular team at Pfizer. I am a medical director and team leader in the Cardiovascular Division, and with me is Dr. Michael Gaffney. He is a senior director in the Statistical Research and Consulting Group at Pfizer.

The purpose of the presentation, as I said, is to address the question of using active controlled trial data to address labeling claims for hypertensives. The basis of our presentation this morning really comes down to the ALLHAT trial and how can use a non-inferiority analysis to access the data to support a claim.

So, what I will do for about five or six minutes is give you an introduction of why we chose the ALLHAT trial and how we set up the methodology that we use for the non-inferiority analysis, and then I will hand it over to Dr. Gaffney, who will spend about 15 minutes or so walking through the analysis in a lot more detail and showing you step

by step the rationale for each process and the outcomes that we generated.

The background really in choosing ALLHAT began with the understanding that numerous clinical trials have proven that lowering blood pressure reduces the complications of hypertension, but it is also well recognized that conducting placebo-controlled trials in hypertensive patients is no longer ethical.

Therefore, the effectiveness of antihypertensive treatments in increasing cardiovascular mortality and morbidity must be determined by comparisons from all the therapies that have shown to reduce cardiovascular risk in placebo-controlled trials.

Until recently, however, there was very little information available to document cardiovascular risk reduction with amlodipine specifically in hypertensive patients. Then, in 2002, the results of the ALLHAT trial were published, providing the first substantial evidence of amlodipine's cardiovascular effects in the

treatment of hypertension.

So, using this non-inferiority analysis, which you will hear about more in a few minutes, Pfizer submitted a supplemental NDA for the inclusion of these results in the amlodipine label.

So, in the context of class labeling, and as part of the discussion around how we use outcomes data to support class labeling claims, we were invited today by the FDA to present this methodology as an illustrative example of how an active controlled trial what showed no superiority might be used to support an outcomes claim.

So, briefly, I will give you just a quick overview of ALLHAT. You have already heard some information from Dr. Black this morning, and I am sure many of you are familiar with the trial.

It was run predominantly by the National Heart, Lung, and Blood Institute, and it was designed to determine if the newer antihypertensive agents, in this case, amlodipine, lisinopril, and doxazosin were superior to the first-line agents, the diuretic chlorthalidone.

It was begun in 1994 and it was the first major trial to assess the long-term cardiovascular effects of amlodipine, as I mentioned earlier, in a very large hypertensive population.

Now, since its publication, the study has enjoyed a lot of press and coverage in medical journals, some lauding its strengths and some asking questions about some of the study limitations, but I think the comment needs to be made that overall, this is a very, very important trial that has been viewed by many to provide an example of the type of trial that needs to be used to determine the differences between risk-benefit ratios in agents and perhaps other therapeutic classes.

So, a trial like this certainly has its merits in terms of looking at risk-benefit ratios for different products.

Just a brief summary again of ALLHAT, it enrolled a diverse population of patients specifically looking to enroll patients who were susceptible to cardiovascular disease, morbidity,

and mortality because of their high burden of hypertension, so it had lots of black patients, women, elderly, and diabetics.

A very large number of patients were enrolled, just under 42,500 patients with a minimum age of 55 years. The patients had to have mild-to-moderate hypertension and at least one additional risk factor, and they were followed up for just under 5 years.

They were randomized to either amlodipine, lisinopril, doxazosin, or chlorthalidone, and used a step approach to get to blood pressure goal of less than 140/90. The primary endpoint was a composite of CHD death and non-fatal MI, and as you all know, the results showed no superiority amlodipine over chlorthalidone for this primary result.

So, the conclusion that we drew from ALLHAT was that it showed that the long-term based therapy with amlodipine had no superiority over chlorthalidone-based therapy with respect to cardiovascular outcomes.

Now, what I am going to do is walk you through a schematic overview of the type of approach that we took to showing non-inferiority and some of the things that we, in discussions with the FDA, decided were important to do along the way to support the overall non-inferiority analysis.

Since ALLHAT was an active trial and did not have a placebo group, direct assessment of the reduction of CV events was not possible for any of the treatment groups. Strictly speaking, the results must therefore be interpreted as showing that amlodipine-based therapy, as I said earlier, was not superior to chlorthalidone-based treatment, but because superiority was not demonstrated, what we then did was use a post-hoc analysis to show that amlodipine-based treatment was not inferior to chlorthalidone-based treatment. So, schematically, let me walk you through this approach.

In order to assess whether the new treatment, in this case amlodipine, is not inferior to the standard treatment, in this case chlorthalidone, the effect of chlorthalidone

relative to placebo must first be decided to be consistent and reproducible.

Next, using these results, taking the effects of chlorthalidone comparable to placebo, we then have to impute that into ALLHAT to show that the new treatment amlodipine preserves a substantial portion of chlorthalidone's effect.

Then, in addition to or parallel to the step, if you like, what we also have to show are the effects of amlodipine relative to placebo, and we do this by estimating indirectly by taking the effects of chlorthalidone versus placebo from this analysis, as well as the effects of amlodipine relative to chlorthalidone in the ALLHAT trial.

The point that I want to end off here is that together, these two steps provide the confidence that the study in question, the ALLHAT trial, provides the true benefit with the treatment with amlodipine.

So, I am going to hand it over now to Dr. Gaffney, and Dr. Gaffney will walk us through each of these steps in more detail, showing us rationale

and then outcomes that eventually lead to the finding for amlodipine.

Methodology and Analysis (Overview)

DR. GAFFNEY: Good morning. As Dr. Berman has indicated in a formal way before we can show the benefit of amlodipine in the ALLHAT trial, we have to first quantify the benefit of chlorthalidone.

There was one trial, as has been pointed out, the SHEP trial, which was a direct comparison of chlorthalidone-based treatment with a placebo-controlled treatment group. This trial was conducted in a population of isolated systolic hypertensive patients, and the chlorthalidone-based treatment was shown to reduce the risks of fatal coronary events and non-fatal MI and stroke.

We augmented the findings of the SHEP trial by conducting a meta-analysis. The intention of the meta-analysis was to identify all randomized placebo-controlled hypertension studies that used low-dose diuretics to evaluate CV risk reduction.

The trials that were included in the

meta-analysis are shown here. There is the SHEP trial, which I referred to. That, as you know, was preceded by a SHEP pilot trial, which we are using as a separate trial in this analysis, and two other studies were applicable, the Medical Research Council Study in Older Patients, and the European Working Party High Blood Pressure in the Elderly study.

I won't go into the details of this trial other than to point out that these last two trials listed here used low-dose diuretic regimens which were different from chlorthalidone, which was used in the SHEP trials.

Secondly, the populations were all older hypertensive patients, but they were somewhat different in the entrance criteria.

I also want to point out that these are the same four trials that were used by Dr. Bruce Psaty to characterize the benefit of low-dose diuretic therapy in his meta-analysis which was published in JAMA in 1997, so we haven't reinvented the wheel, we just made sure that no additional

trials have come forward since then.

The results of the meta-analysis for the primary endpoint that was used in ALLHAT are shown here, that is, CHD death and non-fatal MI. On the right side of the slide are presented for each of the treatment groups, the number of patients that were enrolled in that treatment group, the number of patients with the primary event, and the percent of patients with the event.

On the left side is given the relative risk of chlorthalidone or low dose diuretic to placebo along with the 95 confidence interval. You can see they are all on the left side of 1 showing a consistent benefit for low-dose diuretic therapy.

The combined relative risk overall for trials yielded a value of approximately 0.72, 28 percent reduction, with a confidence interval where the 95 percent upper confidence bound was 0.85.

In our calculations, I will use both the point estimate of 0.72 to estimate the benefit of chlorthalidone in ALLHAT, as well as the upper confidence bound of 0.85.

The use of the 0.85 is a way to incorporate the variability around the point estimate of 0.72 in the calculations.

Having characterized now or quantified the benefit of low-dose diuretic therapy, I will now extrapolate that and look at how much of that benefit is preserved in the ALLHAT trial by the amlodipine therapy.

This is a quick summary of the primary results for the chlorthalidone treatment group and the amlodipine treatment group in ALLHAT. Again, it's the fatal events and non-fatal MI, which is the primary event.

There were 1,362 events in the chlorthalidone group or approximately 8.9 percent. The amlodipine group had 798 event or approximately 8.8 percent. The relative risk of amlodipine to chlorthalidone was very close to 1, 0.98. The one-sided 97.5 upper confidence limit of this relative risk was 1.07.

I want to point out the tight confidence bound, which is based on the very large number of

events that were observed in the ALLHAT trial.

Now, if this were a pre-planned non-inferiority analysis, it would be this value, the one-sided upper confidence limit of 1.07 which would have to be below a predefined non-inferiority margin in order for one to claim non-inferiority.

So, in the calculations of the percent of the chlorthalidone effect preserved, I will be using this value of 1.07.

The bottom half of the slide now just gives the calculations. Again, if the benefit of chlorthalidone to placebo is estimated by the point estimate that came from the meta-analysis, which was 0.72, then, the imputed placebo relative risk in the ALLHAT trial is simply the inverse of that or 1.39.

So, that would imply that had there had been a placebo used in the ALLHAT trial, there would have been a 39 percent higher event rate for the primary event in that group relative to the chlorthalidone group. As we see the upper 97.5 confidence bound for the amlodipine to

chlorthalidone relative risk, is about 7 percent, so a straightforward calculation using the 7 percent and the 39 percent yields a value of about 82 percent of the effect of low-dose chlorthalidone that is preserved by amlodipine in the ALLHAT trial.

Now, the 0.72 again is a point estimate and has some variability associated with it, so if we incorporate that into it by using the upper confidence limit that comes from the meta-analysis to estimate the benefit of chlorthalidone in ALLHAT, we would then impute an 18 percent higher event rate for the placebo group had there been one in ALLHAT, and going through again the same calculations for the percent of that effect preserved by amlodipine, one arrives at a value of 60 percent.

I just want to stop and take a second to point out that what determines these high percentage values are two things. One is the very tight upper bound of the confidence limit that came from the ALLHAT trial. The second component is the

large effect of low-dose diuretic therapy or, more specifically, chlorthalidone therapy, which was established in the meta-analysis.

In a pre-planned non-inferiority trial, the non-inferiority margin would not have been selected to preserve such high a value, high a percentage as appears here, so that for that reason, we can conclude that the amlodipine therapy relative to chlorthalidone in the ALLHAT trial is non-inferior, and that is based again on the tight results within ALLHAT and the estimation that comes from the meta-analysis.

I want to move now to the second approach that we took to this problem, and that is simply to get a direct estimate of what the amlodipine risk relative to placebo would be.

Again, we used the information from the two independent components. From the meta-analysis, we are able to estimate the chlorthalidone to placebo relative risk. From ALLHAT, we have the amlodipine to chlorthalidone relative risk. A simple multiplication of these

two relative risks yields an estimate of the amlodipine to placebo relative risk.

If we do this calculation on the log scale, it becomes additive and one can obtain the standard errors and easily get a confidence interval around the amlodipine to placebo relative risk.

The top half of this slide just again repeats the information that I have already shown. From the low dose diuretic studies, we estimate the chlorthalidone to placebo relative risk to be 0.72, and one can see the corresponding log and standard error of that value.

From the ALLHAT trial, we estimate the amlodipine to chlorthalidone relative risk, which was close to unity, we see the log of that value and the standard error that comes from the large number of events in the ALLHAT trial.

Putting these two pieces together in an additive way on the log scale or multiplicative way on the normal relative risk scale, one can arrive at an estimate of the amlodipine to placebo

relative risk to be 0.71, and you can see here the 95 percent confidence bound extends up to only 0.85, indicating a significant benefit for amlodipine.

I would like to point out also that this confidence internal takes into account the variability that is present in both sources of the data, from the meta-analysis, as well as from the ALLHAT trial.

I would like to now take this method and apply it to two secondary endpoints from the ALLHAT trial. One is stroke and the other is heart failure, which we have heard a lot about in this morning's discussion.

I choose stroke because we selected that endpoint out in our submission to the FDA, and the reason why we selected it out was pretty much for the data that Dr. MacMahon had presented earlier from the Blood Pressure Lowering Trialist Collaboration paper. There was an indication that CCVs may be particularly effective in lowering stroke relative to diuretics or beta blockers.

As important to having the prior information, we had also, in correspondence to FDA, made the selection prior to our knowledge or publication of the ALLHAT results, so it wasn't a selection based on having seen the results from ALLHAT.

These again are the analogous results, but for the endpoint of stroke. From the meta-analysis, which I haven't shown you for lack of time, the relative risk turns out to be 0.66, again, the corresponding log and standard error, so the benefit for low-dose diuretic therapy was slightly larger on stroke than it was for the primary endpoint in ALLHAT.

The results in ALLHAT for amlodipine relative to chlorthalidone showed a small 7 percent benefit for amlodipine. That was not significantly different from relative risk of 1, but again in favor that the Blood Pressure Lowering Trialist Collaboration would indicate, again, the log of that value and the standard error.

Putting these two pieces of information

together again, we can arrive at an amlodipine to placebo relative risk of 0.61 and a confidence bound, with the upper confidence bound as 0.76. So, the meta-analysis and the ALLHAT data taken jointly would indicate close to a 40 percent reduction in the stroke endpoint for amlodipine.

I would like now to move to the congestive heart failure endpoint. As we have heard, there was a significantly higher event rate for congestive heart failure for the amlodipine group compared to chlorthalidone group, however, I think the results from the meta-analysis and this methodology can help put that in perspective and address some of the questions or attempt to answer some of the questions that were addressed to Dr. MacMahon earlier in his presentation.

Now, again, in the meta-analysis, which I have not shown you, but the estimate of the relative risk was 0.58, so that the low-dose diuretic therapy has its largest effect on the heart failure endpoint, resulting in approximately a 42 percent lowering relative to placebo,

corresponding log of that value, and the standard error.

As has been mentioned in the ALLHAT study, there was a significantly higher relative risk on amlodipine relative to chlorthalidone, 1.35, with a log of that value and the standard error.

However, putting these two pieces of the puzzle together in the same way as we did for the two other endpoints, either by a multiplicative relationship or adding the logs, one arrives at an amlodipine to placebo relative risk of 0.77 with a 95 percent confidence interval that includes 1.

So, at least with regard to the magnitude of the effect that we see for chlorthalidone in the low-dose diuretic trials, it appears that the result in the ALLHAT trial is one which is consistent with a neutral effect to placebo, or even possibly a small beneficial effect that is still maintained by amlodipine.

Simply put, a way to look at it is that a 35 percent increase over an agent which is already responsible for a 42 percent decrease in the event

yields a relative risk which is still below 1.

Now, in considering these results and considering this methodology, there certainly are points to consider, and I have listed a few of them here. The first is the consistency of the effect of the active control. We were fortunate in this example to have the historical studies where we were able to characterize the low-dose diuretic benefit and to look at the consistency of it.

The second point, the particulars of the meta-analysis have to be considered, what are the four trials that we use to get the combined event and was that the reasonable thing to do, is the combined estimate the right estimate for estimating low-dose chlorthalidone effect.

Probably the biggest point to consider is that there is an extrapolation going on here, the extrapolation of chlorthalidone benefit to ALLHAT. In considering that the population of ALLHAT compared to the populations of the trials in which this benefit was established, namely, the meta-analysis trials, have to be considered.

The conduct of the ALLHAT study itself has to be considered. In these very large trials, endpoint trials that go on for a long duration, there are many factors which can move the relative risk towards 1, and that has to be considered in the non-inferiority approach.

Also, there are many other secondary outcomes in the ALLHAT trial, which are probably in a whole gestalt about whether drugs are approved or not, have to be taken into account.

Although all of them in some ways have a statistical component, there are some that are truly statistical, which I have listed here in a grab bag category, such as adjusting for the multiplicity in this trial, there are many endpoints.

There is also another treatment group altogether, and also the whole post-hoc nature of the analysis that was done.

So, in summary, to put it in the same schematic that Dr. Berman used to talk about the methodology, our starting point was the ALLHAT

trial, which was a large active-controlled study that showed no superiority between the newer agent, amlodipine in this case, and the standard agent chlorthalidone.

However, we were able to go into the literature, in the meta-analysis, and be able to characterize the benefit, quantify that benefit for the standard therapy, and putting these two pieces of information together, we were able to come to the conclusion that the new agent, amlodipine, was found to be non-inferior to the standard therapy, chlorthalidone, and using point estimates, about 82 percent of the chlorthalidone effect can be said to be preserved by amlodipine in ALLHAT.

Secondly, the new agent was determined to reduce the risk of CHD death and non-fatal MI by 29 percent relative to placebo.

So, I am giving you a summary of the information as it relates to the primary endpoint in the ALLHAT trial.

Finally, with regard to the question that was asked, our overriding conclusion is this

proposed non-inferiority analysis provides an illustrative example of how an active controlled trial, ALLHAT specifically, can provide important outcomes data for amlodipine.

So, I thank again the FDA for the opportunity of presenting this analysis, and certainly Dr. Berman and I will be happy to try and answer any questions that you may have.

Thank you.

[Applause.]

DR. NISSEN: I saw Bill's hand go up.

DR. HIATT: I think you answered the question I posed earlier, at least in terms of ALLHAT, that calcium channel blockers don't seem to cause harm in terms of heart failure, but that they are neutral in terms of preventing heart failure.

If that is the case, then, would you agree there is a difference between diuretics and calcium channel blockers in terms of their effect on that endpoint, it is not just the blood pressure?

DR. GAFFNEY: Yes, I would say that the ALLHAT results clear show that the low-dose

diuretic therapy is more beneficial with regard to the heart failure endpoint, I don't think there is any question about that particularly when you put it into the context of the meta-analysis.

DR. HIATT: Not more beneficial, but there is lack of benefit for the calcium channel blocker, and there is benefit for the diuretic.

DR. GAFFNEY: I don't think the data is conclusive to say there is a lack of benefit for the calcium channel blocker. You saw the estimate of the relative risk through the multiplicative method. The point estimate anyway was a 23 percent reduction. The upper confidence bound does include 1, so you can't distinguish it from placebo with the data, but I wouldn't rule out that there is still a smaller beneficial effect for amlodipine on the heart failure endpoint.

DR. FLEMING: I think it is very appropriate that you have used these data to try to infer, as best possible, what the overall effects are when you compare to the chlorthalidone. I am onboard with a significant part of what you are

doing, and I am definitely not onboard with a significant part of what you are doing.

The part that I am onboard with is I think you have done a very logical analysis of using the historical data, and I am seeing all this for the first time, but I followed all the logic, I believe, of what you were doing.

You used the historical data to basically assess chlorthalidone's effect on the primary endpoint of cardiovascular death and MI, and essentially you come up with a relative risk of 0.719, and you appropriately recognize that there is variability in that estimate.

There is also the issue of uncertainty about the validity of the constancy assumption that we always have to take into account in the sense that those historical trials could readily be different from ALLHAT in the way supportive care was done and patient selection and duration of follow-up and adherence and in dosing and assessment of the outcome, and you acknowledged some of that at the end.

But I think you reasonably, appropriately, following more standard approaches here, took the approach then of using the upper limit of the chlorthalidone 95 percent confidence interval, which was 0.85, to create the margin, basically saying 1.18, invert that 1.18, and half that is what you have to preserve, and because your point estimate was favorable, of 0.98, the upper limit was 1.07, there is where I am with you.

I am with you that that is an analysis that is a rational approach to looking at this and establishing non-inferiority. Where I get off the bus, so to speak, is when you then use this to compute the estimated effect because you are taking a relative risk of 0.72 and 0.98 and essentially you have got the strength of the non-inferiority trial, and then you have got the ambiguities of using historical data to obtain estimates of chlorthalidone's effect in that context, and you are imputing it in the context of non-inferiority trial, and that is where all of the uncertainty of the constancy assumption issues arise, and you are

ignoring that, and you correctly pointed out your point estimate with the confidence intervals addresses the variability of both estimates, but it is putting apples and oranges together, and it is not acknowledging that.

So, when you are coming up with the point estimate of 0.71 for a 29 percent reduction, that is what is really treacherous.

However, I still accept the fact that the valid analysis that you did, which was the one that came up with the historical data to set the non-inferiority margin and preserving half the effect did allow you to draw the conclusion on that primary endpoint.

But the second analysis becomes particularly problematic when, interestingly, that is the only analysis you showed us for heart failure. You didn't show us both of the analyses, and you could have done that saying that the same proper analysis for heart failure setting up a margin, and if you did, in that heart failure, you were estimating with chlorthalidone a relative risk

of 0.58. You gave us the standard error, so I quickly computed what you didn't give us, the upper limit of the confidence interval is 0.76, so, therefore, the margin I would want to be ruling out there would be that that relates to half the effect on a 1.31. Well, your point estimate is 1.35, so your point estimate actually suggests that your excess is at the full level of the upper component of the confidence interval. You are not even estimating you are preserving any of the benefit, much less half of the benefit.

So, essentially, the conclusion that I follow, and I think is logical, is your non-inferiority analysis as it relates to cardiovascular death and MI. Where I am not at all so confident is the validity of a conclusion that you are actually providing a suggestion on heart failure.

DR. GAFFNEY: If I could respond to the last part of what you said, certainly to the heart failure, because it relates to the answer that I just gave with regard to the benefit issue as to

whether chlorthalidone is more beneficial on this endpoint than amlodipine was, and because in the ALLHAT trial, the 1.35 was significantly higher than 1, I think the exercise to go through talking about what the percent preserved was is illogical and futile because you are already acknowledging that it is inferior to it with regard to this endpoint.

So, once there is that acknowledgment to it, there is no reason to go through method 1 for the heart failure, which is why we don't have that here.

DR. FLEMING: It is entirely possible that you could have been somewhat worse than the active comparator, and if the active comparator is highly effective, that you would still be able to hit a non-inferiority margin and rule out that you are having no effect or even preserving less than half the effect.

Unfortunately, in this case, the estimate of where the placebo would lie, if you used the 95 percent upper limit of the confidence interval, is

at 1.31, and your estimate is at 1.35, so your estimate is consistent with a neutral effect, I would say, a neutral effect on heart failure as opposed to the implication you gave that it was suggestive of a beneficial effect of 0.77 where that analysis did not take into account the variability in the estimate and the uncertainty of the constancy assumption.

DR. GAFFNEY: I have to disagree with you somewhat, because I think you are misinterpreting it. If you look at heart failure data, the point estimate was 1.35. The upper confidence bound on that is 1.50. So, if you take that upper confidence bound relative to what would be the imputed placebo heart failure rate in that trial, there is still a small percentage preserved of the--

DR. FLEMING: That's because you are not taking into account the variability in the estimate of chlorthalidone's effect on heart failure.

DR. GAFFNEY: I am going to finish the second point, because I did two lines of it

remember, so on the first line was the point estimate. There is still a percentage of it preserved. If you then move and incorporate the variability around the point estimate for the benefit of chlorthalidone that comes from the meta-analysis, take the upper 95 percent confidence bound, and if you formally go through those calculations, you will now get a negative percent preserved, indicating that all of the benefit of chlorthalidone is given back in a sense.

DR. FLEMING: That's correct.

DR. GAFFNEY: So, I am in total agreement with that, and that is why I make the statement that it's clear from that study that chlorthalidone is better on the endpoint of heart failure.

The second analysis, though, was to put the two pieces of information together to put it into the context of the questions that were asked earlier today, does this appear to be due to harm of amlodipine or is it consistent with a neutral effect relative to placebo, and that second analysis was done to come to the conclusion that it

is consistent with a neutral effect relative to placebo.

DR. FLEMING: Just a final point. Indeed, it is consistent with a neutral effect, and if you, in fact, use your historical data for the effect of chlorthalidone on heart failure, and you use the upper limit of the confidence interval of what that effect is, then, your point estimate is then consistent with slightly less than a neutral effect, but close enough that I can accept your statement of a neutral effect.

So, it is far short of anything that we would want to see for establishing a favorable profile on heart failure, and that is my objection to your pointing out the point estimate of 0.77, which could give the impression that we are actually doing favorable.

DR. NISSEN: Jonathan, you were next.

DR. SACKNER-BERNSTEIN: My comment relates to some of the discussions we will have later, but I would like to take Tom's point and move it back up one step earlier where you presented your

meta-analysis approach.

That meta-analysis approach relied on a combination of studies using chlorthalidone and hydrochlorothiazide. It is important to realize that de facto, the ALLHAT investigators declared that those drugs cannot be considered interchangeable because they didn't randomize people to a diuretic, they specifically made sure it was chlorthalidone.

So, while you may want to argue you are talking about low-dose diuretics, the data set really should apply to chlorthalidone, so at the risk of showing myself to be somewhat of a statistical novice, I tried to get a sense of how certain I could feel about amlodipine preserving the impact on coronary death or non-fatal MI.

By looking at these studies, presuming that your upper confidence interval is about 0.95, and running through the same analyses, it looks like you can't be certain that you have preserved much more than 18 percent of the effect, which is a relatively small effect, certainly not as

impressive as the 60 percent calculated here.

I think that kind of analysis needs to be included when we are thinking about this, as will become more relevant in the afternoon session, because chlorthalidone/hydrochlorothiazide probably can't be assumed to be interchangeable.

DR. NISSEN: Bob, you were next.

DR. TEMPLE: Well, anytime you are doing a non-inferiority study, your struggle is to narrow the confidence interval for your estimate of the control, and what was done here is what is done all the time. We have seen it repeatedly where people will combine several ACE inhibitors to try to get an estimate. Whether you feel comfortable with that or not, I don't know.

In this case, however, the overall impression of the effect is quite consistent with what we have been saying earlier in the morning, is the effect size on something like stroke for essentially all drugs that lower the blood pressure, so it's a little less worrisome than it might be in other cases, but it is perfectly clear,

if you are going to just do SHEP, then, the upper bound is 0.095, and you are never going to be able to show anything, so, I think it's a question of how uncomfortable you get.

It is worth noting that a relatively conservative approach to non-inferiority is to use the so-called 95/95 method, which they at least in part survive if they do that. That is taking the upper bound of 0.85, taking half of it, so you get about 0.09, and showing that the upper bound of your confidence interval for the difference is 0.07, so you are under that, and that is a relatively conservative method which has been criticized as being slightly too conservative.

So, by that method, there is some evidence that you preserve half of the effect of the control agent, you know, how reassuring you find that is another question, but it has been the standard used for non-inferiority assessment in a lot of cases, because you can't do better without studies of, you know, hundreds of thousands.

DR. FLEMING: By the way, that was the key

analysis you did that I do accept, that I do agree with.

DR. TEMPLE: Yes, they did a less conservative analysis that I don't know about.

DR. NISSEN: Bob, you meant to say no less half the effect, didn't you?

DR. TEMPLE: They make the case that they preserved at least half.

DR. NISSEN: Michael, I think you may know something about the ALLHAT study, and you wanted to ask a question?

DR. PROSCHAN: Actually, I was going to just comment on the key assumption clearly is the constancy assumption, and if you buy into that, then, there is no reason to do this upper limit of confidence interval.

You just take the product of the relative risk, take the log value, you know what the standard errors are, but I think it's that key assumption that's, you know, what Tom is bringing up, you have to buy into that, and I guess people are not willing to necessarily buy into that.

DR. GAFFNEY: Well, I think also that that is a key assumption also to that second analysis, but it is not too dissimilar from the key assumption that one is extrapolating a relative risk from four trials to another trial even to get the imputed placebo response whether you use the point estimate or whether you use upper 95 percent confidence limit, which happens to be conservative.

So, I think for consistency sake here, we have to say that these type of extrapolations and assumptions are going on for both of these methodologies rather than just pick on the second one.

DR. NISSEN: Did you want to say something else, Tom?

DR. FLEMING: Just quickly. I certainly agree that a major component to using that upper 95 percent confidence limit is the uncertainty of how much adjustment we need for the constancy assumption validity, but another part of it is there is variability in that estimate, and part of the adjustment, even if you believe in the

constancy assumption, it's about half, to be about 1 standard error is necessary to address the fact that you have variability in the estimate of the active comparator effect here, in this case, chlorthalidone.

DR. NISSEN: We are going to come back to this.

DR. PROSCHAN: Just taking that into account, because when you take the log of the product of those relative risks, you get the standard error.

DR. FLEMING: Right, for his second method he is, so when he uses the product, he is there, and there, my concern is apples and oranges, but in the first method, the 95/95 method, part of the reason for that 2-standard error adjustment, I would say about 1 standard error of that is that in that method, you have to take into account the uncertainty of the variability in the estimate of chlorthalidone's effect.

DR. NISSEN: I am going to give the last word to Bob, and then we are going to move on to

the next talk.

DR. TEMPLE: Without diverting this into an interminable discussion of non-inferiority studies, we have been engaged in agonizing discussions about these all the time, because all of the cardiovascular diseases you can think now have treatments that save your life.

You are not going to see any more placebo-controlled trials ever. The only way to study a new drug is to compare it with something else, or maybe added to it, those are fine.

One of the things we have been thinking about is whether there are somewhat less conservative approaches to some of these things that we have been inclined to use. They would probably come under the heading of Bayesian reasoning, I suppose, although I shouldn't say words like that if I don't understand them, I realize that.

We have been talking all morning about, you know, with Dr. MacMahon's data, about the consistency over a wide range of drugs of the

beneficial effect on stroke, that is, drug after drug after drug, different mechanism, different population, blah-blah-blah. They all seem to have about the same effect.

It seems to me that would be ordinarily part of your non-inferiority discussion. I don't know how to manifest it, but we have thought of things like narrowing the confidence interval for certain measures, using a less stringent insistence of retention in a wide variety of ways.

Again, I don't want to divert us into a major discussion of that, but I wonder, Tom, if you have any thoughts about some of those things, because there is much more data than those four studies, although those are the ones that best apply to the actual control here, but it is not as though we don't know anything about this.

DR. FLEMING: I think that is a valid point, Bob, and it is obviously very subjective how you incorporate the totality of evidence of antihypertensives to strengthen your sense of what the actual effect, in this case, of chlorthalidone

is, but what you are saying is valid.

It is certainly relevant to know that wide classes of agents have effects on stroke, and as you are estimating the effect of chlorthalidone on stroke, that you are reinforced in your sense of the validity of what you are imputing or what you are assuming the effect is. Yet, it is obviously very subjective as how you would try to incorporate that.

DR. NISSEN: Just one comment, Bob. I think what you are saying is that your confidence in blood pressure as a surrogate measure for outcome in stroke is increased by the fact that you have got dozens and dozens and dozens of trials that show that this effect is very consistent over a very broad population, and other surrogate measures will have more variability in that effect and will make your confidence in using those surrogate measures less.

I mean really, it is as much about surrogate measures as anything else.

DR. TEMPLE: Yes, well, in this case,

someone has done actual trials of an effect on a surrogate and what the consequences of that for stroke are.

I don't know, in non-inferiority studies, it is all about the sample size, and when you start calculating what the sample size is, for example, if they had only SHEP, and the upper bound was, I don't know, like 0.095, I don't know, Tom can tell us what the study will be, but to preserve half of that, you will probably need a study of 100,000 people or something like that. It's clearly impossible.

So, and maybe impossible is the right answer, but it might not be the right answer, because maybe you do need to evaluate new therapies even though you can't do placebo-controlled trials anymore.

One way to think about that is to narrow the confidence interval, get an upper bound that isn't as high as 0.095, and one way to do that is to incorporate prior data maybe, but there is very little track record in doing this and very little

public discussion of it, so I am just throwing it out for later, I don't expect a discussion of that now.

DR. NISSEN: I am going to move us on and I am going to try to squeeze in one more talk before we break for lunch, and that is going to be Tom Pickering.

I think it is actually a very important question, which was: Does the pattern of blood pressure effects during the day matter?

Does the Pattern of Blood Pressure Effects During the Day Matter?

DR. PICKERING: Thank you.

The focus of today's meeting is blood pressure, and all the studies we have heard about so far have basically relied on a couple of measurements made at a single time point during the day.

We have known for many years that blood pressure varies hugely throughout the day and night, and from one occasion to another. So, the purpose of this talk is to look at these issues

here and how they might impact how we interpret these data:

The diurnal rhythm of blood pressure, diurnal rhythm of cardiovascular events, the duration of action of antihypertensive drugs, the effects of drugs on the diurnal rhythm of blood pressure, and how the effects of timing of administration of the drugs.

What we would really like to know is what is the true blood pressure which is the hypothetical component of blood pressure that we think leads to adverse cardiovascular outcomes.

Traditionally, as I said, we have used clinical blood pressure, but it was shown more than 40 years ago by Jeffrey Rose that serial measurements in healthy subjects over a period of several weeks could lead to differences as high as 25 mm of mercury without any intervention whatsoever, and we know that this unreliability of single measurements can be improved by taking multiple measurements, such as can be done with out-of-office measurements.

It would be okay if the measurement error between the clinic measure and the measure over a more prolonged period of time was random, and if you had a million people, then, the error would go away, but there is a lot of evidence that the error is not random, there are systemic differences between the clinic blood pressure and the pressure measured at other times, which may vary in different populations and according to age.

At the present time, I think we don't know which is the true blood pressure. There are a number of possible candidates. It might be the daytime level, the dipping pattern that is the difference between the day and the night blood pressure, the nighttime blood pressure, the morning surge of blood pressure, blood pressure variability, or the home blood pressure.

It could also be different for different outcomes, it is not necessarily the same for causing MI as it is for stroke.

We do know that, in general, in hypertensive patients, the diurnal profile of blood

pressure is shifted to a higher level throughout the 24-hour period, and this is, as you can see, somewhat discrepant between the differences in the conventionally measured clinical blood pressure, so it is reasonable to suppose that what we want to achieve with treatment is a resetting of the diurnal profile of blood pressure back to a normal level, both throughout the night and day.

There are several clinical situations in which this normal diurnal rhythm of blood pressure may be lost or diminished, and these include importantly conditions like diabetes and renal failure, both of which are of particular concern, and we have lower target blood pressures for these conditions, also, in African-Americans particularly in the United States.

All these conditions tend to be associated with a relatively small decrease of blood pressure during sleep, and we don't yet understand fully the implications of this.

There is some evidence that this so-called non-dipping pattern or high nocturnal blood

pressure may have an independent effect on cardiovascular outcomes. This is from a large population study done in Japan, and as you can see, if the dippers are given a relative reference level of 1, that the risk of cardiovascular mortality over a follow-up period of about 10 years is increased more than double in the non-dippers, and this may be--we don't yet know if this is because they have a higher overall level of blood pressure throughout the 24 hours or whether it is something specific to the actual pattern of blood pressure as opposed to blood pressure level.

It has been well known for many years that there is a diurnal rhythm of cardiovascular events, and there was some earlier discussion of instantaneous effects of blood pressure, and I guess this is the best manifestation of that.

Just about any type of cardiovascular event that you look at does show this type of diurnal rhythm, that is, an increased incidence between the hours of 6:00 a.m. and noon, and this is a recent study showing episodes of ventricular

tachycardia detected with patients with implanted cardioverter/defibrillators.

Here is another example, both ischemic and hemorrhagic strokes tend to show the same type of diurnal rhythm, and this has led to an increased interest in the increase of blood pressure that occurs in the morning hours, associated both with waking up and with getting out of bed and becoming physically active that is now often referred to as the "morning surge" of blood pressure.

Here is a study that we published in Circulation a couple of years ago based on a Japanese database. This was a four-year prospective study of elderly Japanese patients, who were evaluated with 24-hour blood pressure monitoring at the beginning of the study and followed for stroke occurrence.

Basically, what it shows is that there was an independent predictor of fact of the morning surge, which was defined as the difference between the blood pressure at the lowest level during sleep and the first two hours after waking up.

There was a 29 percent--for those of you who can't read the numbers at the back of the room--increase in risk independently of the average 24-hour level and other factors.

So, this suggests, I don't think it proves, that the increase of blood pressure during the morning may have something to do with precipitating these events.

Coming on now to the duration of action of drugs, this obviously is something that can only be adequately evaluated by 24-hour blood pressure monitoring, and I think is pretty much requisite now for any new drug to get FDA approval, that is has to have evidence of sustained duration of action.

Here is an example of two, long-acting antihypertensive agents, an angiotensin receptor blocker telmisartan and amlodipine, both showing a sustained decrease of blood pressure throughout the 24-hour period without any marked change in the pattern of blood pressure, so I think we would intuitively regard this as a desirable effect.

There have been other studies that suggest that some of the drugs which are approved for once daily dosing may not be as effective towards the end of the dosing period as others, and this could have important consequences.

In this particular study comparing two angiotensin receptor blockers, they looked at the effects of a missed dose, a common event I think in all our patients, and it shows that the longer acting candesartan had a more sustained effect on the blood pressure measured over a 36-hour period than losartan, and it also shows incidentally that it had some--in the doses used at any rate--had a more sustained effect on lowering blood pressure throughout the 24-hour period.

Now, looking at the effects of drugs on the diurnal rhythm of blood pressure, there is not much actually published on this, and there have been suggestions that because renin-angiotensin system shows pronounced diurnal rhythm of activity, there might be different effects from drugs that impact the renin-angiotensin system from drugs that

act by other methods.

So, the question is: Do different drug classes have different relative effects on the daytime versus the nighttime blood pressure?

We are in the process of attempting to look at this, and this is data that is unpublished and still being analyzed, but basically, what we did was to look at the published data of 24-hour blood pressure studies where there were reports of effects of antihypertensive drugs on the daytime, nighttime, and 24-hour blood pressures, and we found 55 such trials.

We grouped them into drugs that act against the renin-angiotensin system, ACE inhibitors, receptor blockers, and beta blockers, and then calcium channel blockers and diuretics, and combinations of the two.

The main finding was that across all the studies, the absolute change of daytime blood pressure was significantly, but not very largely, greater than the change of nighttime blood pressure, and there was no obvious difference

between the different drug classes.

However, there was one rather surprising finding. This just summarizes the differences between the different classes of drugs - ARB and diuretics, ACE and diuretics, diuretics on their own, and so forth. But the surprising finding, and we don't quite know what to make of it, is that when we looked at the effects of the drugs as a function of the baseline pressure both during the day and night, it appeared that calcium channel blockers, and in this, we included diuretics, but taking out the diuretics, you still see the same thing, there appears to be a linear relationship between the effects of the drug and the resting level of blood pressure which is not apparent with the ACE and the ARBs, suggesting that lower levels of blood pressure, the calcium channel blockers on their own are less likely to lower blood pressure than drugs that antagonize the renin-angiotensin system.

There is some other data that supports this, and looking in the literature, there is a

suggestion that the effects on clinic blood pressure, shown on the left, are generally larger than the effects on ambulatory blood pressure, and that is well established.

Here, there is a suggestion that the threshold blood pressure, which was estimated from the published regression lines of resting blood pressure versus blood pressure change, in this study, may be lower for the ACE inhibitor than the others.

Another study has also shown that the threshold blood pressure appears to be higher for the daytime level than the nighttime level.

It is certainly possible to change the dipping pattern of blood pressure with antihypertensive medication. This is one example showing that diuretics given to non-dippers tend to have a bigger effect on the nighttime blood pressure than given to dippers who show the normal fall of blood pressure.

Again, this may be a reflection of the higher level of baseline blood pressure and a

greater change. We don't know what the therapeutic implications of this type of thing are yet, but certainly it is possible to change the dipping pattern.

Coming back to the morning surge of blood pressure, we don't yet know if selectively lowering the morning surge of blood pressure is going to have a favorable impact on outcomes. There is this one study comparing metoprolol with carvedilol.

On the left, you can see that there is no significant difference between the two on the clinic blood pressure or the daytime average day or nighttime blood pressure, but the carvedilol did appear to lower the morning surge of blood pressure to a greater extent.

They also found that it had a greater effect on carotid intima media thickness, so there is a question of whether there is a connection between the two, which I think is an interesting research question.

Again, it is possible to selectively lower the morning increase of blood pressure. This is a

study using an alpha blocker doxazosin. I think you can see that the morning rise of blood pressure was lowered with doxazosin, and as I said, in the earlier study I showed you, with an ARB and calcium channel blocker, we didn't see that, however, it is perfectly possible to prepare formulations of antihypertensive drugs that can do this.

This is a study published recently using an extended release form of diltiazem, and I think you can see that it did lower the increase of blood pressure during the morning hours.

The only outcome study that has attempted to look at this was the CONVINCE study, which, as you know, was basically negative, and unfortunately, did not include any 24-hour monitoring sub-study, so we don't know what happened actually to the difference in the increase of morning blood pressure.

Finally, the effects of timing on administration of drugs. This is something that is not usually referred to in the drug labeling, and I am just going to show you one example, which I

think is of some relevance.

This is a study of valsartan given either in the morning on awakening or at bedtime, and the message here is that the daytime blood pressure was lowered to a greater extent when the drug was given the night before than when it was given in the morning.

As we have seen, the daytime is the time when most of the bad things happen, and if you look at the labeling for diovan, it says it can be used over a dose range of 80 to 320 mg given once a day. It doesn't say anything about time of dosing.

It is interesting to speculate what would have happened in the VALUE study if the valsartan had been given at night rather than during the day, and it is also worth noting that in the HOPE study, that, of course, achieved quite dramatic results, the drug was given at night.

Finally, this is a couple of slides I got from Steve Nissen, but when we talk about blood pressure independent effects of these different classes of agents, I think in very dangerous

ground, because we are talking about very small differences.

Steve MacMahon was talking about differences of 1 or 2 mm of mercury, and in the HOPE study, the argument for the blood pressure independent effect was based on a decrease of systolic blood pressure of about 3 mm, which on the Staessen curve, that we have seen so many times this morning, puts it on the boundary of the limits of the curve.

But, again, you are probably familiar with this, but there was a very small sub-study of HOPE that did use 24-hour blood pressure monitoring, and found a 10 mm decrease of 24-hour blood pressure, which puts the HOPE results right in the middle of the line.

So, again, I think we have to be very cautious about how we interpret these blood pressure independent effects of different classes of drugs given the potential inaccuracies in the conventional method of measuring blood pressure.

So, in conclusion, there is a pronounced

diurnal rhythm of blood pressure and events, with both tending to peak during the morning hours. The normal dipping pattern is lost in some patients and may be associated with an increased risk. The data is not entirely consistent on that.

Drugs approved for once daily dose may have different durations of action, particularly after missed doses, which could be important.

Most classes of antihypertensive drugs lower daytime blood pressure more than nighttime blood pressure.

The effects of calcium channel blockers may be more closely related to baseline blood pressure levels than those of ARBs or ACE inhibitors.

Different antihypertensive drugs or formulations may have different effects on the morning surge of blood pressure.

With some antihypertensive drugs, the time of dosing may have significant effects on the diurnal variation of blood pressure. This is not true, for example, with amlodipine, where it

doesn't seem to matter.

The implications of these time-dependent differences for cardiovascular morbidity are largely unknown and need to be more fully investigated.

Finally, implications of blood pressure independent effects of antihypertensive drugs based on small differences of clinical blood pressure may be unwarranted.

So, I think my message to the FDA is for future trials, I hope you will encourage the sponsors to use out-of-office monitoring and 24-hour blood pressure monitoring to help resolve these potential blood pressure independent effects.

Thank you.

[Applause.]

DR. NISSEN: I am sure everybody's stomachs are growling, but let's take a few burning questions and then we are going to break for lunch. Anybody?

DR. KNAPKA: As a non-physician and a patient, I do have a little bit of background in

statistics, but after hearing this morning about 2 mm in blood pressure makes a big difference, and then listening to Tom's talk, I wonder, for all these studies we have been reviewing and looking at, what is the standard for taking blood pressure? Is there a standard time? Unless there is, I don't know what some of this data really means.

DR. NISSEN: Well, it's a great question. One comment I would make, Tom, I think your point is very well taken, and that is that there is a tendency for sponsors of studies, and in the development of drug, to want to give drugs infrequently, because it is obviously easier for patients to give a drug once a day than twice a day, and it obviously has marketing implications, but it also may have implications on clinical outcome.

I am very troubled by the fact that if you give a drug in the morning, and then you measure blood pressure in trials, which is almost always going to be done in a clinic visit, you are pretty much measuring the peak effect of the drug, or if

you give the drug at night, you are measuring, in the daytime when you come to the clinic, a trough effect, and that was one of the issues that I brought up about the HOPE trial where the drug that was given was specified to be given in the evening, but the blood pressure was being measured the next day, you know, which was really a trough blood pressure, so that 3-mm difference reported in HOPE was as trough pressure, not a peak pressure.

DR. TEMPLE: In the studies that we use to approve drugs that lower blood pressure, they are very explicit about whether it's a trough pressure or a peak pressure, we insist on both, but you are right, in the outcome studies, I am sure there is much less control over that.

DR. NISSEN: Again, different studies will specify different regimens, so unless you actually factor that in, you know, this question of are there effects beyond blood pressure, well, it depends on when you are measuring it.

If you are measuring it at trough, the drug tends to look better. If you are measuring at

peak, the drug tends to look worse, that is, with respect to the relationship between blood pressure reduction and event reduction, so it's complicated.

DR. PICKERING: I don't think it was necessarily measured at trough during the HOPE study, because they would have had to measure at night before the patient took the medication. The paper was actually very vague about how blood pressure measurement was actually made. I think in the initial paper, they didn't even say that it was taken at night.

DR. KNAPKA: One other comment. Being a 70-year-old and supposed to take drugs twice a day, I forget sometimes. Thinking about it, well, I took it, was it yesterday or today, and in these studies, how do you account for people, and in these studies, there are 70- and 80-year-old people, how do you account for people that miss their drugs, and I am sure it happens?

DR. NISSEN: You know, it is interesting. I am only 32 years old, and I occasionally forget to take my drugs, too. The issue of compliance, I

think maybe we will come back to that a little bit, too.

My stomach is definitely growling, but if there are burning questions, I will take them.

DR. TEMPLE: You are forgetting your age.

DR. NISSEN: Yes, of course.

I would like to get us started again at 1 o'clock exactly. We are running about an hour behind and we have got a lot of work to do this afternoon.

[Whereupon, at 12:08 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

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

[1:08 p.m.]

Open Public Hearing

DR. NISSEN: In order to be on time for our open public hearing, I think we are going to take that first and then we will turn to Ron Portman's short talk.

I think there is at least one person who has requested to speak at the open public hearing.

Charles Pamplin has requested time to speak.

I am sorry, I am going to read this script.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So, Charles Pamplin.

DR. PAMPLIN: Good afternoon. I am Dr. Charles Pamplin. I am the Vice President for Medical Affairs at King Pharmaceuticals. I am representing King Pharmaceuticals this afternoon.

We would like to take this opportunity to recognize the FDA for bringing greater awareness to

the medical community on the importance of risk reduction. As you have heard this morning, hypertension is an important public health issue which is too often under-treated despite all that is known about its effects and the numerous evidence-based treatment guidelines.

We support the use of the product label as a means to link the importance of hypertension treatment with disease outcomes. As noted at the most recent meeting of the American Society of Hypertension, and also earlier this morning, hypertension is a complex cardiovascular disorder. It is not just a collection of elevated blood pressures taken at various times of the day and by various methods, but rather "a progressive cardiovascular syndrome with many causes that result in both functional and structural changes to the heart and vascular system."

We believe that it is important to acknowledge the complexities and limitations of extrapolating benefit between drugs of the same class and drugs of different classes.

Traditionally, we have relied on mechanisms of action to determine a drug's class.

While this provides a framework to compare and contrast therapeutic agents, it certain does not imply equality. Clinical studies have often shown differences among drugs with similar mechanisms of action. Significant differences related to bioavailability, distribution, metabolism, clearance, receptor affinity, genetics exist both within and between various classes of antihypertensives.

Of key importance and not to be underestimated, dosage is a critical aspect of achieving benefit. Not only dose, but as you have heard recently, time of day of dosing may be an important factor. Assigning similar benefits to drugs within a class without a clinical outcomes trial that is powered appropriately and capable of identifying the optimal dose, may expose patients to inferior treatment and unacceptable side effects.

Any labeling which includes common

information pertaining to the importance of lowering blood pressure, and the possible benefit on cardiovascular disease, must recognize these differences as matters of both efficacy and safety and allow for clarifying information about what is known and importantly, what is not known about drugs in the class.

Drugs with similar blood pressure lowering effects may have other "non-class effects," which are unrelated to the decrease in blood pressure, but which can have an important impact on clinical endpoints, either positive or negative.

Drugs with similar effects on blood pressure do not always have similar effects on outcome. As we have heard today, stroke is the clinical endpoint most closely associated with blood pressure reduction, and yet in randomized trials, such as LIFE, similar blood pressure reduction led to different outcomes in stroke.

In the ALLHAT study, treatment with doxazosin, which achieved blood pressure control, was associated with a doubling of rate of heart

failure.

Altace, King Pharmaceuticals' branded form of ramipril, is one of the medications with proven clinical cardiovascular endpoint data that is widely interpreted to support risk reduction beyond that expected by blood pressure reduction alone. Remember that this was not primarily a hypertensive study.

While blood pressure in the HOPE trial was relatively modest as I say by design, the impact of ramipril on the composite endpoint of reduction of cardiovascular death, myocardial infarction or stroke far exceeded the expectations of the study investigators.

Utilizing independent observational analysis from other studies and that derived jointly from the World Health Organization/International Society of Hypertension, the relative risk reduction in myocardial infarction and stroke was significantly greater than estimates based on actual achieved reduction in blood pressure in this study.

Furthermore, outcomes data from HOPE indicates a similar risk reduction benefit in patients who were either normotensive, the majority of the patients I might add, or who were controlled hypertensives.

Therefore, while ramipril does reduce blood pressure, the majority of its benefit on cardiovascular risk reduction cannot be attributed solely an antihypertensive effect. Thus, to extrapolate its cardiovascular morbidity and mortality benefits to other agents solely on the basis for reduction in blood pressure may be inappropriate.

I want to emphasize that hypertension is an important public health issue. We should, as a medical community, do everything possible to improve its detection and adequate treatment. We support labeling that would recognize the importance of this syndrome. However, differences between classes are real and significant, and in the interest of appropriate medical treatment, these should not be ignored.

While differences in molecular structure within a class may appear subtle, the consequences of those differences are far from subtle. Evidence-based practice paradigms and individual patient needs must be taken into account when choosing an antihypertensive agent to maximize reduction in cardiovascular morbidity and mortality.

Optimizing risk reduction would be best achieved by identifying a patient's comorbidities and utilizing agents with proven effective outcomes data.

Thank you.

DR. NISSEN: Thank you very much. Are there other speakers for the open public hearing?

[No response.]

DR. NISSEN: Seeing no one, let's turn to Ron Portman's presentation, and then we are going to have to dive in, in the time we have left, to a very complex discussion.

Does the Benefit Associated with Treating Hypertension Apply to Children?

DR. PORTMAN: Thank you to Dr. Stockbridge, Dr. Temple, and members of the Committee and guests for asking me to make this presentation on pediatric hypertension. Hopefully, our cerebral to gastric bloodflow bypass, we will still be alert, and particularly Norman asked me to address this issue, does the benefit associated with treating hypertension apply to children.

Hypertension has now taken a prominent role in pediatrics from the standpoint of chronic diseases. It is up with asthma as one of the most prevalent chronic diseases in children and trailing only obesity now that that has been recognized as disease, as chronic diseases of children. Of course, over a third of obese children have hypertension.

Last summer, the fourth Working Group Report from the NHLBI gave us some important and comprehensive guidelines for the management of blood pressure in children including the issue of measurement techniques and the dilemmas in measurement with disappearance of mercury and using

oscillometric monitors.

Our normative values continue to be based epidemiologically by gender, height, and age. We have a new definition of hypertension in concern with JNC-VII.

We have now, and the most important factor in my opinion is that the presence of end organ damage was presented, and I will go over that in some detail.

We have evaluation guidelines including comorbidities and the most comprehensive therapeutic guidelines to date.

This is our classification of hypertension in children and adolescents, which should look very familiar to you as it parallels JNC-VII. Normal is less than the 90th percentile for age, gender, and height.

Prehypertension is defined as the 90th to the 95th percentile, however, for teenagers, the 90th percentile often exceeds 120/80, which is the lower limit for adult definition of prehypertension, and so we use 120/80 even if it's

below the 90th percentile.

Stage 1 hypertension is from the 95th percentile to the 99th plus 5. That is clearly arbitrary, but one has to look at JNC-VII and see that there is a 20-mm mercury spread in Stage 1 to Stage 2, whereas, in pediatrics, as I will show you on the next slide, there is only 7 mm mercury spread, which given the variability of blood pressure, is just too small. So, we arbitrarily added 5 to that in our definitions.

Then, Stage 3 hypertension is greater than the 99th percentile.

This is just a sample of the complex curves that we have to use. Fortunately, it is now computerized, and you can download it off the NHLBI website to your Palm.

Here, we have 12-year-old boys across what would be the x axis, we have the percentile of height. We had the 50th percentile of blood pressure for the first time, so we know what true norm should be, the 90th, 95th, and 99th percentile.

You can see there is, over the various heights from the 5th to the 95th percentile, we have 102 to 109 in this example, about a 7 mm of mercury spread for the same age, which holds true at all the different percentiles.

Again, from the 90th to the 95th, we have about a 3- to 4 mm of mercury spread, and from the 95th to 99th, about a 7 mm of mercury spread.

So, in evaluating a patient who has been diagnosed as hypertensive in children, from the patient's standpoint, we asked four questions: Am I really hypertensive? Well, in order to determine that, due to the regression to the main phenomenon, and just the discomfort associated with blood pressure measurement for a child, we used repetitive measures at last three times greater than 95th percentile to make that diagnosis and/or use ambulatory blood pressure monitoring.

What other modifiable risk factors for cardiovascular disease do I have? The same as adults, diabetes, smoking, hypercholesterolemia, and proteinuria.

What has hypertension done to my body, in other words, do I have any end organ damage? Well, as opposed to all the discussion we have had earlier this morning about stroke and heart attack and end-stage renal disease, we don't have those kinds of hard endpoints in pediatrics, thank goodness. We have evaluations of subtle subclinical changes.

Finally, what is the cause of my hypertension? Primary hypertension is now the most prevalent cause of hypertension in children, particularly adolescents, but secondary causes are more common than in adults. Our mantra is that the younger the child, and the more severe the hypertension, the more likely to be of secondary etiology.

Of course, or final question is what do we about that, which is not a small question.

If we look at the etiology of secondary hypertension in children, the reason the I, as a nephrologist, am involved in this, and Fred, as well, is that 90 percent of the causes of secondary

hypertension are renal.

Now, target organ damage is obviously a big issue. A decade ago, if I were standing here, people would not even necessarily know that children have hypertension, and now we have some pretty good data to suggest that this hypertension actually causes damage even during the childhood years.

LVH has been reported even using the adult norms of 51 grams/meter
2.7, in 34 to 38 percent of children with mild untreated hypertension with a high correlation to blood pressure and, in particular, ABPM.

So, using Dr. Cohn's paradigm from this morning, these patients have gone already way beyond the earliest changes of hypertensive damage into LVH.

The Working Group recommendations based on these findings is that echocardiograms should be assessed for LV mass at diagnosis of hypertension and periodically thereafter.

The presence of LVH is an indication to

initiate or intensify antihypertensive therapy in children. However, no studies have been done as yet to demonstrate regression of this LVH with therapy. We have one study that is completed and the results are currently pending.

This a very scary graph. It looks at cardiovascular disease in children from the USRDS, and this is the death rate per 100,000. This is the general population here, from zero to 14, and 15 to 19 years of age. You can see the prevalence is really quite low.

However, if we look at pediatric transplant patients, it's 100-fold increase over the general population, and for dialysis patients, it is 1,000-fold increase in death, cardiovascular death.

So, this is obviously very concerning to us, and in pediatrics at least, one of the most important contributors to cardiovascular disease is hypertension, and that is the one that we can have a major impact.

In fact, if we look at hypertension in

this patient population, we see that in the NAPRTCS database, for children with chronic kidney disease, 38 percent of patients with CRI have hypertension, 60 percent of dialysis patients, 74 percent of transplant patients have hypertension.

If we look at the corresponding population with LVH, we see about 22 to 31 percent have LVH in the chronic kidney disease, not dissimilar from the general population of hypertensive patients, 55 to 85 percent of dialysis patients and 30 to 75 percent are transplant patients.

If we look at hypertension and chronic kidney disease progression, again, this is from the NAPRTCS, North American Pediatric Renal Transplant Cooperative Study database, looking at patients whose creatinine clearance is less than 75 with the standard definition of hypertension, about half were hypertensive, half were normotensive, looking at endpoints of a decrease in GFR of 10/1.73M

2

or

renal replacement therapy, you can see that there is a significant difference between those patients who are hypertensive and those patients who were

normotensive in this group.

Finally, in looking at other things other than the heart, we are also doing studies looking at carotic intima media thickness. This is a study, a very small study done in our center looking at patients who are either hypertensive or overweight compared to their normotensive and normal weight controls, and I think you can see that by the time you have hypertension and overweight, that the carotid intima media thickness is at least 70 percent larger than a normal weight, normal blood pressure patient.

Also, we have the ESCAPE trial from Europe, and this is 352, which is the largest study we have, not 352,000, like we heard this morning, but 352 kids aged 3 to 18 years of age with GFRs of 11 to 80.

They were treated with 6 months of ramipril at 6 mg/M
2 with no placebo. Blood pressure was reduced by 7 mm of mercury. They noted that the higher the initial blood pressure and the greater the proteinuria, the greater the

blood pressure lowering effect.

They were able to normalize blood pressure in 87 percent of patients, and 56 percent of them being less than the 50th percentile. Interestingly, proteinuria in this population was reduced by more than 50 percent.

So, once we have made the diagnosis of hypertension in a child, we treat them first, all patients, with therapeutic lifestyle changes. If they have normal blood pressure, obviously, we are not going to treat them, if they are prehypertensive, as noted in JNC-VII, we do not initiate pharmacologic therapy unless there is a compelling indication, such as chronic kidney disease, diabetes, heart failure, or end-organ damage.

Stage 1 hypertension, we will initiate therapy based on the next slide. Stage 2 hypertension, we will initiate therapy immediately.

For those with Stage 1, we will treat them if they have symptomatic hypertension, secondary hypertension, hypertension-induced target organ

damage, diabetes or chronic kidney disease, and obesity is still kind of up for grabs at this point, or persistent hypertension despite therapeutic lifestyle changes.

We start our pharmacologic therapy with a single drug. The goal for antihypertensive treatment--and Henry is not here, but we use goals, as well--should be the reduction of blood pressure to less than the 95th percentile unless there is a concurrent condition in which we shoot for less than the 90th percentile, or we look for resolution of any end-organ damage that we might have.

Now, talking about the FDAMA legislation, the Food and Drug Modernization Act of 1997, prior to FDAMA, we had almost all antihypertensive had been used for the treatment of hypertension in children off label. No drugs have been approved for children with hypertension. No doses were established for safety or efficacy. No available dosage forms.

Since then, we know that if a drug has the potential for use in children, that a written

request is issued, that a suggested study design was furnished, and the design was then reviewed by the FDA before a study began.

This was a voluntary program with a 6 months additional patent protection as compensation for the company. The new Pediatric Rule would make these studies required for drug approval,, but the FDA has discretion to first obtain approval in adults before a pediatric study.

This FDAMA program, I can't tell you what this has meant to the pediatric nephrology and hypertension community. It has been an extremely successful program. We have learned more about hypertension in pediatrics through it than anything that had been done in previous history.

The FDA, I applaud for being very cooperative, interested, innovative, and definitely an advocate for children.

These are the studies that have been done to date, either completed or in progress, and you can see that it encompasses almost all of the available antihypertensive agents. Those with

stars are already completed and published. Those with the cross hatching have not yet been published, and the rest of them are still in progress.

Norman asked me to address a specific question, which I will do now, and give my opinion at least.

The question is that the agency can require studies of antihypertensive drugs in children prior to approval for use in adults, should they do this?

Well, before we answer that question, we have to first ask are antihypertensive drugs used in children, and they are, and is their use warranted.

Well, the answer to that question we believe is yes, but is there proof of efficacy beyond blood pressure lowering, and the answer, quite honestly, is not yet.

So, back to the question of whether the FDA should require the child study before approving the drug, and our feeling is no, they should not,

that any new compound should be thoroughly tested for safety and efficacy in adults first, unless there is a compelling indication or some reason that we think the drug would be more effective in children first.

However, and this is the worry, is that once that drug is approved, pediatric studies still must be done after the adult approval.

The agency can also promote studies in children by granting additional exclusivity for assessing the effects of antihypertensive drugs in children. Should they do this?

Well, our answer would be yes. This program again has yielded tremendous knowledge about pediatric hypertension, and let me just give you some samples here.

These are the studies for exclusivity for safety and efficacy. The initial studies, quite honestly, the first two or three, weren't the best done, and we had really rather low expectations for what they would give us, but that was quickly rectified.

Pharmacokinetic studies have been required and we have them for virtually every drug I showed you previously. The latest set of FDA written requests require an interpretable study, in other words, the study must be powered to prove one way or the other whether the drug actually works in children.

The age group is from 6 to 16 years, and 40 to 60 percent of the children must be African-American. That is very important, but we also have multiple sub-studies for end-organ damage that are ongoing, and hopefully, we will be seeing the results of these studies in the next year or two.

That includes also sub-studies for metabolic effects. The FDA has encouraged all companies to obtain labeling. They have encouraged, in fact demanded, that every company that comes up with a study drug, that for use in children, a liquid preparation, for instance, that that preparation be made available, that it be compounded and prove that the company can actually

do this, so that we can have this drug available for children.

They don't necessarily have to have it commercially available, but at least we need to know what the formulation is, so that it can be compounded. That is obviously extremely important, why have the drug be approved in kids if you can't use it.

Then, we put in a year-long safety study instead of just 4 to 6 weeks to see whether this drug is really safe over a long term.

We are now also in the latest studies, beginning to examine the effects on development, school performance, and so forth, and very excitingly, we have now moved down to a younger age group where we have three studies from age 1 to 5 to see what effects these drugs have on that particular age group.

Finally, we have a new study that is not yet approved with an endpoint actually other than blood pressure lowering.

So, another question that Norman put to us

is: Is the study of effects on blood pressure adequate alone? The answer to that, in my opinion, our opinion, is not anymore.

So, FDAMA: The Next Generation. Studies need to be designed to determine optimum dosing or use, not just an effective dose as our current studies do.

We need a study to determine the most effective drug for pediatric hypertension. It would be a fair question for you to ask me, well, what drug would you recommend that we use in a patient who has hypertension, and I can tell you. I don't know.

Studies to determine end organ damage and disease reversibility, studies using other endpoints besides blood pressure lowering, studies for long-term blood pressure control, studies of antihypertensive combinations. We have heard all morning long that it takes more than one drug to control blood pressure, and we need to address this in children, as well.

We need to examine specific therapies for

the most prevalent diseases associated with hypertension, being obesity and CKD. We need to have commercially available preparations as there is no Medicaid funding for drug compounding. Even if I have the formulation, and I have a child with Medicaid who needs it, they can't get it, because Medicaid won't pay for it to be compounded.

We also now need to begin to examine neonatal and infant hypertension, and then finally, the issue is prevention. Hypertension begins maybe in the womb, but it certainly begins during pediatric years.

We need to identify these kids early on, those who are at risk, intervene early on whether it be with drugs or with therapeutic lifestyle changes, and prevent hypertension from happening altogether.

The child is truly father to the man, and while the question asked to us was whether the benefit associated with treating hypertension in adults applies to children, I could also ask does the benefit associated with treating hypertension

in children apply to adults.

Thank you.

[Applause.]

DR. NISSEN: Let's take any specific questions for Ron, and then we are going to move on into the main discussion.

DR. CARABELLO: Just a quick question. I noticed that in the pediatric data, you normalize for height.

DR. PORTMAN: Yes.

DR. CARABELLO: Is that just because of Pascal's laws, and if so, how come we never do it in adults?

DR. PORTMAN: I paid you to ask me that question, didn't I? In point of fact, many times when I have spoken like this, I have gotten on the case of my adult colleagues to tell them that they should be, in fact, using height.

Can you imagine a 60-year-old lady, who is 5 foot, 90 pounds, whose blood pressure is considered the same as a 6 foot 4 inch, 250-pound football player? And yet that is what you do.

DR. CARABELLO: But that is Pascal, right?

DR. PORTMAN: Yes.

DR. CARABELLO: I mean you were talking about gravity and the height of a column of fluid.

DR. PORTMAN: To a certain degree.

DR. CARABELLO: Just so you understand, Pascal's first name was Blase, my only real interest.

DR. PORTMAN: I agree with you completely, I think that is something the adult group needs to pay much more attention to.

DR. FLEMING: Ron, you did say a couple of times that we should do studies with measures other than blood pressure, and I think your slide said end organ damage reduction.

DR. PORTMAN: Right.

DR. FLEMING: Do you have suggestions, more specific suggestions than what the size of those studies might?

DR. PORTMAN: I think one very good study, particularly aiming at a very high-risk population, which would be chronic kidney disease, or diabetic

population, and you are probably aware, not only is there an epidemic of obesity, but there is an amazing epidemic of Type 2 diabetes, and looking at microalbuminuria as a marker for nephropathy in these patients. We would propose that a study be done to look at the disappearance of microalbuminuria with these medications.

Another one is chronic kidney disease where you have microalbuminuria and using a similar measure. Then, of course, we have in a number of different populations, left ventricular hypertrophy as a marker of cardiac damage, and we would suggest that that also be used as a marker.

DR. KASKEL: I wanted to thank you, Ron, for an excellent review, and our colleagues just completed a study that will be published in the Journal of Pediatrics I think next month, on the role of ambulatory blood pressure monitoring in adolescents and younger children with Type 2 diabetes and who have BMIs above normal, finding very good evidence that the ambulatory blood pressure monitorings are abnormal in these

children, they have abnormal nocturnal dipping and abnormal systolic/diastolic patterns, and microalbuminuria, so this whole population is at risk and needs to be studied.

DR. PICKERING: I would just like to endorse what has been said about the importance of this issue in children, and mention that there are some very interesting animal studies that suggest that treatment of hypertension for even a limited period of time may substantially affect the time course of the blood pressure during maturation.

We don't know if it is the same in humans obviously, but I think it is an extremely important area.

DR. PORTMAN: Well, it is, and, in fact, that study is in development following along with the TROPHY study that is being done currently. We are planning TROPHY, JR. in a younger population.

DR. NISSEN: Bob?

DR. TEMPLE: One of the things we have to worry about is what kinds of studies people can still or are willing to do, so my assumption is if

a person has kidney damage and an elevated blood pressure, probably no one is going to want to leave them untreated, so what kinds of studies to document that a particular drug--this is a little bit like the adult situation, it is hard to do those studies now--what kinds of studies can you actually do in a reasonable amount of time to add to the fact that you know the drug, in fact, lowers blood pressure? What do you think are the areas you can actually look at?

DR. PORTMAN: You mean outside of just lowering blood pressure?

DR. TEMPLE: Well, yes, because you said--I am responding to your conclusion that that wasn't enough anymore.

DR. PORTMAN: Right. I think that you are right, and a study that we are currently contemplating actually looks at an issue where the patient may be hypertensive or maybe not be hypertensive, in other words, our goal is microalbuminuria.

We are taking a group of patients who, in

fact, have probably been hypertensive for months, if not years, and plan to do a phased study where there actually is a placebo-controlled trial for a period of 3 months, followed by the target drug compared to a standard therapy or a different kind of therapy, if you will, for a period of time, followed by a withdrawal phase to see if the effect persists, and that is the kind of study that I was referring to.

DR. NISSEN: Just one comment, and that is that one of the things that strikes me about this hypertension issue in children is that the time horizon is so very long. I mean if you start at that age, and it is obviously not advantageous for the pharmaceutical industry to do long-term studies, but it would certainly be very interesting to have the NIH or somebody else do this to sort of look at what 10- and 15-year outcomes look like in childhood hypertension.

My guess is that there would be a tremendous magnification of effect over time. Is anything like that being planned?

DR. PORTMAN: Well, we have a retrospective study based on the Working Group, that looks at four years of tracking based on the new blood pressure definitions, but as far as the long-term studies are concerned, we are sort of relying on, at the moment, at the ongoing studies like Muscatine in Bogalusa, you know, to see what happened to them long term.

Committee Discussion and Questions

DR. NISSEN: We are running somewhat late and we have got a lot to do. Ron, thank you very much.

Now, organizing our thoughts in this discussion will be a challenge, and let me make sure I understand, Norman, where we are going to go here. You don't want any votes on anything, you want to hear a very robust discussion, is that correct?

DR. STOCKBRIDGE: Yes. I don't think you need to vote on any one of these questions.

DR. NISSEN: But we really want to make sure all the points of view get aired out and that

we have some dialogue. What I would like to do, and Tom had this suggestion, that we allow some free dialogue to take place here where people can kind of do a little back and forth as we explore these issues.

I think the questions help us to structure that, so I am going to suggest that we move into the questions, unless there are broader issues you want to discuss.

DR. HIATT: Just remind us what the outcome of this discussion is going to be.

DR. NISSEN: I am going to guess and then I will let Norm and Bob comment on that. As is clearly stated upfront here, there really aren't very many outcome claims for this class of drugs, and that does, in fact, inhibit to some extent informing the users of these drugs about what to expect.

So, as I understand where you want to go here, is that you would like the labels to say more, if they can, if we agree that there are more things that we can say, to inform the people that

have to use these drugs about how best to use them.

DR. TEMPLE: Yes. Did they get the four sample versions?

DR. NISSEN: Yes.

DR. TEMPLE: We are not wedded to any of those. They are all in flux. The first question is really designed to get at the question, do you think we should do this? I mean nobody, except for maybe Pfizer, which you just heard, nobody is coming forward with a burning desire to include these things. Everybody is sort of content to leave it alone with essentially no claims, and yet that is weird for a class of drugs like antihypertensives.

So, part of this should be do you think our idea of going actually beyond class almost into sort of all drugs that lower blood pressure and saying something about them. Of course, we are going to get into the details of how valid you think that is, do you think it is a good idea to try to put something into labeling that says lower blood pressure is good, and then modify it

appropriately, or not, because we have been surviving without this for a long time.

So, part of it is how do you feel about the general idea of doing it.

DR. NISSEN: Let's dive in. I think it will become clearer in just a minute. Go ahead, Susanna.

DR. CUNNINGHAM: I have one question. I would like to know what the FDA knows about the reading of labels and the use of labels, and who does read them, who doesn't read them, what impact will changing the labeling have.

DR. TEMPLE: Well, that's a fair question, and, of course, information technology keeps changing. One fact of life is that labeling determines promotion. It limits it and in some ways encourages it.

So, if we had something that was attractive to somebody who brought out a not yet generic antihypertensive, then, they might have a responsible education/promotional campaign that says it is really important to lower blood

pressure, here is why, and they might quote the statement, and then it might be manifested.

There are other ways we sort of hope that people might get the idea. We have hopes, who knows, that various health organizations, if they found these kinds of statements useful, would, in addition to JNC, whatever, find it possible to quote some of these things, and labeling and things from labeling get circulated in various ways.

Do people sit down and call up the labeling for a drug they are familiar with and read it? Probably not, not very often anyway. So it is the translation of labeling by commercial sponsors that is an important component of education, or could be. It is whether you think what goes on now is education or not is something we can debate at a later time, but it can become part of what people are told, and it can be educational, there is no rule against it.

I think that is all I would say. That is probably how it would be manifested.

DR. NISSEN: And just to further that,

right or wrong, it sometimes appears in direct-to-consumer advertising and other public education things that might have some impact on public health.

DR. TEMPLE: It is worth noting, people are conscious of this, that some of the drugs that everybody thinks should be on the list of drugs that are used, are off patent and generic, and promotion of those drugs is very unusual, to say the least.

DR. CUNNINGHAM: So, how will that be influenced in this case, then, if a lot of this is done by the companies?

DR. TEMPLE: Well, that is an interesting question and it depends a little on what we write. If the statement gets widely circulated that says that a wide variety of drugs are known to have favorable effects on outcome, you might think that encourages people to look for drugs that don't cost much, in addition to the ones that cost a lot.

But again, I can't predict how these statements will be used, the marketplace will.

DR. NISSEN: And, of course, we are not going to be asked to predict how they are going to be used, but we are going to try to accurately and scientifically reflect what we know based upon a lot of trials involving a lot of people, and then we will have to let the chips fall where they may in the future as a consequence of that.

I am going to bring us forward here, because I don't want to get stuck on this. Let me take it up to Question No. 1, because I think Question No. 1 is pretty pivotal to the entire discussion.

The Advisory Committee is asked to opine on class labeling for antihypertensive drugs.

Antihypertensive drugs, with few exceptions, have no outcome claim in their labeling. This is inconsistent with their approval based upon the surrogate of blood pressure and with the advice given to practitioners. This meeting is to consider how, if at all, labeling should address the relationship between blood pressure and outcome.

Question No. 1. Since outcome data come from studies of drug regimens and not single agents, what can one determine about the effects of individual agents or drug classes? Is it appropriate to generalize any observed benefits to all agents or classes, or should one conclude that one does not know enough about most single agents?

Obviously, a very important issue that drives a lot of the rest of our discussion.

Let's hear some thoughts. I definitely have some. Go ahead, Tom.

DR. PICKERING: First, let me say why I think this is extraordinarily important. If you look at the labeling in the PDR for antihypertensive drugs, you basically find the indications for treating hypertension, period. The only drugs that I am aware of where it says anything more about risk reduction are losartan and ramipril, and we heard this morning about some controversies about the LIFE study, and we have also heard controversies about the HOPE study.

If you look at chlorthalidone, I couldn't

even find an entry in the PDR for chlorthalidone alone, so this is the sort of landmark drug. So, I think there is an urgent need to rectify this, and a good analogy is the statin drug labeling where you have incorporated a lot of the NCEP guidelines, and I think there are at least three reasons why this is beneficial.

One is for education of the patients and physicians. Another is that it might shape the behavior of the pharmaceutical companies in the claims that they make and the studies that they perform.

A third problem, which is increasingly important, is this issue of therapeutic substitution that many of the insurance companies are treating all members in a class equally, and if a physician writes a prescription for one drug, they can substitute another in the same class, sometimes without any consultation, and this practice has I think been condemned by all the professional societies. So, again, the labeling might address this issue.

DR. NISSEN: I wanted to make a couple of comments. First of all, I think this is really a step forward. It is difficult, but very important, and one of the reasons is that hypertension is sort of like the Rodney Dangerfield of cardiovascular medicine, it doesn't get any respect.

We know as much about blood pressure lowering agents as any other class of drugs for any other reason in any field of medicine. I mean the number of studies on blood pressure, going back as far as they go, and yet we don't say very much about them in the labels, and what that means for the practitioner is that--what I have seen in the last decade is this intensity of focus on lipid lowering, because lipid lowering is kind of more recent, there is more data, there is more information kind of coming out year by year.

I see patients coming in my office with lousy blood pressure control, no one is paying attention. So, the opportunity exists here to refocus the attention of practitioners, the public, everybody on the fact that we have got a lot of

information that says that controlling blood pressure is really, really important, and can save a lot of lives and a lot of morbidity.

So, the more we can say that will create some noise, some discussion around this, the more the public health is going to benefit. Now, the challenge, of course, is what can we say, because of all the legacy issues involved, but I think that it is really important that we try.

DR. TEMPLE: Let me mention one thing. There is no intent here to try to sort of cover all the things that drugs that are nominally antihypertensives do. So, for example, if a so-called antihypertensive is used to treat heart failure, apart from blood pressure, we are not trying to change any of that.

The trial that they have done would still be there. If there is a post-infarction study for one of them, they still have that, no intent to influence that, but a little bit, like going to the previous comment, there is some tendency for this to decrease the distinctions or potentially, it

depends on what you advise us, there is the tendency to decrease the distinctions when it comes to just lowering blood pressure.

So, you have got to decide whether you like that idea, but we are not.

DR. CARABELLO: But I see this as a positive obverse to cigarette labeling. We went from cigarettes are dangerous to your health to cigarettes cause a whole series of things, and that is what is on the label.

I think that instead of you should treat hypertension, we should come up with a label that says you should treat hypertension because it will save lives from stroke, heart attack, et cetera, how far we want to go with that, and whether cigarette labeling had an effect, I have no idea, but we are, with the exception of the VA, doing a lousy job in controlling blood pressure, and I think anything that we can could do to make that better we should.

DR. HIATT: Clearly, this is an important discussion from a public health point of view, so

related to Question No. 1, it seems the overwhelming weight of evidence going back decades to the first thing internists could do to modify a disease outcome, it's all about the blood pressure, and what we heard today is very consistent with that.

I don't think that is terribly debatable. I mean the public health consequences of proclaiming that are huge, I think, or would hope to think so.

The issues that I think are going to be more of a struggle in my mind are two things. One has to do with the sort of a Bayesian approach to the absolute benefit, and I do think it varies by population. So, whether we are talking about a relatively low risk primary prevention population versus a relatively high risk quasi-secondary prevention population, I do think that the labeling and the discussion around this issue should reflect the pre-test probability of an event, because we all know that the absolute risk reductions are much bigger when you have a higher background event

rate.

I think the second thing is that the discussion should focus a bit on there are some class differences that may, in fact, matter, and there are probably some things that maybe really don't matter, so the diabetes discussion, you know, maybe isn't quite there yet, prevention of renal disease, that is not there yet, but maybe the heart failure discussion is worthy of serious consideration where the public ought to know that there might be differences between drug classes.

But my thought would be to limit the amount of distinction between these drug classes and focus more on the blood pressure control as the first point, and the second point to focus on the event rate issues and how these relative risk reductions apply to different populations, and then very, very carefully raise up any class differences that might truly matter, and minimize any differences that don't matter.

DR. NISSEN: Tom.

DR. FLEMING: I guess in general terms, my

sense if what we need to do is to state what we know, but not overstate what we know. What is it that we are trying to do with antihypertensive drugs, what is the biological process, what are the clinically tangible benefits we are trying to achieve, and I found all the presentations today very helpful, very informative, and just quoting Jay Cohn's characterization about hypertension, it's a progressive cardiovascular syndrome associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidney, and vasculature.

I find that helpful because it helps me kind of think in terms of, to put it into context, what are the mechanisms of action here that the disease process at hand is using to induce what we care about, what are the outcomes. The outcomes are measures, such as stroke and MIs, heart failure, cardiovascular-related deaths, renal damage. These are the things that we are trying to impact.

Being someone very conservative about

surrogate endpoints, it is quite an acknowledgment for me to say that I am persuaded that lowering of blood pressure is one of the best established surrogates that we have.

It does, in my view, with all the preponderance of evidence here, substantially represent how these interventions are influencing outcomes. Having said that, I am highly inclined to think that there are still a lot more to the story, that there are still a lot of things we don't understand about how each of these interventions can be influencing outcome, and, of course, how these interventions can be inducing unintended effects.

So, to simply state that an intervention that lowers blood pressure is, as a result, going to yield these benefits, is I think overstating what we know, and some extreme cases, we know that high-dose diuretics, we think it is through hypokalemia, we know that short-acting calcium channel blockers, we have specific examples of where we know enough that there are some unintended

mechanisms that are occurring.

We also know that there are differences in heart failure between what ACE inhibitors and beta blockers have in a more favorable sense versus what doxazosin and calcium channel blockers have in an unfavorable sense.

There are a lot of additional analyses that we have heard today that leave me very uncertain. I had thought coming into today's discussion that examples, such as LIFE and HOPE, potentially characterized interventions that might have had beneficial effects on our targeted endpoints, not fully captured by blood pressure lowering, and yet I think some very good explanations have been given about the fact that if blood pressure lowering isn't necessarily what we measure it to be, our measurements are not always captured in a consistent way, at the right times, to fully understand what that overall effect is.

We have heard some other analyses from Steve MacMahon that pointed out, for example, there might be differences in how ARBs and ACE inhibitors

are achieving effects on MI, for example, but might not be fully captured by effects on blood pressure lowering.

So, just to kind of stop, there is much more to say, but just to kind of stop at this point, my sense is there clearly is more to the story than we currently are including in the labels, that should be included about what we do understand about the implications of blood pressure lowering.

Clearly, however, those implications are still specific to classes of interventions, they can be specific to issues that in many cases we don't fully understand, which is how dose and schedule and PK influences outcome, and what unintended mechanisms, what influence they would have.

So, my sense is we should say more, but we should still be cautious not to overstate what we know.

DR. NISSEN: Well, you know, it is very important what you say because, in fact, unintended

mechanisms are a hazard of all drug regulation. I mean the example of the thiozolidinediones, where one drug in the class caused liver failure, and the rest of them didn't. I mean it's an idiosyncratic effect, and they do all the same beneficial things, but one drug has a hazard that we weren't aware of.

So, we can't immunize ourself against that. There always has to be, in drug approval, an adequate safety database, an adequate postmarketed surveillance to find the unintended consequences.

What I am coming down to is that we can say something about lowering blood pressure, we can't say as much about that as we can say about some individual agents based upon studies, but there are some things we can say about blood pressure in general based upon the totality of evidence.

There are other things we can say about classes of drugs, that it appears that there are certain benefits of some classes of drugs that have been pretty robustly shown, and that should be considered a class benefit unless there is evidence

that it's not the case.

Then, we can say even less about individual agents, but as we walk through this, it seems to me we have got to find those commonalities. What can we say about blood pressure in general? What can we say about ACE inhibitors and calcium channel blockers and diuretics, and then what can we say about individual agents? Well, that comes down to individual drug labeling.

I think the challenge is where to draw each of those dividing lines in a scientifically appropriate fashion.

Bob, you wanted to say something.

DR. TEMPLE: The unintended consequences issue is very important when you are relatively unfamiliar with classes of drugs, but every class of antihypertensives, I am not sure there are any exceptions, has had in one form or another, not necessarily in hypertension, but it could be heart failure, hypertension, postinfarction, very substantial outcome studies, almost all of them,

maybe not alpha blockers so much, but most of them.

You are reasonably comfortable about those, it's not as though it's a brand-new class like might cause liver disease or something that you don't know about. These have mostly been through that, so we are relatively unworried, I would say.

I guess the one thing to keep remembering is that what we know about the drugs that aren't as good at heart failure as some of the others, is that they are not as good at heart failure as some of the others. We don't really have evidence that they are bad, which is an important potential distinction.

DR. SACKNER-BERNSTEIN: I think the need for accuracy in the labeling, as evidence continues to accumulate is very important, so I would agree very much with Tom's point, but I think that when we start talking about class effects, we are being somewhat naive.

The only thing we know for sure about a class is that it affects a particular receptor. It

is not possible for us to know, with a new chemical entity, even if it's within a certain class, that it doesn't have these untoward effects.

You can look at beta blockers. There is the atenolol story that we discussed earlier, about its lack of efficacy at reducing strokes and cardiovascular events based on the meta-analysis despite lowering blood pressure based on those controlled trials.

So, while I would agree that saying something is very important in order to make sure the message is out there for people to follow, while we should talk about the importance of blood pressure lowering, because I think that is the overriding factor, we do need to recognize that there are these exceptions, and by putting these exceptions in there, in the following paragraph or the following sentence, it also creates a level to which new applications and new development programs will hopefully realize they need to strive to, to prove that they shouldn't be listed as one of the exceptions that may have some concern.

DR. CARABELLO: Then, what about antihypertensives before randomized controlled trials, alpha methyldopa, quinidine, I don't think we know specifically what they do to mortality. Will we include them in this labeling?

DR. NISSEN: That is part of the discussion, and I think you would like to air some more discussion about that. That is what I meant when I said that there are some things we can say about all antihypertensives, they are more limited than what we can say about specific classes, so we are going to try to divide those lines up a bit today.

Dr. McCleskey.

DR. McCLESKEY: Thank you. I would like to just perhaps throw some comments out that might be representative of at least some members of the pharmaceutical industry. We are certainly key players and stakeholders in this issue, and I think I can represent the industry fairly by saying that, number one, we want to encourage this committee and the FDA to do what is best for the public health,

as well.

If it's in the public health interest to publicize this kind of benefit of these classes of drugs, we certainly would want to endorse and encourage that, as well. It does beg the question, however, that Dr. Cunningham raised earlier would a change in the label actually produce a beneficial result. I think it would for some of the reasons that you mentioned, Bob, but nevertheless, it does beg that question.

But in balance, in fair balance, as you consider this issue, keep in mind the impact that it might have on the pharmaceutical industry and the future of pharmaceutical inquiry. We heard today from Dr. Cohn and Dr. Pickering about issues that challenge the overall statement about a class effect.

if there is a class of label that is applied generally, it seems to me that then that increases the importance of maintenance of specific trial information in labels that differentiate a given product from other members of the class. In

fact, it may enhance the importance of that differentiation being included in future labels.

Secondly, the considerations that were articulated very nicely I thought by Dr. Pamplin of King Pharma, were assigned benefit more universally without a clinical outcome trial raises issues of safety very much like the issues that you just spoke to a moment ago, does that, in fact, oversimplify the issue and hurt patient safety as a result rather than doing what we are striving to do by including some general statement.

Finally, I was struck by Dr. Portman's comments earlier, complimenting the FDA on FDAMA, and how much increased scientific understanding has resulted because of the encouragement of industry to do further studies and further inquiry.

I just hope that by virtue of applying some kind of class label, in fact, the opposite wouldn't result, that it would result in some kind of disincentive to further inquiry from future pharmaceutical research.

So, I would say, in general, I think the

pharmaceutical industry would be very interested in supporting and encouraging class labeling if, in fact, it enhances patient safety and care, but at the same time, is there a way to devise a methodology and a mechanism to where specific scientific inquiry and pharmaceutical inquiry in the future can also be supported and encouraged.

DR. NISSEN: Before Bob speaks, I just want to point out that none of this precludes including specific trial information in a drug label, where you have done a trial. I mean that is always going to be the case, and I assume, Bob, you are not going to take away that opportunity.

DR. TEMPLE: No, but the recent conversation points out the difficulty here. In order to label a drug as effective in hypertension--I am not talking about heart failure or something else like that--you need unequivocal evidence that it has a favorable effect on stroke, et cetera, et cetera, et cetera.

None of the drugs are going to be labeled except chlorthalidone probably, because there

aren't any more placebo-controlled trials. You just saw someone try to make the case for a drug that was the subject of the largest hypertension trial ever done, and it might just make it, it might just make it. Nobody else is going to make it.

So, if that is what it takes to get into the label for none of the other CCBs, none of the A2Bs, none of them are going to make it, they would be relying on active control trials. The constant assumption will be the devil to make the case for, and it won't happen. It absolutely, positively will not happen. That is why it never has happened.

So, doing this depends on deciding that you are convinced enough that lowering blood pressure, maybe even with clonidine is a good thing, and that the doubts you have aren't enough to keep you from doing it.

Again, I am not taking a position on this, but there is no way each of these drugs is going to get a claim for heart--I mean maybe stroke for some

of them, nothing else, no chance. They are never going to make it, because you don't have any more placebo-controlled trials since, you know, since SHEP, that is the end of it.

So, the only way to have a general labeling about outcomes in hypertension is to make some assumptions that we are all going to be very uncomfortable with at least until we talk it through. So, I just want to be clear on that, because individually, they are not going to make it.

DR. NISSEN: Tom, you were next.

DR. FLEMING: I just wanted to follow up, Bob, on this, and my comments here actually related to what I was wanting to discuss on Question 3.2, which relates to how specific should we and can we be when there are direct data on that specific agent.

I guess my sense about all this in the spirit of what I was saying before, which is saying what we know, but not overstating what we know, laying out what in general terms is known about

antihypertensives and about the specific class in which this agent lies, but then to be very explicit about the extent to which there are data on this specific agent.

So, why can't we, in fact, when there is an agent in a class for which there isn't a formal valid placebo-controlled or non-inferiority assessment on clinical endpoints, acknowledge what we know about the class and about antihypertensives in general in the relationship and what is likely to occur relative to these clinical endpoints, but reward those sponsors that have done trials that definitively establish what the effects are on those endpoints, and make that explicitly clear in their label?

DR. TEMPLE: That is the thought. I am just pointing out very few of them are going to have that. You know, chlorthalidone, lots of data on SHEP, whatever.

DR. FLEMING: But Dr. McCleskey's comments were right on target on that point. What we do should not be a deterrent to sponsors having the

incentive to do more detailed studies that actually more conclusively establish effects on those clinical endpoints, and when they do, they should be rewarded.

DR. TEERLINK: I was actually going to pick up and say much of what Tom just said, that I think one of the things we can include is this concept of level of evidence. I think one of the things that has been useful for a lot of the more recent guidelines and things, not only do they say what the statement is, but also the level of evidence for each of those things, so as we do a general statement, a parenthetical comment can say this drug was part of a class that contributed this, this drug was specifically studied within this context and contributed to this finding, or this drug is from a class that we don't really know, but we think blood pressure is important.

So, we can include those different levels of evidence as we develop going from a generic to a more specific discussion of the drug specs.

DR. NISSEN: I don't want to be one to

throw a monkey wrench in this, but I feel compelled to point out something here, and that is that for almost all the classes we are talking about, there is at least one outlier I know of.

For beta blockers, beta blockers with intrinsic sympathomimetic activity, do some nasty things. There is at least one drug in the ACE inhibitor class that causes agranulocytosis, short-acting nifedipine had some potential hazards, high-dose diuretics, as has been pointed out, have some hazards, so we had better be pretty careful here, because, you know, there have been plenty of examples where things, you know, in a class that looks pretty good, did something we didn't want it to do.

DR. TEMPLE: Clearly, you mention some bad adverse effect, if there is one, you know. Labetalol has liver problems. Nothing changes on those things, nothing, nor would there be any intent to.

DR. NISSEN: I guess what I am pointing out, though, you know, I share Tom Fleming's

general discomfort here, and the general discomfort is around the fact that unintended consequences of drugs will always be with us, you know, things that we just never anticipated.

So, now you come along and a class looks fantastic, and you bring a new drug to market in that class, and there is something about it that is bad, that we don't know about. It looks very good, it gets marketed very aggressively because it is now a patented medication, and then we find out later we screwed up.

I am trying to be sure we don't make ourselves excessively vulnerable to that.

DR. TEMPLE: You have got to divide that into two parts. If you screwed up because it turns out to be hepatotoxic, that is the normal order of things. If you screwed up because it doesn't lower stroke rate, that's different. If that is what you are worried about, then, you might be very uncomfortable about doing this, you might want to just leave labeling the way it is, because that would be very unnerving. The fact that it causes

some toxicity, that happens sometimes to any drug that is new--

DR. CARABELLO: Obviously, the question is simply do we want to write the same label for every medication conceivable that lowers blood pressure, and I think I have my answer to that, but--

DR. NISSEN: What is your answer, because I mean that's what we are talking about here?

DR. CARABELLO: My answer is no, because I mean I think I know, I mean because the data have accrued from the drugs we have talked about today, but I have not a clue whether alpha methyldopa or short-acting nifedipine or beta blockers with intrinsic sympathomimetic activity do those things.

DR. NISSEN: Dr. McCleskey.

DR. McCLESKEY: Just one other little appendage to what I was saying before, and I appreciate this discussion, the fact that you state that specific study information will be retained in the label, in fact, potentially enhanced.

I think unstated by many of the industry people here, the proprietary industry here, if some

kind of a class statement is contained, would the overall result of other information in the label then be somewhat diluted, would its importance be somewhat diluted?

Again, we don't want to stand in the way of this, we want to encourage this if it will improve patient safety and patient health, but is there a way these kinds of comments can be incorporated to where the industry's concern will be appeased, and, in fact, others will subsequently be enhanced?

DR. TEMPLE: Let's be clear. At the present time, drugs for hypertension say this is for hypertension alone or in combination with other drugs. That is what they all say. There is, to my best knowledge, with the single exception of I guess the comparison with atenolol, that is in labeling, there are no outcome studies for any of these drugs with one or two exceptions, at least partly because all the placebo-controlled trials came a million years ago and are for drugs that are off patent, and nobody cares about them.

I guess you could put in SHEP if somebody cared about chlorthalidone, you would probably get SHEP in the label or you could have asked. No one ever did, because no one ever cared. So, the current situation is there isn't anything about hypertension. There is a lot about heart failure, there is a lot about treating diabetics. Those things are there.

There isn't anything about this now, and little prospect of there ever being it, because as we discussed before, there aren't any more placebo-controlled trials. It is very unusual to beat an active drug, not that the answer is never, but it is not easy. So, there is little prospect of any of those getting in.

DR. NISSEN: There are two other issues that are implicit in your Question No. 1 that worry me. Let me see if I can articulate them. Let me use a concrete example. Both ACE inhibitors and ARBs are not so effective at lowering blood pressure except if you give them with a diuretic where they tend to work pretty well.

So, because a lot of the studies we were looking, and you asked this question very explicitly, at combinations, we are looking at regimens, you know, it is very hard to tease out from a study where you could give diuretics. How much of the benefit came from the lisinopril and how much of it came from the diuretic, or what?

So, this always bothers me about all of this, because, you know, not only do we not have placebo-controlled data, even the data we have uses various combinations and permutations.

DR. TEMPLE: We totally agree. If somebody asked to say something about a single drug, I don't know what data they would use. There are no such studies.

The closest in a way is ALLHAT where at least you weren't allowed to use anything sensible as an added-on, so you do get a pretty good idea of what the drug does by itself.

DR. NISSEN: In addition to this issue of the fact that we are looking at combinations, you know, Tom, I have watched you do some mental

gymnastics at these committee meetings before to try to answer those questions, and it is really tough statistically, but the other issue is intraclass heterogeneity.

This differs a bit from drug to drug. Maybe all ACE inhibitors are the same, but are amlodipine and nifedipine the same? Probably not. Are amlodipine and verapamil the same?

I mean the calcium channel blockers, for example, some have very big peripheral vascular effects, some of them have more central effects, and so within these larger classes, depending on which class you are talking about, there is a fair amount of intraclass heterogeneity, and it depends on what class you are talking about, how much heterogeneity you have.

So, we have to be willing to talk about that when we talk about class-related effects, because I have a harder time in some classes than I have in others in making sure it really is a uniform class.

DR. TEMPLE: Let me just tell you what our

thought was and see if that helps. The only thing that you have to suppress your concern about differences is if we are going to be able to do this, is the idea that lowering blood pressure is good, and I think in light of what Dr. MacMahon showed, that pretty uniformly across all classes, it has favorable effects on several major outcomes, and you can debate other outcomes, and maybe you are not ready to say that.

That in no way says there aren't reasons to choose one therapy over another on a wide variety of grounds, because of other effects it might have, because of concerns about toxicity, because of ease of taking it. There is a whole bunch of reasons. Nothing says those wouldn't still be there, and they should be, and if a drug has a particular disadvantage or has hepatotoxicity, that is going to be prominent, it is going to be a warning, and all of those things would still be there.

The crucial and I think difficult question, it is not the way we usually work, is

whether you are comfortable in saying lowering blood pressure is good, we know of no exceptions. So, it is clear as for stroke, it is not as clear for some other things, whatever modifications it has, and being able to say that, and that is why we use these drugs, and then you choose the drug individually based on a whole lot of reasons including the size of the effect it might have. There is a lot of reasons, some are different in blacks and whites, and there is a million of reasons for individualizing therapy.

DR. NISSEN: Tom.

DR. PICKERING: I think we all agree that blood pressure is the number one, but I don't think realistically, you can ignore class effects. There is a lot of published guidelines from organizations like JNC VII, the National Kidney Foundation, the American Diabetes Association that all makes specific recommendations, well, general recommendations about class effects.

My feeling is that you should probably refer to these without necessarily being very

specific about individual drugs, and certainly any statement that the FDA makes should not conflict with these other statements.

I think if you talk to nephrologists, they would mostly agree that ACE inhibitors probably should be used to prevent the progression of renal disease.

DR. KASKEL: Thank you for bringing that up. I was going to mention about an initiative from the NIH called the National Kidney Disease Education Program, now in its fourth year.

They are meeting next Friday here to discuss the progress of this program, which is aimed at educating the public and primary care doctors about taking care of patients with renal disease, and hypertension is the first thing they talk about.

You need to control the blood pressure to prevent progression, and if you are a diabetic, you need to think about a class of drugs, and they make it quite clear what they are talking about based on the controlled trials that have shown some

efficacy. It's on the website, for anyone who wants to look at it.

So, with that said, we are telling the public and we are telling primary care doctors now about a preferred class of drugs for treatment in that group of patients.

DR. NISSEN: You know, there is another problem here that I wanted to also make sure we got on the table, and that is this. For diuretics, you know, we had obviously this huge trial ALLHAT and some very broad statements. I mean I watched every television program the night that it was reported, and heard the same message over and over again, that diuretics are unsurpassed in efficacy, and I thought about the fact that I haven't seen a patient on chlorthalidone in five years.

So, now I have got a really big problem, you know. I am glad to know you take it, because you are the first person I have met that takes chlorthalidone.

The reality is--maybe our hypertension experts can tell us--what percent of patients

taking diuretics are taking hydrochlorothiazide and what percent are taking chlorthalidone. Is it possible that hydrochlorothiazide is sufficiently inferior to chlorthalidone that that generalized recommendation is actually not a good recommendation, because it is actually taking people to use a weaker drug, that if it had been really tested in ALLHAT would have been slightly inferior?

So, it is pretty tough when the drug you have tested so much of is not used by anybody.

DR. TEMPLE: The fact is you are not going to get good dose-response information these days on diuretics. Chlorthalidone has a 30-plus hour half-life. You actually can take it every other day, and it's not exactly the same.

Having said that, though, does that matter for this statement? That is what you have to decide. You are not going to say choose chlorthalidone or choose hydrochlorothiazide. You are going to say lowering blood pressure with a wide variety of drugs has good outcomes, and then

people will, on various grounds, choose the particular drug they are going to use.

For example, if you get your dose of chlorthalidone up too high, you are going to get hypokalemic, so you might decide to use it or not use it depending on whether you are on other drugs that raise the potassium, and a wide variety of things.

This doesn't free you of the need to think, but maybe you can say something general about it. That is really what the question is.

DR. PORTMAN: I guess another question that I have is how we classify the particular drugs that we are talking about. If we call an ACE inhibitor an antihypertensive, well, certainly it does that, but it does other things, as well, and I think many people who take care of diabetics, who take care of patients with chronic kidney disease, will have patients who aren't even antihypertensive, and will have them on these drugs for their mechanisms in the kidney, not necessarily the systemic hypertension.

So, how do we deal with that issue?

DR. NISSEN: Well, that is not precluded. I mean again I heard you loud and clear. What you are saying is that drugs that have specific benefits for specific diseases demonstrated in clinical trials will always get to put that claim in.

You know, if you show you reduce albumin excretion or protect against worsening kidney function--I know you don't like albumin, but that's all right--the bottom line is that there is nothing here that says you can't give specific claims to drugs for specific benefits demonstrated by specific clinical trials. I get it, I understand what you are saying.

DR. TEMPLE: Right, and if your patient is diabetic and has--I mean there is actually a clear distinction between several drugs that are normally antihypertensives and their effect on that. We actually have data on that point.

DR. NISSEN: Some of these drugs reduce angina frequency. You are not going to take that

way, right?

DR. TEMPLE: Right.

DR. NISSEN: Some of them work if you have had a heart attack, and some of them don't.

DR. CARABELLO: Obviously, we could craft a label that was somewhere in the middle, where we say that medications in this class that have lowered blood pressure have done so-and-so, saved lives. We don't know whether this specific agent has done that, because it has never been tested, but isn't part of what we are doing here is to use the label as an education device to increase the number of patients whose blood pressure is treated adequately?

DR. TEMPLE: The format, I mean they are all different, but one of the formats is a sort of general statement about why lowering blood pressure is good, followed by a paragraph that says you will find the specific studies of this drug in the Clinical Trial Section, or something like that, and then obviously, any other claims they have, those are unaffected.

DR. NISSEN: Jonathan.

DR. SACKNER-BERNSTEIN: The comment that was there before, that we really need to agree with, treatment guidelines I think is very important, but there is an exception that I think would be reasonable to that, would be that if there are data that the FDA has access to, that the Guidelines Committee may not have had access to, from which the FDA can actually comment, those data should be used in a way that can go beyond what the treatment guidelines committees would be able to say.

But as it goes to the label, maybe I am getting ahead of the order that you guys had envisioned, Version 4, I think does a nice job of both saying that blood pressure lowering is important, but also focuses on some of the exceptions that have been noted.

Specifically, what it includes that I like, is the difference between the impact of low-dose diuretics and high-dose diuretics, particularly without dealing with potassium loss,

and how that is associated with a differential effect on clinical events and clinical risk.

I think that it is important to get back on the table, the discussion of atenolol, and maybe I am a lone voice here, but I know Tom brought it up before. The meta-analysis of atenolol, I think is very important because I know that previously, there was a discussion by Dr. MacMahon that by taking the influence of beta blockers out of the statistical modeling, it showed that that didn't have an effect, but it does have an effect.

If you have a patient who is being treated in clinical practice with a medicine that lower blood pressure, that gives the physician a false sense of security, number one, because it doesn't reduce events, and it furthermore reduces the ability to treat with another drug, because then maybe the next drug wouldn't be tolerated because of further blood pressure lowering, so in that setting, I think that atenolol, from the best data that I have found in the literature, is associated with potential for risk from a public health point

of view, because it may be a barrier to blood pressure lowering with drugs that also favorably affect natural history of disease.

DR. FLEMING: I am glad Jonathan made that point, because it leads right into the point I wanted to make, which was, Steve, you asked a question before, I don't think we fully addressed, and that is, you said the guidelines have come out now and have strongly indicated the merits of diuretics, and you pointed out that chlorthalidone has been the basis of the scientific evidence for that, and yet in your sense, hydrochlorothiazide is what is being predominantly used.

The discussion that ensued indicated appropriately that we can make clear when certain agents have been the specific agents studied, we can make that clear in the label, and that would, in fact, provide potentially greater encouragement toward chlorthalidone, but it wouldn't necessarily prevent the risk, that now Jonathan is pointing out, and that is--and I don't know the answer to this--but if, in fact, hydrochlorothiazide is, in

fact, providing less benefit relative to the amount of blood pressure lowering that it provides than chlorthalidone, if that were the case, then we would be potentially misled.

One example of that, that I was going to use, as well, is my sense of the LIFE trial coming in today was that it might be an example of where the effects that we are having on stroke is exceeded by what the blood pressure lowering component of the effect would indicate, and yet what we are hearing or what I have heard is that it might be that atenolol is providing less actual effect against stroke reduction than what you would expect from the blood pressure lowering.

So, I need to understand. Is, in fact, that realistically possible? If it is, then, as Jonathan is pointing out, we are at risk of misguiding people by just giving global information about what the effect is on stroke and other major morbidities as a result of blood pressure lowering.

DR. NISSEN: Let me help you with that a little bit, Tom, and say that no one here is saying

necessarily that every drug has the same impact on every endpoint. I mean what the real conclusion of ALLHAT was, when you throw everything into the mix, the hazard ratio for lisinopril, amlodipine, and chlorthalidone was indistinguishable, and that is what it showed, but that doesn't mean that individual endpoints for individual drugs don't go in one direction or another.

DR. FLEMING: If hydrochlorothiazide had been in that mix, I thought you were saying earlier on maybe it wouldn't have come out the same, isn't that what you asked?

DR. NISSEN: What I am saying is I don't know, but I did hear Tom and I have heard other hypertensionalogists, who do this for a living, tell me that there is pretty strong evidence that hydrochlorothiazide, it is not because there is a difference in outcome, it is because there is difference in effectiveness at lowering blood pressure, that is, one is a more potent agent that has this very prolonged duration of action that seems to drop blood pressure.

Now, Tom, was it you that pointed out that there was pretty robust differences between the two in at least one recent trial?

DR. PICKERING: Not between hydrochlorothiazide and chlorthalidone, but it has been suggested, for what it is worth, one of the reasons why the ANBP-II trial showed an apparent advantage of ACE inhibitors over diuretics was that they used hydrochlorothiazide, whereas, ALLHAT used chlorthalidone, so it's consistent.

DR. TEMPLE: But it's all the dose. I mean the VA studies initially used hydrochlorothiazide at 100 mg, and maybe that is why the cardiovascular death rate wasn't improved so much, but there really isn't--it is hard to say what corresponds to 25 mg of chlorthalidone, is it 50? And then that is thrown into a cocked hat because you can always add triamterene and probably go on to 100, which we know work from the VA studies, had a profound effect. So, it is very hard to get good data on that question.

DR. FLEMING: Before leaving this point,

what about atenolol?

DR. NISSEN: Again, what you are referring to, Tom, is that we have some uncertainties. It is interesting, because on the LIFE debate, you and I were on opposite sides of the question. I was not prepared to give the superiority claim because I wasn't convinced that we knew enough to be able to do that, and I knew that was a precedent setting sort of action, and I was being very conservative about what I was willing to say.

There is some suggestion that maybe atenolol and some endpoints isn't very effective. I know Franz Messerly [ph], who is a very smart guy, thinks atenolol is much closer to placebo, you know, that it is not a very effective agent at reducing hypertension and mortality, and he has done a lot of analyses that convince him that that is the case.

I can't verify one way or the other whether he is right or wrong, I just know that these issues have come up.

DR. HIATT: I, too, have jumped ahead a

little bit, and I would like to get back to Bob Temple's point. I strongly support the concept of some kind of informational statement about the class of drugs that lower blood pressure, and I am wondering if this committee could reach some consensus on what those key points might be.

I would suggest that they might be hypertension does bad things, lowering blood pressure does good things, the lower the blood pressure the better, and there may be a comment about what, of those cardiovascular events, seems to be most effective. That is my short list.

If we could come to some agreement about whether that is appropriate or not, then, you could segue into, well, what about the class differences, and what about this and that.

DR. NISSEN: I think, Bill, we are going to do that in Question No. 2, which I would like to get on to fairly shortly, where we are going to say which of the specific benefits are we willing to comment on and which of them do we not think there is enough evidence to comment on.

DR. HIATT: Not exactly, because we are still skipping ahead. I realize that I now a bit more appreciate the pitfalls of trying to go too far with this. I mean phlebotomy lowers blood pressure, too, and that is not a good thing. So, I don't want to go that far.

DR. NISSEN: Tell that to my barber.

DR. HIATT: So, if there is some way about what do we absolutely know about lowering blood pressure and how much that is worth saying, that doesn't preclude rewarding specific kinds of outcomes studies to go forward, I would appreciate that.

DR. TEMPLE: I think that is the goal. Let me ask you before we leave it, if one drug that lowers blood pressure about as much as any other drug, doesn't have the expected effect on stroke, what does that mean for the whole concept, how can that be?

DR. HIATT: Totality of evidence.

DR. TEMPLE: No. The premise here is that for the most part, lowering blood pressure, however

you do it, is a good thing because it reduces stroke, heart attacks, blah-blah-blah. If the atenolol finding is a true bill, is that is convincing, I don't know whether it is or not, what does that do to the whole theory?

DR. FLEMING: Couldn't you be having other effects that counterbalance and some mechanism, blood pressure lowering would actually be reducing stroke rate, but other mechanisms could increase?

Jaconite [ph] and fleconite [ph] suppress arrhythmias, but, in fact, might there be other counterbalancing mechanisms that lead to an increase in sudden death?

DR. TEMPLE: Suppressing arrhythmias is not in the category of hypertension, it has never been shown to be of any value. This is different. We are saying, or the premise here is lowering blood pressure always turns out to be a good thing.

DR. HIATT: I am a little worried about the logic, because I can see where that would take you, and then you start looking for all the exceptions and avoid the public health issue that

it is good to lower blood pressure.

I think we can craft language that says in most cases, for most agents, lowering blood pressure reduces events. There may be exceptions to that. I mean you obviously have a little bit of wiggle room there, but I wouldn't let one study--beta blockers have been used since the beginning of time to reduce blood pressure.

DR. CARABELLO: I really think that is an important comment. While the totality of data may say one thing, what we learned this morning is a single trial may go in an opposite direction, and we have specifically said that in order to grant an individual finding, we wanted two large randomized controlled trials to show the same thing.

So, I don't know that I believe that atenolol isn't effective in preventing strokes.

DR. TEMPLE: I agree, I don't know that I believe it either, but if you did come to believe, and the data were strong, that one member--and, by the way, it's a member of a class, there are a lot of other beta blockers, too--not only that, it is a

drug about which you know a lot of things.

It has been in reasonably sized outcome studies, it didn't do anything bad in those, did sort of good things, borderline good things anyway. If it turns out to lower blood pressure and not have a favorable effect, what does it do to the whole theory?

DR. NISSEN: Bob, what I didn't say was we shouldn't expect there to be uniformity of benefit. We already heard from Steve MacMahon, for example, that it really does look like that calcium channel blockers, millimeter per millimeter on blood pressure, do a little bit better on stroke than other classes, so there are classes that are a little better than average and classes that are a little bit worse.

We heard that ACE inhibitors look better than calcium channel blockers on heart failure. I am not troubled by that. I am not troubled by the fact that for a specific endpoint, that a millimeter of blood pressure lowering doesn't always get you the same benefit. I don't think

atenolol is bad for you. I just don't think it's as good on that endpoint as, say, amlodipine, where you saw in ALLHAT it had a terrific result with stroke.

DR. TEMPLE: I was addressing the question of whether, if it had no effect at all, that would shake you. I have got to say effects on stroke to me are different from heart failure. I am not surprised that drugs that aren't effectively treating heart failure don't look as good on heart failure. I mean I would have told you that was going to happen before you did the trial.

DR. TEMPLE: Not being as good on stroke is much more of a problem.

DR. NISSEN: I agree with you, that's fine.

I think you did hear Steve MacMahon's analysis that suggests that there is a class of drugs that looks, for every millimeter of blood pressure lowering, it does a little bit better on stroke, does a little bit worse on some other things, and you have to live with that.

I mean specific endpoints may, in fact, be more favorably affected by one class than the other, and that is what you may want to say in the discussion that relates to the class as opposed to the discussion that relates to all hypertensive drugs.

You can drill down to those class-based things and then to individual benefits. So, there is kind of a pyramid here of what you can say at the top level, at the next level, and the next level, and hopefully, we are going to drive those lines in a reasonably logical and scientific way.

DR. SACKNER-BERNSTEIN: Can I just say one more thing about atenolol and then I will be quiet about it?

The meta-analysis that was in Lancet actually had, although they included four control trials with atenolol, not one, one of them was an open label trial. That was the one that made stroke look better.

The three that were blinded, even stroke was not affected despite blood pressure lowering.

So, it's three studies, three outcomes studies with long-term exposure. The only other outcome study I know of with atenolol is one of the ICIS ones, ICIS-I or II, would be one week of therapy post-MI that had the beneficial effect. That is a one-week exposure.

Perhaps that is enough to do something good where some other unknown effect of the drug, because we haven't tested for it, we didn't know about half the receptors, enzymes, or genes then that we know now. Maybe there is something bad about that drug, and I just think it is important not to throw it away just because there is one exception.

There is always going to be an exception, and to disclose that is an important incentive for physicians, for investigators, for sponsors to know that if you do the study and prove you are not an exception, you will get something good, and if you prove you are the exception on the good side, you will get something even better.

DR. PROSCHAN: So, would you say on the

label that atenolol is an exception?

DR. CARABELLO: What about if you have high blood pressure following non-cardiac surgery where atenolol extends life?

DR. PICKERING: I think of all the classes where there are major differences between individual drugs, beta blockers are probably the most. There is intrinsic sympathomimetic activity.

There are three drugs approved, three beta blockers approved for heart failure, three for post-MI patients, atenolol has not made the grade in either of those, and there are other beta blockers that have been tested in heart failure, and not been found to be effective, so I think this is one area where we need to be cautious about class effects.

DR. TEMPLE: Atenolol does have an acute post-infarction claim, not long term, just short.

DR. KNAPKA: I think we are forgetting one thing. We are talking about differences in classes, but could a lot of this be individual difference from people, that they react

differently, and we say, well, it's the class of drugs, but maybe it's individuals will react differently to certain drugs.

DR. NISSEN: You make a very good point, and that is going to be a part of the discussion we are going to have tomorrow for sure, but we are not in the pharmacogenomic era yet. Some people predict that it is coming, and we will see. I will keep my eyes pealed for this.

But, you know, in the absence of that, then, we have got the problem that we don't know. I think there is no question that there are individual patients that have genetic increased susceptibility to both the benefits and the hazards of specific drugs.

It is how prevalent they are in a population that determines what happens. Now, let me give you a very good example. We haven't talked about this yet, but you are talking about labels for everybody, but African-Americans don't respond terribly well to drugs that affect the renin-angiotensin system.

They respond particularly well to drugs like diuretics, so obviously, that doesn't absolve us of our responsibilities to inform in those circumstances where we know that to be the case.

You remember, Tom, in the LIFE discussion, the very troubling finding where everything went in the other direction for atenolol versus losartan in the African-Americans, and quite robustly, I thought.

So, I think that there are individual variations, and we have got to make sure that we don't let that get missed in the gamisch of a sort of an overall label. So, I think your point is very well taken.

Are we ready to move into Question 2? I would kind of like to get there someday. First of all, I thought that was a terrific discussion. Norm and Bob, did you get some of what you wanted there, or a lot of what you wanted?

DR. TEMPLE: Some.

DR. NISSEN: I think we are moving forward. I am going to take us to Question 2, if

everybody will agree to that.

A variety of benefits are associated with drugs that reduce blood pressure. Reduction in the risk of ischemic stroke. Reduction in the risk of hemorrhagic stroke. Reduction in the risk of myocardial infarction. Reduction in the risk of cardiovascular mortality. Reduction in the risk of mortality from any cause. Reduction in the risk of other manifestations of coronary disease. Reduction in the risk of end-stage renal disease. And anything else you want to put in there.

Which items in the above list are attributable to blood pressure reduction and would be expected of any drug that lowers blood pressure?

Discussion, please.

DR. PICKERING: Well, I think the meta-analyses that have been done have provided some of the answers, if I can quote, reduction of 4 mm systolic pressure leads to approximate 23 percent reduction in stroke, 15 percent in coronary events, same in heart failure events, and about the same for total mortality. I think we are much less

sure about prevention of renal disease, because most of the major studies haven't looked at that.

DR. CARABELLO: I think the word "any" is poison, because I think we don't know that. Obviously, there has been discussion about atenolol. There is not much data. I think the word "any" is the word we are struggling with. I know that is at the apex of Bob's question.

I don't know that I would be willing to go with the word "any."

DR. NISSEN: For purposes of discussion, let me take a position here and I will let you throw bricks at me afterwards.

I have been convinced for some years, in fact, I had this discussion with Bob Temple at a meeting many moons ago where I said it is the blood pressure, stupid. I added that to it. What I meant by that was that until proven otherwise, if you look at the results in a clinical trial of a blood pressure lowering drug, that 80, 90 percent or more of the benefits can be attributable to the blood pressure reduction.

In most of the trials, for example, you see the results tend to line up along with blood pressure. In ALLHAT, you got a little bit more blood pressure reduction with chlorthalidone and most of the things trended in a favorable direction.

You got a little bit less from amlodipine, and you got the least from lisinopril, and you kind of see that. So, when you look at the more versus less, is another place where you get that, when you do the Steve MacMahon kind of analysis of more versus less.

So, I guess I am convinced that if there is anything we know in medicine, is that in hypertensive patients, lowering blood pressure produces certain favorable effects. Now, we know it with greater robustness for stroke than almost anything else.

We probably know it for a lot of the manifestations of coronary heart disease, and actually, i think that renal disease is probably also pretty clear that the higher your blood

pressure, the worse your deterioration of renal function over time. We know that pretty strongly.

So, my view would be that we can say that blood pressure reduction has favorable effects. That is not to mean that every millimeter gets you exactly the same amount on every endpoint, but, in general, lowering blood pressure is a good thing, and we can say that, and I don't think there are very many exceptions.

I mean the atenolol argument is about attenuated benefits, not necessarily about absence of benefits or about harm. So, that would be my conclusion here, but I am sure others may not agree.

DR. CUNNINGHAM: Couldn't you just change it from "any" to "almost all," or some little wiggle room statement, or "most," that would make everybody comfortable, and not be stuck out on the end of a limb?

DR. NISSEN: The problem is it doesn't help the FDA, because if you can't live with "any," then, you can't say much. Then, you have to

require the drug or the class to prove something individually.

I know what you are up to here, is you want to know if we are comfortable with saying, you know, if you come out with a new ACE inhibitor or a new calcium channel blocker, and you have got good safety data, and you lower blood pressure by a reasonable amount, that you can say that that drug is likely to benefit people on these endpoints.

DR. TEMPLE: There is another thing thrown in the mix, I don't know whether it would be convincing or not, the epidemiologic data on blood pressure alone, perhaps modified by all the things Jay was talking about, does seem to have a continuous relationship to blood pressure for all of these things.

So, at least for starters, it is not so crazy to think that rolling the blood pressure back would affect those things, perhaps unless the drug cause a vasculitis or did something weird.

The other thing that has always convinced me a little is you can replicate many of these

things in animal models, and they get the same effects or many of the same effects, which sort of makes it seem once again like it is the blood pressure, stupid, if you like, and lends all of this some plausibility.

DR. NISSEN: Blase, you are not comfortable.

DR. CARABELLO: Well, what if Dr. Cohn is right, that what we are doing is intervening with a cardiovascular disease which most of the time, when you lower blood pressure, that coincides with relieving some of the aspects of that disease, but that would certainly leave for separation of those two. That would mean that if the two, in fact, necessarily always go hand in hand, then, lowering blood pressure would not always reduce the risk of cardiovascular disease.

DR. NISSEN: Fortunately or unfortunately, Dr. Cohn has a habit of being right. You know, it usually takes a while, sometimes takes 20 years, but often he has proven to be correct.

DR. TEERLINK: I would share Blase's

concern, though, I think, because I don't know if I would feel comfortable approving a drug coming here if it just showed that it reduced a new class of drug. We have been talking about a new ACE inhibitor or a new beta blocker, but that is not what we are really talking about here.

What we are talking about is a new class of drug come around, and they say, hey, we have developed this new class of drug, it drops blood pressure by 5 mm of mercury, here is the safety data in 1,000 patients, we want an indication for hypertension, and please give us that nice label that you wrote that tells everybody that it reduces mortality and makes people feel better and live longer, and all that other good stuff, and thanks very much.

I wouldn't be comfortable in that situation.

DR. NISSEN: You can set a regulatory threshold that is a little bit different for new drugs and new classes than you do for existing classes, and I think, for example--

DR. TEERLINK: But we are talking about a blanket statement that just reducing blood pressure is good.

DR. NISSEN: We can opine anything we want. I mean you might be comfortable with saying that in classes where this benefit has been previously shown, that new entries to the class can get this benefit, but if you are a completely new class, you need something more. You need more data. Now, what that might be, I am sure you would be interested in.

Is that implicit in your question, or do you think that if somebody came out with a new class, you know, gruntamycin, the gruntamycin class, that lowered blood pressure by 10 mm of mercury, that this would apply to them?

DR. TEMPLE: How is the situation different from when the A2Bs first came along? We approved them because they lowered blood pressure, established what the dose was, had a reasonable amount of long-term data, but there were no outcome studies, and there still aren't really in

hypertension.

So, you want enough information, I mean this is a drug intended for long-term use, you need a certain amount of long-term data, and most of it would be comparative, but you don't expect them to do ALLHAT, at least not now. We could change our mind, so I guess it would just be against chlorthalidone if it were a new drug, so you could get away with only 20,000.

Then, in the end, you wouldn't quite know what you have, but still you would have done something.

DR. NISSEN: Bob, I want to disagree with John and say that there is a very good public health reason why new drugs, now, they may need a bigger safety database because they are newer, in order for us to feel comfortable, because we need at least a couple more classes of antihypertensive drugs, we desperately need them.

I have a clinic full of patients that are on four drugs and five drugs, and I am having trouble getting to the goals that I want for them.

So, what is good public policy? Good public policy is to encourage the development of drugs that are likely to yield very important public health benefits.

I think this would be an incentive for people to develop additional drugs if they knew that they could get something right off the bat from that, that would be potentially useful, so I am kind of leaning toward this generalized label because I want to encourage industry to develop for us the new classes we desperately need in order to be able to control the out-of-control hypertensions that we are seeing.

DR. CARABELLO: But let's go back to the moment for gruntamycin. Suppose gruntamycin--

DR. TEMPLE: That's an antibiotic.

DR. CARABELLO: Well, he made it--just very subtly increases platelet aggregation. It won't show up in any liver test, it won't show up in any of the standard safety things that we do, and it won't show up maybe in the first 4,000 patients that are put on it.

It lowers blood pressure, but it increases thrombogenicity, and at some point, that might bite us in the rear end.

DR. NISSEN: Like a Cox inhibitor.

DR. CARABELLO: Could be.

DR. PICKERING: I am comfortable with the statement. It actually said would be expected of any drug that lower blood pressure. It doesn't say automatically that it will happen with any drug that lowers blood pressure, and I don't see that it necessarily has any impact on the approval process for a new drug, and it is up to this committee to ask the relevant questions when gruntamycin comes up for approval.

DR. FLEMING: I wrote something close to what Tom just said. The furthest that I would go would be to say "and would generally be expected of drugs that lower blood pressure." So, you are giving credit to the preponderance of evidence here, but you are certainly stopping short of a statement that it will always be true of any drug.

By the way, I would make that statement

for stroke. This question relates to 7 different endpoints here, and this is where I come back. I think the clinical trial is collaborative analysis that Steve MacMahon presented. I have been staring for the last several days at Figure 4 in that manuscript, and I think it is very relevant to this particular issue and highly informative.

I think the evidence there certainly does suggest, in my view, that we could say it generally would be expected of drugs that lower blood pressure related to stroke.

Related to the MI and cardiovascular death measures, it strikes me that what we are looking at is some suggestion of blood pressure related effects there, but they don't really become particularly evident until you are at about 5 mm reduction. When you have 2 or even 4, the effect seems pretty minimal. When you get to 5 and 8, then, the effect appears to be more evident.

I don't know if I would go so far as to say there is a threshold effect there, but it doesn't look as linear. When it comes to mortality,

it is very hard to know, because the effects, when you look at total mortality, the effects are difficult to understand.

But when it comes to heart failure, then, the relationship is quite complex, and it is made complex by virtue of the fact that the class that gave the best effect on reducing blood pressure, the calcium channel blockers had a particularly noteworthy adverse effect or lack of favorable effect on heart failure.

So, for heart failure, I struggle more to make the association. For MIs and for cardiovascular death, I think there is an association, but it seems to be more evident when you have large effects, and I am going to keep coming back to this. The analysis that he presented, as well, but suggested when we look at cardiovascular death and MI, and we look at classes, such as the ARBs versus the ACE inhibitors, those analyses really struck me that he was showing today that indicated that the ACE inhibitors may be influencing MI and death in

mechanisms beyond the blood pressure lowering mechanism.

DR. TEMPLE: But that fact shouldn't bother you. I mean if a drug has an additional benefit beyond lowering blood pressure, you know, because it interferes with platelets or something, that is no problem. The question is whether essentially everything that lower blood pressure, or even if it has got to be more than 4 mm before you see it, that is really what the question is.

DR. FLEMING: Although admittedly, as you are pointing out, Bob, if both classes of agents affect MI and affect cardiovascular death, it is relevant that it is acknowledged that they both have an impact, but if we then try to assess our choices based on blood pressure lowering, and we were really caring about, in this population, cardiovascular death and MI, then, that would be misleading, i.e., blood pressure lowering isn't telling the whole story in making comparisons of those two classes relative to those measures.

DR. NISSEN: Tom, let me help you a little

bit. I feel compelled to point out that in this mix here, you have got a variety of levels of baseline risk, and one of the things that it really does is very obvious if you look at all of this, is that as you push the risk to higher and higher levels, you see more and more evidence that even small differences in blood pressure make a lot of difference.

Now, I want to show you how that plays out in some clinical trials, because I think it is highly relevant here.

In the HOPE trial, there was a 20 or 25 percent reduction, very robust statistically. The patients were quite high risk. In fact, they had like 40 percent diabetics. I mean these were really--and they didn't get a lot of other concomitant therapies. They got almost no lipid-lowering therapy, so their risks were kept very high by the fact that a lot of them didn't even get aspirin.

Whereas, in the PEACE trial, a lower risk group of people were treated with a drug which is

pretty much indistinguishable, and the hazard ration was 1.0. So, the question is very difficult because you can't answer it out of the context of the baseline risk that you are talking about.

When I look at the data, if you take a high enough risk population, you can see effects from very small blood pressure differences. You saw that. We were on the Data Safety Monitoring Board for our trial, we took the highest risk people I could find, which are people who already have coronary disease, and showed that a little bit of blood pressure reduction from a pretty low baseline, there were some favorable effects. So, it's all about baseline risk.

So, when you look at these trials, you are looking at a composite across an incredible spectrum of risk categories, and that is one of the problems with seeing the effects.

DR. FLEMING: So, just to be specific, in this analysis, if we look again at Figure 4 here, if we look at the more versus less comparison, which contrasted strategies that had a 4-mm mercury

difference, according to this analysis based on 20,000 people that were in those trials, the effects on CHD and on death, cardiovascular death, were pretty minimal, so that is an aggregation of a series of trials that had the more versus less with the 4-mm difference, whereas, when you looked at the classes of agents that had bigger effects, age, for example, you had much more discernible effects on cardiovascular death and on MI.

DR. HIATT: That was the kind of thing I was concerned about at the very beginning, was that we weren't taking into account the baseline event rate. My interpretation of Question No. 2 is that for some reason the relative risk benefit on stroke has always been high and consistent across trials, but the other event, the endpoints, it is always harder to show mortality effect, we all know that, but it seems to be here if you have the sample size and the risk reductions to show that.

In fact, the point estimates all go in the right direction, in my mind, lends credibility, saying yes for all of 2, and it is just a power

thing, pointing out that patient trials are pretty powered, but that I think, Steve, is a theme that needs to be back on this label is what you expect a patient to benefit is based a lot on their pretest probability of an event.

DR. TEMPLE: Do we think that the absolute benefit is different according to your baseline, or that it is just obvious that you get it? That is what Tom is saying, that even if you look at relative risk, risk reduction, that appears to me more obvious in people who are sicker.

DR. HIATT: No, it's the other way around, isn't it? The relative risk reductions are pretty consistent. It's the absolute risk reductions that are highly different.

DR. TEMPLE: Okay, but that we knew going in, that has got to be almost. But I thought Tom was saying both.

DR. FLEMING: I was saying both for sure.

What I am saying is when I look at the data, not specific to what is the absolute risk, but specific to what is the relative risk, that in

those trials that are comparing strategies that differ by a 4-mm difference, that is impressive in its effect on stroke. It is pretty modest, pretty trivial in terms of its relative effect on cardiovascular death and MI.

But as you move to bigger effects when the strategy is discerned, or yield bigger differences in blood pressure reduction, then, I am seeing more persuasive evidence about how that influences cardiovascular death.

DR. TEMPLE: That doesn't seem troubling at all, Tom.

DR. FLEMING: Who tries for a 4-mm mercury reduction?

DR. TEMPLE: I know that is what you get, but nobody tries for that.

DR. FLEMING: What I am suggesting is for stroke, a 4-mm reduction, you are already seeing very substantial evidence of effect. It looks linear, it looks as though as you linearly increase the effect on blood pressure lowering, you are getting proportionately the amount of additional

reduction in stroke, and I am saying it is not apparent from the data that you have the same relationship. It appears that it takes a larger effect on stroke to discern a larger effect on blood pressure reduction.

DR. TEMPLE: What do you find the implication of that fact, assuming it's true, to be?

DR. FLEMING: Well, are you asking here what conclusions we are willing to say in general, and I would say one conclusion is am I willing to say that you are getting a reduction in MI and cardiovascular mortality through a reduction in blood pressure. I would say there is that relationship if it's a substantial reduction to blood pressure. More modest doesn't seem to be evidence of that difference.

DR. NISSEN: The only problem is, Tom, you are not taking into account the fact going into this that the risk for those adverse outcomes are very different in the population, so that if you take a very high risk population for coronary

disease, and you lower blood pressure by 3 or 4 mm, you will see some really big benefits.

If you take an older population, which is often what those trials did, I mean the early hypertension trials were focused, in fact, many of them excluded younger people, then, the stroke risk starts to become a more prominent risk, and it is easier to show a benefit.

You see where I am going with it?

DR. FLEMING: The analyses that are presented here, at least as it is summarized in this table, are not providing us specifics as to the absolute risk in the populations. If you are telling me the settings in which we achieved an 8-mm reduction, and had a 25 percent relative reduction in MI were settings where the absolute risk of MI is low, and the settings in which we achieved a relative 4 mm reduction with the 5 or 3 percent reduction in MI rate, were settings where the absolute risk was high, then, I understand your point, but that distinction isn't apparent here. If it is the opposite, then, it makes my point even

more strongly.

DR. TEMPLE: The epidemiologic slope of the cardiovascular risks is flatter than, you know, for each given change in the original Peto Collins MacMahon stuff, it shows a flatter--so you don't expect to do as much even if you are reversing it.

DR. FLEMING: I don't expect a treatment-induced change to necessarily reflect natural history, though, Bob.

DR. TEMPLE: Sorry, let me challenge that. If the blood pressure is what is causing this cardiovascular death, and that is what the epidemiology shows, it is hard to imagine it's something that does nothing but lower the blood pressure is going to do better than that.

DR. FLEMING: Well, you are now taking it to a step beyond what I think the data allow us to conclude. I am willing to accept that blood pressure lowering seems to be explaining a substantial amount of the reduction, but as Jay Cohn pointed out, that doesn't necessarily mean that that is the specific mechanism for the

entirety of how I achieved that effect.

It doesn't also indicate that there aren't other mechanisms that could provide some other kind of counterbalancing effects especially when we get away from stroke and we are talking about MI and cardiovascular deaths.

It seems entirely plausible to me that the ultimate relationship that you have here for how a treatment-induced change in blood pressure translates into a treatment-induced change in MI and cardiovascular death, may not exactly mirror or mimic epidemiology.

DR. TEMPLE: Just picking something like a diuretic where you don't suspect any magnificent other mechanisms. How are you going to do better than the epidemiologic effect? How are you going to do that?

Also, some of those data reflect excess doses of diuretics, I believe, and those are definitely different, the older studies differ from the newer studies.

DR. NISSEN: I am going to turn to Tom in

a second, but I just want to answer a question, Tom. There is one thing you should know. I actually asked this question of Ralph D'Agostino at the Cox Inhibitor Panel, and I have known about this for a long time.

If you take a population with a blood pressure of 120, and another group of people with a blood pressure of 140 lowered to 120, there is still excess hazard for those that started higher. In other words, you don't completely negate the epidemiological risk of hypertension when you lower blood pressure to the same target level as the populations.

DR. FLEMING: You are exactly saying what I am trying to argue to Bob, and I am using Jay Cohn's insight to say what I might be doing is partially changing this physiological process here, and blood pressure lowering may not capture the entirety of that disease process, and I may not be affecting the entirety of the disease process, but actually, I am okay with that.

I don't mind if it doesn't exactly mirror

epidemiology. I am just saying it is expecting a huge amount of the biomarker to expect that it would truly match epidemiology. What I care about, what I am saying here relative to MI and cardiovascular death is it is not apparent to me from these data that you get an impressive effect on those measures until you start seeing large effects on blood pressure lowering.

DR. NISSEN: Jay Cohn is dying to say something, so I am going to give him a moment since he has earned it over the years.

DR. COHN: I am delighted to see that Tom is nodding because Tom and I have debated surrogates many times, but the problem that you are coping with, and Bob Temple has expressed this repeatedly, we are now in an era when people with true hypertension advanced disease, and those are the people that are put into trials, are all on multiple drugs, and it is impossible to do a placebo-controlled trial.

It will be almost impossible to find a new class of drug and prove that it actually does some

good unless we are willing to move earlier in the course of the disease. We have pediatricians who want to study hypertension in young children. They can't wait for stroke and heart attacks to occur.

So, rather than making this wild leap, disregarding pathophysiology and cardiovascular, all that we have learned about vascular and cardiac disease, beginning to focus on demonstrating conclusively that the markers for vascular and structural abnormality, in fact, correlate with disease events, and then moving into an earlier stage of the disease and demonstrating that the drugs have a favorable effect on vascular or cardiac structure, whether it be LVH or arterial stiffness or microalbumin or, you know, a variety of markers, and then saying now we know that that drug and that class actually does favorably affect the vasculature, and should--should, therefore, reduce event rates, but we are no longer able to do 50,000-patient studies with multiple drugs added together, and reach some conclusion about a single drug and what that single drug does.

The kinds of patients that I am seeing do not demand, by guidelines, pharmacotherapy, and therefore, we have the chance to do placebo-controlled trials, but we can't wait for events to take place, we have to become comfortable that there is a marker, a structural marker that, in fact, can predict for us that this is really going to lead to events.

DR. NISSEN: So, what you are saying, Jay, is that we should do intravascular ultrasound studies with all these drugs.

DR. COHN: You would go for the intravascular, I might go for something else, but there is lots of candidates.

DR. PICKERING: I would like to make two comments. Firstly, Jay's proposal, I think we are all agreed that people with the same blood pressure are at different levels or risk, and also that people die from vascular disease, and not from blood pressure, but I think the best surrogate marker we have for the risk and the benefits of treatment is still blood pressure, and there are

better methods of measuring blood pressure than we had.

I don't agree that measures of arterial structural changes, of which there are a whole legion, aren't yet ready for prime time. It is a very interesting research project, but we really don't know how to interpret them, and whether you measure Jay's measure or augmentation index or pulsewave velocity, there are a whole lot of them out there, but I think that is sort of peripheral to the discussions of this committee.

The other point I wanted to make, I think we are getting a bit hung up with these small changes of blood pressure with different drugs, and we are sort of hearing what dramatic effects they may have on outcomes, but the big problem for most patients is not 4 mm, it's 14 or 20 mm reductions, and I hope the guidelines will reflect this and encourage the use of combination therapies, since at least 60 percent of patients are going to need combination therapy, and this avoids some of the issues of ethnicity.

Granted that African-Americans respond less to renin-blocking drugs, if you start them on a combination with a diuretic, that problem really goes away.

DR. NISSEN: I wonder if we can't go on one more question, because we are going to be here a long time, and we are going to have lots of opportunity.

DR. CARABELLO: Steve, for 2.1, 2.2, and 2.4, do we want to give a guide?

DR. NISSEN: Have you heard enough discussion to help you get where we are coming from?

DR. TEMPLE: Let me summarize. I hear a best case is for stroke. I guess we are talking mostly hemorrhagic stroke, aren't we, or just strokes? Total strokes. Okay, strokes. And somewhat weaker for myocardial infarction and cardiovascular mortality, but not too bad. I think all-cause mortality, we don't have to talk about.

I didn't hear on renal disease whether people think that is reasonably convincing. I

don't know if you want to touch that.

DR. NISSEN: I opined, I am quite convinced, but it is not so much because of the trial data, but the totality of evidence, the blood pressure and deteriorating kidney function are very, very tightly linked.

DR. PORTMAN: Well, they are, and I am totally in favor of that. The other thing, of course, is that people with renal disease die of cardiovascular disease, so lowering blood pressure has a double effect.

DR. TEMPLE: And we also heard that A2Bs have a role in diabetics with diabetic renal disease and maybe ACE inhibitors, too. You didn't particularly talk about heart failure because we didn't list it. I guess there you would say at least some drugs that lower blood pressure are good, but it is not as clear across the classes because some of the drugs lack beneficial effects on heart failure.

We have got to think more about how to say that a little bit because it could be both are

true. It could be that all drugs improve heart failure, but some drugs actually treat it, so they look better, or it could be that some drugs actually don't do anything good at all.

DR. NISSEN: I don't think there is any compelling evidence at this point. I don't think we can prove hazard, that is, that any of these drugs actually worsen the likelihood of heart failure. I do think that there may be drugs that are more effective.

I would point out that various antihypertensive drugs do, in fact, have other clinical indications, for example, relief of angina, or beta blockers and calcium channel blockers clearly reduce ischemia burden, so you have this class of other manifestations of coronary disease, and that falls in that class, whereas, drugs that are used to treatment heart failure, specific certain beta blockers and certain ACE inhibitors, and a wise clinician uses that information in selecting drugs, and that is something we are not going to ask people, to forget

their brains, and recognize that if you have got a patient that has got a 30 percent ejection fraction and hypertension, you probably want to give them a drug that is effective against prevention of heart failure.

But I don't think we have any evidence of hazard. I don't think we can say, for heart failure, that all drugs for hypertension get the same label for prevention of heart failure, because I don't think the evidence shows that.

DR. TEMPLE: There are actually studies of some of the drugs that didn't do very well in ALLHAT in heart failure, and while they didn't succeed, they didn't worsen.

DR. NISSEN: That's correct. Let's go on to 2.1.2 and ask about whether these benefits apply to most antihypertensive agents with clear exceptions noted. It is sort of a wrinkle on the first question. I think you may have heard about that already.

DR. TEMPLE: You have done that.

DR. NISSEN: Good. Are benefits

associated with specific classes of drugs? This is maybe a little bit different, that is, for these benefits, what can we say about these drugs as classes as opposed to as antihypertensives in the super category? Let's hear some discussion about that.

DR. TEMPLE: Again, that is going to be apart from the fact that some of them have, say, a claim in heart failure, because that's obvious.

DR. NISSEN: I think what we learned from ALLHAT is actually a lot, and it is not necessarily the conclusion that was widely promulgated, but what I saw there was that while I think the most compelling data suggested the overall composite endpoint looked about the same for all three drugs.

For individual classes, the different endpoints seemed to go in somewhat different directions, although the differences were very subtle. They weren't huge, but if you look across all the trials, you know, you really do see that the diuretics and calcium channel blockers look a little bit better on stroke, whereas, the ACE

inhibitors look better on the renal function endpoints, they look better on the heart failure endpoints.

So, I think that it is easier to say that there is a benefit of a specific class of drugs on, let's say, renal disease, a drug that we have got a lot of data that suggests that class of drugs has beneficial effects.

So, I think that there are class-related, subtle differences. They are not, however, predominant, that is, it is still a minority of the benefit is class-specific in my own personal opinion.

DR. PICKERING: A recent study from ALLHAT looked at the progression of renal disease, and did not find any difference between the different drugs, so again, it is probably the blood pressure that is the predominant thing.

DR. HIATT: So, would you be willing to say that diuretics may be particularly effective at preventing heart failure?

DR. NISSEN: Again, the problem you have,

even in a study like ALLHAT, which I think is fairly compelling, is there are blood pressure differences, and so what we have got to be very careful about, the question you are really asking is what is the evidence that one class has greater benefits in relation to the amount, for every millimeter of blood pressure reduction, do you get more protection from heart failure from one class versus another.

That is a different question, and I am interested in discussion about that.

DR. PROSCHAN: For heart failure, I think the differences do not appear to be entirely blood pressure related. I mean blood pressure differences weren't that big, and yet, doxazosin had twice the heart failure as diuretic. We are doing some analyses in ALLHAT right now to try and figure out whether these things are entirely explained by blood pressure.

At least preliminary results suggest that for heart failure, it is not.

DR. NISSEN: Do people buy that argument?

DR. TEMPLE: Why would it surprise anybody to know that one of the well-known consequences of heart failure looks better when you are on a drug that treats heart failure? I would have said that is totally predictable. I guess I am a little surprised that amlodipine wasn't worse than doxazosin, I don't quite understand that.

DR. HIATT: I am not sure that a diuretic treats heart failure. It treats the symptoms of heart failure, but it is not a beta blocker, it is not an ACE inhibitor, and the treatment of remodeling of heart failure.

DR. TEMPLE: We don't know about that. These were just people who showed up with what somebody called heart failure. We don't know whether it was remodeling or anything. It is just do you have what somebody diagnosed as heart failure, and diuretics are the first thing you use.

DR. NISSEN: The reason I am not as impressed as Mike might be is the issue that you would think--you know, heart failure is a diagnosis that carries with it a very high mortality rate,

and so you would think that if these differences are really robust, that it would have driven some other evidence of mortality.

Class III/Class IV heart failure particularly has a very bad prognosis.

DR. TEMPLE: That suggests that what you are seeing is manifestations, but no fundamental difference in the underlying heart.

DR. CARABELLO: That is my concern.

DR. TEMPLE: And what you saw was the symptomatic treatment, I mean diuretics treat heart failure symptomatically. I mean there aren't any outcome studies in heart failure that I know of.

DR. HIATT: You test it with adjudication, then. I mean it's an interesting discussion because that would actually suggest that isn't really the thing that is treating it. It is just treating the symptom of a disease, not the disease itself, and to your point, Steve, if there was a lot more Class III and Class IV heart failure, they were surviving better because of diuretics, we wouldn't maybe know that.

If we don't know that, then, it argues back that it is just the blood pressure.

DR. SACKNER-BERNSTEIN: The other thing that is interesting is about the doxazosin-chlorthalidone comparison is to look back at the studies with alpha antagonists and heart failure back in the early '80s, and there is pravacin [ph] that shows that pravacin is associated with fluid retention, so if you have two drugs you are comparing, one of which causes fluid retention, and the other one treats fluid retention, in a population of hypertensives, probably a large percentage of whom had some sub-clinical diastolic dysfunction, maybe some LVH, it is really not surprising at all that you would see a risk ratio of 2.

DR. HIATT: That is the whole argument for the calcium channel blocker causing edema, making the symptom look worse, the diuretic making the symptom look better.

DR. TEMPLE: Pravacin was once worked up for heart failure, and we actually got a submission

to put it in the label. It had various problems which I won't go into. So, there was once some evidence that it was actually useful.

DR. NISSEN: John, you are next.

DR. TEERLINK: I think one of the points we are getting at here is the difference between a trigger of a symptom or trigger of a hospitalization and the disease progression issue, that I think we have all been trying to grapple with here. I am not sure there would be anybody around the table who doesn't believe that hypertension, at least based on the first Framingham data, the first major heart failure publication saying hypertension leads to heart failure.

The leading cause of heart failure for years and years and years was hypertension. It has been shifting more and more, as we treat hypertension more and more, we are seeing more and more coronary artery disease.

So, to say that lowering blood pressure doesn't relate to decrease in heart failure, I

think is not correct from what we see either epidemiologically or from larger scale observational studies.

I think the difference that we are seeing in these studies is the measurement of a symptom that can only present as those cases, and we are hampered a bit by the fact we don't have the 20-year studies. We don't have the time, and that is why actually I brought up the early point saying that we need to see whether these effects on mortality or heart failure endpoints change over time. One would expect that lisinopril or the ACE inhibitors or ARBs, thing that we think may change the structure of the heart would have these beneficial effects much later down the road than something that helps you pee better.

DR. NISSEN: Mike.

DR. PROSCHAN: I need to remind people that the case fatality rate for those diagnosed with CHF was very much higher than, you know, for people without, and it was similar in the different arm. So, again, this idea that somehow there was

masking and it is really just something else, and it's not heart failure, if it is not heart failure, then, it is something that has high mortality associated with it.

You could call it Fred, if you want. You don't have to call it heart failure. What it was, was bad and killed people.

DR. NISSEN: But you see, the fact that it doesn't impact upon the mortality data overall, what is suggests, then, is that there is some tradeoff involved.

DR. PROSCHAN: No, it doesn't suggest that, because, you know, heart failure is a relatively small component of total mortality. So, it is entirely reasonable that it could have a profound effect on heart failure, and not have an effect on total mortality.

DR. HIATT: Michael, what I am hearing, and I am really a little bit confused now, what you are suggesting is that there is an interaction between drug class and heart failure mortality, heart failure related mortality.

Is that what we are talking about? In other words, we are trying to find out if there is truly a class effect or not, and if that is true, there should be some interaction to explain that.

DR. PROSCHAN: What I am saying is there is a relationship, I think, the evidence suggests that there is a relationship between blood pressure lowering and CHF. It is just that it doesn't explain the entire difference that was seen in ALLHAT.

DR. HIATT: Let's go back to Steve's point. If it doesn't matter, it's just the blood pressure effects, and we all know that is a good thing in preventing heart failure.

DR. NISSEN: I guess what I was trying to say is that there are a lot of good things that blood pressure does for virtually all these endpoints, and then for specific classes, there are some smaller effects that can come out if you do a big enough trial, to suggest maybe some slight benefits of one class over another, and Bob isn't surprised by that, that the class that we used to

treatment heart failure looks better at preventing heart failure, and I think that is right, just as a class that we use for treating angina will lower ischemic events.

DR. TEMPLE: But it is possible we should be careful with the terminology, and this I think is what Bill was talking about. What you are seeing is the difference in the manifestations of heart failure, but you might not want to imply that you know anything about the heart--sorry--you know anything about any differences in the effect on the heart, and what your gut is telling you, whether we should write it down or not, I don't know, is that lowering the blood pressure decreases the damage to the heart that leads to congestive heart failure.

The drugs may differ--the drugs probably don't differ in that--but they might differ in whether symptoms of heart failure become manifest or not.

DR. NISSEN: Let me make sure I get this point across, because there are certain things that are taken as gospel, and one of them, for example,

is that after an MI, if you give ACE inhibitors, it has some favorable effect on remodeling of the heart, and that that leads to prevention of heart failure.

You know, that goes to animal studies and everything else, but to my knowledge, those studies didn't compare to some other class of antihypertensive agents that might have actually done the same thing, at least as far--I mean maybe there is data I don't know about, but what I am getting at here, Bob, is that if those studies have been done with a diuretic or a calcium channel blocker, we don't know, in fact, and so it is all based upon this biological plausible effect on remodeling, and I am not sure I buy it. It may have all just been blood pressure.

Alpha blockers do look like they are the odd man out.

DR. TEMPLE: The--I am going to forget what number it is--showed that a relatively short period of treatment with whatever was in it, enalopril, some pril, led to an advantage 6 months

later, so maybe you did something good pressure in that period of time, but it certainly suggests that there is a structural effect that persists.

DR. NISSEN: Wouldn't you have been a little more comfortable, though, if the control group had gotten chlorthalidone?

DR. TEMPLE: No, but I might like another group.

DR. NISSEN: Well, whatever you want. You know what I am saying, though, I think again, even for these oft-repeated benefits, we really don't know that it is not just the blood pressure, stupid, primarily.

DR. TEMPLE: Right. These people were not in any sense hypertensive, they were postinfarction.

DR. NISSEN: We also know if you are high enough risk, you know, lowering blood pressure a few millimeters can give you a lot. I am challenging some of these assumptions because I don't think we know that with the robustness that I wish we knew it.

DR. TEMPLE: Right.

DR. PICKERING: One additional comment about heart failure that I hope the FDA will address, and that is the issue of diastolic heart failure, which seems to be particularly common in little old ladies with hypertension, and we really have no idea how to treat it. The large studies really haven't subdivided it, and we had the CHARM study recently, so I think that is an important issue.

DR. NISSEN: Ron.

DR. PORTMAN: Again from the renal standpoint, I mean we have already established for a couple of good reasons that lowering blood pressure is a good thing, both for cardiovascular and progression of renal disease.

However, I think there is a preponderance of evidence, ALLHAT notwithstanding, which wasn't designed to answer this question, and a number of guidelines from the National Kidney Foundation, even JNC VII, that have clearly stated that the feeling is that an ACE or an ARB, in combination

with a diuretic when there are kidneys present, are the drugs of choice for their intrarenal effects in preserving renal function, and I think that certainly needs to be preserved in this.

DR. NISSEN: Can I move us on 2.2 now? Did you hear enough discussion of that? You want to hear more? Okay.

For the purposes of this discussion, are ACE inhibitors and angiotensin receptor antagonists the same class?

Now, this one is really interesting, so let's hear Tom Fleming.

DR. FLEMING: I want to raise one more time the analyses from the Clinical Trialists Collaboration, and look at Figures 1 and 2 in that manuscript and specifically, what we see when we look at coronary heart disease, and we look at cardiovascular death, for the ACE inhibitors with about a 5 mm reduction, there is a 20 percent relative reduction on both measures.

For the ARBs, with nearly the same, a 4-mm reduction, there is only a 4 percent, so there is

5-fold difference in the influence of these classes on the measures of coronary heart disease and cardiovascular death.

Then, I went back and looked again at Stephen's presentation from this morning and there is a remarkable parallelism between those curves, indicating that there is something beyond the blood pressure that is influencing how these two classes differ in their effects on coronary disease risk. While the HOPE study is one of the contributing features, when I look at the totality of the data, is looks as though that relationship is not at least solely driven or even necessarily heavily driven by HOPE when I look at this.

By the way, there is one other quick thought and that is, we have evidence that the ARBs prevent diabetes.

DR. NISSEN: Well, that's again relative to other classes that may actually worsen insulin resistance, so, you know, again, that is a bigger issue.

DR. FLEMING: So, I am thinking

specifically, relative to ACE inhibitors, is there a difference between ACE inhibitors and ARBS.

DR. NISSEN: No evidence for that. I mean the ACE inhibitor trials seemed to show similar effects. I may be wrong about this, but I have been troubled by the ARBs from the very beginning, and I guess one of the reasons I am troubled is that there is--again, I have been the one that has been telling you not to worry about biological plausibility, but I have got to say it anyway--you know, bradykinin may have some beneficial--there may be some beneficial effects related to the bradykinin effects of ACE inhibitors, which are not present for the ARBS.

I think--was it BMJ--one of the British journals had an analysis which I thought was mostly wrong, that suggested that ARBs actually increased risks for myocardial infarction, but, in fact, when head-to-heads have been done, and you can argue about dose, and so on, even against an agent like captopril, where you have got to give it three times a day, and it is probably not necessarily the

optimal approach, you know, certainly there is no evidence of superiority for a lot of these endpoints.

So, what I tell people is that ARBs are drugs to be used exclusively in people who don't tolerate ACE inhibitors, because until proven otherwise, they are certainly not superior to, but maybe there are people who disagree with me about that.

DR. TEMPLE: You are talking about hypertension or heart failure?

DR. NISSEN: Well, I am talking about, you know, I think in hypertension, you have got the problem that the different drugs in the class clearly have different effects on blood pressure, and we already gave a label claim at this disease to candesartan as having a better blood pressure effect than losartan, so that is a confounder.

DR. FLEMING: That's because they don't have the right dose.

DR. NISSEN: Well, they probably don't have the right dose, but there are some differences

in effect related to the agents and/or their doses.

DR. TEMPLE: I was just going to point out we have now concluded that in heart failure anyway, you get further benefit from adding an ARB to an ACE inhibitor after having definitely not concluded that previously. So, I don't know what that has to do with hypertension, but I just thought I would make sure everybody knew.

DR. PICKERING: I think it would be a mistake to say they are the same class. Of all the classes, there is the biggest overlap because they both block the renin-angiotensin system, but that they do so in completely different ways.

As has been mentioned, we have already approved a combination for the CHARM ADDED study. There is also evidence from the COOPERATE study in renal disease that there may be additional effects with the combination, and they have very different side effect profiles. I think we should treat them separately.

DR. NISSEN: But we should also recognize that they do work by generally the same mechanism,

and I think the fact that, for example, what we know about ARBs is they seem to work in heart failure, similar in the way that ACE inhibitors work.

I mean there is certainly substantial overlap, and there is a lot more in common between ACEs and ARBs than there are between ACEs and calcium channel blockers for sure.

DR. TEMPLE: This doesn't actually go to the major overall statement. This is a later part of labeling.

DR. NISSEN: I am going to give class labeling. The question is how big is the class

DR. TEMPLE: Well, the class we are talking about is all antihypertensives and then what you are going to say later.

DR. NISSEN: Later, about specific classes. So, are they the same class or not, and so far we have heard some opinions that say they are not. Tom doesn't think so, and Tom and Tom don't think so.

DR. TEERLINK: I would also agree that I

don't think that they are similar and shouldn't be treated as the same class, as well. I think Optimal and Lead-II are enough to show that there are some differences, dosing effects aside.

DR. NISSEN: It's a little bit different from the opinion I think that predominates at the agency, which is why I think it's an interesting discussion.

I am going to keep going here. If everybody is really disciplined, you are going to earn a break around 4 o'clock. If you are not, they will be no break.

2.3. Are the magnitudes of the benefits the same among members of a class? Ooh, isn't that fun. So, let's try that one.

DR. PICKERING: I would volunteer that the major differences are probably related to the pharmacokinetics and the dose effects and durations of action, and that's it.

DR. CARABELLO: What do we call a class?

DR. NISSEN: Beta blockers.

DR. CARABELLO: Among beta blockers, there

are those that are selected, non-selected, others selected with intrinsics and patho, and I can think of at least--and those with alpha--I can think of five classes of beta blockers.

DR. NISSEN: The amount of heterogeneity in each of these classes depends on the class you are talking about, and I happen to think that ACE inhibitors generally share a lot of the same properties.

If you give the correct dose at the correct interval, and you block ACE, you are going to get about the same benefits, but it is hard to believe that nifedipine and amlodipine are the same. We already know there is differences in outcome, and amongst the beta blockers, we see a lot more heterogeneity.

So, my answer to the question, Bob and Norm, is that it depends on which class you are talking about, and I think some classes have very low heterogeneity like ACE inhibitors, and the ARBs again, assuming that you take out the dose effect, more in beta blockers, a lot in calcium channel

blockers--what are the other classes we are talking about here? Diuretics, what about diuretics? I can tell you diuretics aren't all the same.

Furosemide is not the same as hydrochlorothiazide or chlorthalidone in terms of its antihypertensive effect, so I think you have got to be very class-specific here.

DR. STOCKBRIDGE: A quick comment. I think Question 2.1.3, Question 2.3, a couple others coming up here really are trying to get at the same sort of issue, and that's how much generalization by class do you want to see in the label?

I mean we can talk about what we generally see, but really, the issue is where do you think it is so clear that you want to say something generally about ACE inhibitors or generally about beta blockers, and expect to see that in a way that's frankly going to discourage people to do further studies.

DR. NISSEN: I have a lot of trouble with it, and I mean again, there is so much evidence here or some of these areas, like again, as you

point out, Blase, beta blockers with ISA are very different from--some of the beta blockers have other effects like carvedilol has some alpha blocking effect, labetalol, too.

There is some evidence of heterogeneity there, and I think we can't ignore it. Certainly, the difference between a short-acting dihydropyridine and a very long-acting one, I think most of us are comfortable that there are real differences there.

So, I think you have got to tread very lightly here about this in certain classes.

DR. STOCKBRIDGE: Did I hear you say you think all ACE inhibitors are interchangeable? Is that what I heard you say?

DR. NISSEN: Yes, I think there are pretty much the same.

DR. STOCKBRIDGE: Do you want to see that in a label?

DR. NISSEN: I didn't say that.

DR. TEMPLE: The models for labeling we gave start with general statements about drugs in

general. What I have heard is that you thought that if there is any class or individual drug matter where you are clear that there is an exception to this, you would want to hear about it, but ordinarily, we don't make class statements about drugs at all, and we were not particularly proposing to do that unless you wanted to say, well, with respect to manifestations of heart failure, it doesn't look as though CCBs do as well, or something like that, just as an example, although you might even want to refine that with individual drugs, too, because they are not all the same.

But most of those suggestions we have had here are a broad statement about what treatment of hypertension does, and then you get down to the labeling.

DR. NISSEN: Norm, the concept that you can't say anything about the class of ACE inhibitors, I mean there are some things you can say about ACE inhibitors as a class, and again, these are general statements, they are not

specific, but in general, ACE inhibitors have favorable effects on preventing heart failure. I mean we have seen that across a lot of trials.

DR. TEMPLE: Wait, wait. There is a reason we don't do that. If you do that, then, no one ever does a trial again, so for heart failure, not hypertension, I am not talking about hypertension, the only drugs, the only ACE inhibitors that have statements about heart failure are people who have the study.

Nowadays, it could be an active control study and make the case, but you don't get that--I wouldn't say it has never happened, steroids have class labeling, you know, but class labeling is perceived as discouraging any attempt to learn anything further.

So, we are not proposing that here with the single exception that we are proposing that we say the drugs that lower blood pressure do certain good things, but we are not proposing heart failure labeling for ACE inhibitors or anything.

DR. NISSEN: No, but you are asking the

question about--and when used to treat hypertension, there may be some differences between the classes.

DR. TEMPLE: Yes, and if there were something like that, that is of interest.

DR. NISSEN: And that is what I am talking about.

DR. TEMPLE: Okay.

DR. NISSEN: That is exactly what I am talking about, is that if we have learned anything from the trials, is that--and we use this information in clinical practice. Why is this important? It is important because if I am going to choose an antihypertensive agent to use for a patient, I like to choose it based upon what I know about the risk profile of that patient, and what I know about the benefits of drugs in the class that I am going to use.

If I am very concerned about stroke, it is going to drive me towards using diuretics and/or calcium channel blockers. If I am worried about heart failure developing, I am going to tend to use

an ACE or an ARB. So, by giving people some information about that, it is informing them about what we think is appropriate.

Now, maybe that is for guideline writers, and not for the FDA.

DR. TEMPLE: No, if there is something clear, and I hear everybody saying that with respect--how to say it isn't clear--but with respect to manifestations of heart failure in hypertensives, patients, there may be some differences, maybe calcium channel blockers don't protect you against those manifestations as much, but are there are any other things that should go in there?

I doubt people are ready to say that two classes of drugs have better effects on strokes than others, and I would be very unhappy saying that yet.

DR. HIATT: And, Steve, just to be clear, we are talking between, not within, but you were saying, you were making some examples of both earlier, and I would be very cautious about doing

within-class kinds of statements between class and very general ways. You couldn't feel comfortable saying that.

DR. NISSEN: The only way you answer that is you do head-to-head studies that are really sufficiently large and robust, and they are very hard to do, and they require enormous sample sizes, and so on.

Maybe the answer is you don't.

DR. TEMPLE: People would be reluctant to take it from one drug to a class in general. I mean we have a very high barrier for doing that, for sort of obvious reasons. I mean the atenolol discussion shows why you don't do class things easily.

DR. NISSEN: Go ahead, Jonathan.

DR. SACKNER-BERNSTEIN: One of the other things I am wondering if you might consider would be based on the idea that we want to make sure that there is adequate disclosure for anyone who will read these or who will use them to send their messages forward, but also acknowledgement of the

kinds of information that may encourage more studies, and to that end, perhaps as we talk about the general advantages of lowering blood pressure, we also may want to point out examples of the fact that there are some drugs that have been approved and within the first two and a half years, as they have been used more, idiosyncratic issues have arisen that have led to the need to change the interpretation of their safety, something along those lines because you get to examples like mabafadil [ph], you get to an example of labetalol, which was out for a little bit longer.

You know, you can find a lot of examples, and I wonder whether just a small sentence in there for someone who is reading it, that acknowledges that merely because a drug appears safe and effective enough to be approved for hypertension, doesn't necessarily mean it should be considered to be interchangeable as a choice with other medicines in that class.

DR. TEMPLE: That is a more general problem. That doesn't only apply to

antihypertensives. What, if anything, we should say about how scared you should be when a drug hasn't been marketed for a long time is the subject of some discussion.

I will tell you that in a proposal for labeling revision--I can't tell you about the final rule because I would have to kill you all--there was a proposal to put the date of approval on, so as people become conscious of the fact that things get learned, they will at least be able to do something about it by seeing that.

I don't know if you read the paper, but one large company has said they are not going to do any DT [?] advertising for the first year, Bristol announced that this morning.

DR. NISSEN: I did see that actually, which I thought was very interesting. I think we have had some discussion about that. There are some things, that at least I think you might be able to say based upon what we know, but they are obviously very limited between classes, and recognizing what a class is and which agents belong

in that class is an entirely different discussion altogether.

I guess the other thing I think we have said, which I hope everybody agrees with, is that the degree of heterogeneity within classes does differ to some extent with which class you are talking about.

So, our comfort level with whether a class is really uniform or not differs according to the class.

Does everybody agree with that? Okay.

Now, are there other important distinctions among drugs in a class? Have you heard enough discussion about that or do you want more? Yes?

DR. TEMPLE: I think that's okay. Where somebody shows that one member works better than another on something, and it were persuasive, they would get to put that on the label.

DR. NISSEN: And we have already done that in the ARBs, and I suspect you have done that to other classes, as well, when the data is good.

DR. TEMPLE: Not too many.

DR. NISSEN: But some, okay.

This is another interesting one. How are the benefits affected by age, gender, diabetes, or other risk factors? This is a very interesting discussion because this again--and there is one more thing I want to say here, and that is that the purpose of all of this is not to take away from those of us that are involved in writing practice guidelines from what we need to be able to do in writing practice guidelines.

We have to actually tell people how to operationalize some of these decisions. Some of these questions may, in fact, ultimately be better answered, not by what you put in the label, but allowing the professional societies that talk to all of us give guidelines about what we think the data show, because what you needed for a level of evidence for regulatory decision, may be somewhat different than what we need for a guideline decision.

So, I want to make sure we all understand

that. We are not trying to write a guideline. We are not turning the FDA into a guideline writing organization. But let's hear some discussion about these questions.

Dr. MacMahon wants to say something.

Make sure that microphone works, so that we get a permanent record of this, so we can go back and hold your feet to the fire if you are wrong.

DR. MacMAHON: Thank you for that.

Just before I get on the plane to go back, two things. I guess the first is about benefits and how they are affected by different characteristics like age, gender, and diabetes, and so forth.

The evidence that our Collaboration has put together, looking at those first three points specifically for macrovascular major events, suggests that the relative risks are not dissimilar, they are approximately the same size benefit, but obviously, given that, as older people are at high risk, men are often at high risk,

diabetics are at high risk, the absolute benefits do substantially change with those factors.

So, I think the critical thing probably to reflect, if you want to reflect anything at all about how benefits differ by patient characteristics, is to reflect the fact that higher risk people get bigger absolute benefits, and there is nothing surprising about that.

There is nothing in the data that we have seen that suggests that any characteristic, with the possible exception of the African-American ACE inhibitor issue, but that everything else basically follows that broad premise.

Maybe the last thing I could add, and it is not directly relevant here, but when considering what general labeling suggestions might be made, I think it could be important to try to capture the evidence strongly suggesting that the size of the blood pressure is an important determinant of the size of the benefit.

DR. NISSEN: Let me ask a rhetorical question of the group here, and that is, for those

of you that practice clinical medicine, if you have a patient who has borderline diabetes, does that affect the choice of--Tom, when you see a patient with borderline diabetes and hypertension, does that affect your choice of drugs?

DR. PICKERING: Well, I think all the three guidelines, JNC VII, the American Diabetes Association, National Kidney Foundation would all suggest that an ACE inhibitor might be appropriate for that patient.

DR. NISSEN: Would you be less likely to give a diuretic?

DR. PICKERING: The other issue is that the target blood pressure is lower for diabetics, and the issue about diuretics worsening diabetes, I think is not so much an issue as lowering the blood pressure, so with the combination of an ACE inhibitor and a diuretic, I think it would be perfectly fine.

DR. FLEMING: It seems to me from at least what I can glean from the data, that we are probably talking more about quantitative

interactions rather than qualitative interactions, or even about whether there are subgroups that don't benefit. It really is more a relative degree of benefit that seems to be the case.

If you have patients that have particularly high levels, very high levels of blood pressure, then, they seem to get the most benefit, and as we were just hearing, if you had a diabetic population, you might be more inclined for an ACE inhibitor and ARB.

In congestive heart failure, you might be more inclined with an ACE inhibitor or beta blocker, and obviously, race is an issue, it will come up again tomorrow, and my understanding there at least of the data isn't that you are not getting benefits with, for example, ACE inhibitors, but there potentially is less benefit, so it seems that for most of these issues, there is some evidence to suggest that there is differential levels of benefit, but not an issue of no benefit.

DR. NISSEN: But the question, of course, that the agency has to decide, is how much of that

is appropriate to say about these drugs.

I actually wonder if this isn't the sort of thing that is actually best left to guideline writers, and not necessarily to the agency in the absence of very clear statistical evidence from clinical trials that there is a differential effect.

I mean I am not sure you want to be in the position of saying to people that this class would be preferred in this group unless there is very, very clear evidence from clinical trials.

Now, we may say that, we may choose to say that, and they have actually said that for ACE inhibitors, right or wrong, but I think it is pretty difficult to answer the question.

Now, sometimes, of course, the guideline writers are wrong, and we change our guidelines all the time. When you are wrong, however, it ends up on the front page of the business section of the New York Times, and you get flailed by Congress. So, it is a different question.

DR. HIATT: I think the endpoints you are

talking about, if the endpoints are stroke and death, then, the benefits are the same. The example you gave about the progression to diabetes or microvascular renal disease, those are different and meaningful. They are probably not worthy of our discussion today.

DR. NISSEN: My feeling is that there are biologically important effects, but it is very hard to specifically speak to them. I think that there is some evidence that both beta blocker and diuretics worsen insulin resistance and will hasten the transition from the pre-diabetes to diabetes.

Now, whether that makes a difference in long-term outcome or not, I think is much less clear since you are probably talking about a continuum rather than a--you know, diabetes is one of those diseases where we have a threshold for what is called diabetes, and if you are on one side, your 1 mg/deciliter lower blood sugar, you don't have it, and you are l mg higher, you do have it, and that, in fact, isn't the way it really is, of course.

DR. TEMPLE: We certainly have not been inclined to put in blood pressure goals, things like that, for something they change constantly, and different guidance gives different exact goals, so actually, the cholesterol-lowering drugs do refer to a particular guidance which has been fairly stable, but even that, now that there is new data suggesting that what used to be the goals, may not need to continue to be the goals, that is not a comfortable thing for labeling. You don't like to change it very two minutes.

So, we might just say something like the particular choice of treatment could be affected by other properties of the drug, blah-blah, their diseases, blah-blah, and leave it at that.

DR. STOCKBRIDGE: But if you really thought that people would use the label in a really useful way, to decide who got treated, you would, of course, want to change it and provide the best instructions for use possibly.

DR. TEMPLE: Except that guideline writers are allowed to use levels of evidence that we

wouldn't touch, which makes a problem.

DR. NISSEN: Let's take something where there is somewhat more evidence. Let's take the African-American question. There is a fair amount of data from several sources including LIFE and ALLHAT that the blood pressure reduction in African-Americans from drugs that affect the renin-angiotensin system is not as robust, and that should be described.

DR. TEMPLE: Labeling always has that, although it is less consistent that you might think.

DR. NISSEN: My view is that you should tell people that, because can I tell you that, believe it or not, you may think that everybody reads those labels and does it, but I can't tell you how many patients--you know, Cleveland, Ohio, has a very large African-American population, and I see an awful lot of African-Americans who get an ACE inhibitor as the very first drug to be given to them for hypertension, and guess what, they are not well controlled.

It is happening all the time.

DR. TEMPLE: We would put any of those things, any properties of the drugs that are different among different demographics, we are very committed to putting in, so that is not the issue. I was addressing whether we want to put therapeutic goals in according to somebody's latest guidance. We might say you should refer to those or something, but we are unlikely to want to put those in, I think, because they change.

DR. NISSEN: You would not want to be saying that if the patient happens to be diabetic, you ought to treat them more intensively, and that sort of thing?

DR. TEMPLE: We will listen to what you think. That is relatively uncommon. That is what I meant to cover by the question of how aggressive treatment should be and what particular drugs might be affected by other diseases that the patient has, and things like that.

One could leave it at that, but tell us what you think.

DR. NISSEN: Anybody want to offer any additional comments?

DR. KASKEL: You have a conflict then, because the National Kidney Disease Education Program is targeting the African-American population at risk, and it is saying blood pressure has to be controlled, and your first line of drugs is a class such as the ACE inhibitors, which have been shown to lower progression of renal disease if you have microalbuminuria.

If you go to any inner city clinic or rural clinic in the country and see a 10- or 15-year-old African-American who has microalbuminuria from a Type 2 diabetes, they are going to be put on an ACE inhibitor.

DR. TEMPLE: But that is for his diabetes.

DR. KASKEL: Right. This is even before they have hypertension, that is the thing. The studies show that you don't have to have hypertension to lessen the progression.

DR. TEMPLE: That is what I mean. I mean there is already rather less ACE inhibitors than

for A2Bs, but there are specific claims for diabetic nephropathy for A2Bs.

Nothing would make those go away, but it seems sort of obvious that if you then had a patient who was also hypertensive, you would certainly think about including one of those, personally, I would add a diuretic, I think.

DR. NISSEN: Let's keep in mind that we are not going to take away anybody's earned claim for a benefit. We are talking about this whole business of treating blood pressure, and there is lots of other claims for drugs in all these classes for other indications, you know, like giving beta blockers for angina or post-myocardial infarction.

That is all there, and it is not going to go away.

You all have been extremely good, so what do you say we take just a 10-minute break and we will come back and we will see if we can't keep marching on through this.

[Break.]

DR. NISSEN: I am just going to launch

right in and as people come back, they can join us here. We do need Cathy, I suppose, but she will come quickly, I hope.

Where we left things off was on No. 3, so I am going to take us to No. 3.

Most modern labels for non-antihypertensive drugs describe the supporting data under Clinical Trials and then cite the specific benefits of treatment in the indications.

Should labels for antihypertensive drugs follow this pattern?

Bob, you are going to have to help me a little bit with what you are after here. Maybe Norm can help us here. On Question No. 3, Norm, we are trying to make sure we understand what you are looking for here.

DR. STOCKBRIDGE: Well, 3.1 is just to make sure we know where we are putting something.

DR. NISSEN: How is it structured now I guess is one of my questions.

DR. STOCKBRIDGE: Let's get everybody on the same page here. Right now there is no general

statement about antihypertensive drugs, so I just want to make sure that where we are talking about putting a general statement that we think if more or less applicable to all antihypertensive drugs.

Does that belong under Clinical Trials, or does that belong, you know, to be followed by specific data on a drug, or are we talking about laying out in the Indication Section what we think is true of all antihypertensive drugs.

DR. TEMPLE: Another possibility is to divided the general statement into something fairly brief in the Indications because we used to do this sometimes, we really don't like very long Indication Sections anymore, we are getting away from it, but you still could give a little intro to the thing and then put the rest of it in Clinical Trials.

DR. NISSEN: You might say, you know, those statements that we have all agreed belong in the general group of antihypertensive drugs would go in that brief statement. Is that your thinking, Bob?

DR. TEMPLE: When you look at them, they take up half a page.

DR. NISSEN: Yes.

DR. TEMPLE: We have negative feelings about doing that in an Indication Section. It makes it very long. But you might have a statement that says treating hypertension alone or in combination in order to: reduce, reduce, reduce, reduce, and then you have got it in a sentence, and then you explain it later. That is a possibility.

DR. NISSEN: I do like the idea of keeping it fairly brief, because, in fact, the issue of the readability of drug labels for me has become worse and worse over time as they become more and more complex. I actually read drug labels, believe it or not, which I think is uncommon, but it is getting harder and harder to read the drug labels as they become more and more complex.

Are you limited to these classes, or could you have a general statement in an entirely new category? Could you call it Background or whatever, are you really fixed in that? You are

fixed. Okay.

DR. TEMPLE: You saw several samples.

DR. NISSEN: Yes.

DR. TEMPLE: I would say those are fairly obviously too long to put in Indications as currently conceived, but we could extract a sentence or two, and then put that as the introduction to Clinical Trials. That would certainly be a possibility.

You have some idea from the samples of the sorts of lengths we are thinking of, although they vary by a factor of 2 or 3, the examples we gave.

DR. NISSEN: I personally like putting something up in the Indications, because that is, in fact, what we are saying, is that that is what these drugs are indicated to do. Now, exactly what we say, we have had a lot of debate about, and you are going to take that under advisement, but with the caveat that brevity is probably very valuable here, my own personal view is to put something up in the Indications.

Other people want to comment?

DR. TEERLINK: I think my preference would be to put it in the Indications, because I think of the sections that are read, which I am not sure people read them that often, but of the sections that are read, I think the Indications Section is one of the sections that physicians will look at. So, from that standpoint, I would put it there.

DR. STOCKBRIDGE: So, you are suggesting a more comprehensive statement, and not just Bob's one sentence look elsewhere for more details?

DR. TEERLINK: I think I would be in favor of a three-sentence, you know, in general, lowering blood pressure is good, lower is better, and this drug is indicated for lowering blood pressure and then whatever specific claims are there.

DR. NISSEN: Now, again, what you say will depend a little bit on whether you buy the narrower view that Tom was expressing, which is that we are very clear for stroke, and becomes less clear for other things. I think you have heard some discussion about that, but putting that up there, I think, to me, is very useful and informative to

physicians who use these drugs.

DR. SACKNER-BERNSTEIN: As you think about where you would want to put this information in the label, maybe there is one other way of thinking about this, and this may be completely out of my field.

There are a number of places where physicians who look for information look, so they will look at Hippocrates, Med-X, the Washington Manual, there are a whole bunch of sources, electronic and print.

Perhaps they all have a common process as to where they pull information from, and there can be a way that if you put it in a certain spot, they are more likely to pull it from the label and include it in their version of the data, so that people have more access.

DR. NISSEN: It is interesting. I assume you all know this, is that every one of our residents is carrying these things around in their pocket, you know, these little electronic things, and, of course, they are a very abbreviated form of

the label, but that is where a lot of them are getting their information from, and I suspect that a lot of practitioners do that, as well.

DR. TEMPLE: Indications is probably the thing that they all have at least something of. None of them carry the whole labeling? I thought Hippocrates carried the whole labeling.

DR. NISSEN: The last time I rounded, I was carrying the PDR in my pocket, but I developed a neck injury as a result of that, so I can't do it anymore.

DR. TEMPLE: Also, all the generic drugs are not in the PDR anymore.

DR. SACKNER-BERNSTEIN: I might mention also that chlorthalidone product insert is not even in the About Drugs database on the FDA website.

DR. NISSEN: I actually tried the same thing. I can't find anything about chlorthalidone anywhere.

DR. TEMPLE: Well, not too long from now, electronic labeling will be readily available from the Library of Medicine in some form, and you will

be able to get it on line easily.

DR. NISSEN: It's wonderful that we are entering the modern electronic era in the Federal Government. That is really amazing to me.

DR. STOCKBRIDGE: Before it's over.

DR. NISSEN: Should labeling distinguish drugs on the basis of whether the specific agent or a specific class contributed to the available outcome data? Isn't that an interesting question.

Tom, do you want to say something?

DR. FLEMING: We spoke about this two hours ago. Definitely, yes.

DR. NISSEN: I really do think so, because it could be quite misleading to not tell people that, so I think you have to do that.

DR. TEMPLE: But let's be clear. So, after some general statement, not in the Indication Section, but after a somewhat expanded general statement, there would be something that says what is know from trials about this particular drug probably.

DR. NISSEN: Yes.

DR. TEMPLE: Class, drug?

DR. NISSEN: Again, to the extent that we can answer the question in a way that you would consider and we would consider to be based upon our discussion today, reasonable, then, there are some things you can say about the class, but they are a lot less than what you can say about what is known about a specific drug.

Again, we don't want to take away the incentive to do clinical trials with individual agents, so again I understand why you have been very reluctant, but again we have said some things about the classes that are potentially relevant here.

DR. TEMPLE: So, I hear that as saying that after the general statement, which is nonspecific for the particular drug, we would mention things like, you know, a variety of ACE inhibitors have been studies in long-term trials, not say too much, but we would--this is our proposal really--we would identify any studies that specifically addressed this with, however, the

reservation that you never have a study of a single drug.

DR. NISSEN: I think that caveat should be there. It really is, in my view, an enormous problem, because, in fact, there is some suggestion that some drugs in combination are a bit more effective when used in that combination than when used singly.

I mean I think the example that is often cited is the diuretic ACE inhibitor where there is a real potentiation of ACE inhibitor effects when you add a little bit of diuretic to the regimen, that may be more important in that class. That is why it is always hard to tease out how much is coming from each of the components.

DR. PICKERING: One thing you might think about, there was an editorial by Kirk Furber [ph], in Circulation, showing the table of all the approved ACE inhibitors and the indications for which they have been approved, which I find quite helpful, because it is interesting, you know, they have all been approved for hypertension, but very

few of them have indications for other things.

DR. NISSEN: And new ones aren't going to get indications because you can't do the placebo-controlled trials that you need.

DR. TEMPLE: Well, people are actually quite assiduously looking at the possibility of non-inferiority studies, but now you are talking very large trials and a lot of arguing and stuff.

DR. NISSEN: So, it is pretty tough.

Anybody else on that topic? Let go to 4.

Various draft statements have been identified in the background package. Rather than trying to edit them, which I think is a good idea not to try to do, please identify which of the following should be elements of labeling?

4.1. The specific benefits thought to apply.

I think we have all pretty much said yes to that.

Anybody dissent on that?

4.2. The magnitude of those benefits. This is trickier.

DR. TEMPLE: As an illustration one conceivably could try to say what percent reduction occurs with a given change in blood pressure, the kind of thing Dr. MacMahon has put into place.

DR. NISSEN: I think this is really risky. I think the evidence is just overwhelming in my view, that it all depends on what population you study and how big the baseline risk is, and all of that. I mean, you know, this 4 mm of blood pressure reduction and a starting blood pressure of 139 in a low-risk population is going to have a very different effect than you would see in a high-risk.

DR. STOCKBRIDGE: I thought we had decided that there was pretty good preservation of relative risk.

DR. TEMPLE: Right. We are only talking relative risk. The absolute benefit is going to be bigger, the sicker you are, of course, but I think one of the findings of all of these things is that there seems to be a fairly consistent risk reduction for a given fall in blood pressure,

obviously starting from whatever risk you are at, but do you know that with any precision or are you just drawing lines to fit a model?

DR. NISSEN: I want to hear from Tom Fleming on this one.

DR. FLEMING: My sense is I am very supportive of generalities here, and I am very supportive of stating what we know from the totality of the data, and I am also very supportive of being very specific about what we know about the given agent in trials that that agent was involved.

Where I am concerned is giving real specifics about the benefit achieved from certain reductions in biomarkers even with as good data as we have on blood pressure lowering.

So, I would rather see, Bob, when you talked earlier, and I completely agree with the way you laid it out, that there would be generalities stated about what we know the anticipate benefits are going to be without being specific, and then if we have specific data, we should be very specific about what those data indicate for that specific

product.

When I look at all of these data here, I would be interested in knowing what you would propose. If there is something specific you would want to say that you think would apply in general, can you propose it, so that we would have a sense of whether we could buy into this?

DR. TEMPLE: No, but I can tell you what one might look like. Let's take the one that everybody thinks is best, and that would be stroke.

One could come up with a statement that said there appears to be a 40 percent reduction in stroke rates for every--MacMahon is not here anymore--for every 6 mm of mercury fall in diastolic pressure, I think that is something like what they showed.

Of course, they derived that from studies that had a wide variety of drugs in them, usually not a single drug, but many drugs, and that is not so different from the multitude of data that say what the epidemiologic risk of a 5 or 6 mm of mercury increase in blood pressure is.

So, those statements, that is the sort of thing, that is the question. It gets harder and harder as you leave stroke.

DR. FLEMING: I would agree with you, Bob, I would start with stroke. That is where you have the best shot, but even having said that, I would sure like to see ever more detail than what the Clinical Trials Collaboration showed on that issue, because even for stroke, I don't see necessarily whether or not there is enough evidence that would justify that broad a statement overall, as well as at least within subclasses of agents.

But if you could, if you could basically drill down on the data from this type of meta-analysis and show that there is quite clear consistency in the data with that type of statement, I would accept it reluctantly, I think, but I am actually skeptical that you are going to be able to do that.

DR. NISSEN: Tom, would you feel better about it if there was a range given, if you said for every 5 mm of mercury, you expect between a

blank and blank effect?

DR. FLEMING: Well, possibly, and especially if I had a chance to look at the data and be persuaded that it did look--I mean it is extrapolating beyond what the graphs are that we have been shown, and the graphs we have been shown really basically reflect what these meta-analyses are showing up to 8.

As we have heard, we would really like to go beyond that, and I would like to see what the totality of the data show across these trials when you look overall and when you break it down by class, but if you could, and I am skeptical that you could, but if you could show enough persuasive evidence that that conclusion would generally apply, I would still wording consistent with what we said earlier today, which would be generally could be expected as opposed to this would apply necessarily.

DR. TEMPLE: They don't have much information about much larger changes in blood pressure because, for reasons that have always been

obscure to me, even in placebo-controlled trials, you don't see differences of more than 5 or 6 mm of mercury. That is HDFP.

The early VA studies had bigger differences.

DR. FLEMING: And the epi data is going to allow you a natural history to say a whole lot more, but I am not comfortable extrapolating what clinical trial data show to the broader scenarios that epi data could address.

DR. NISSEN: Not only that, but I think we have some pretty good evidence that trying to take the epi data and translating it is likely to be wrong.

DR. TEMPLE: I think for stroke, it is actually likely to be right, but apart from that, look we will take the best shot at writing something and eventually show it to you and see if you like it.

DR. NISSEN: I would love to see it, but let me tell you why I think you ought to try, is that what we are trying to do here in all of this

is affect public health, and the more you can say to physicians about expected benefits from a treatment that we think is good for people, the more likely there is to be some noise around that and implementation of that strategy.

I mean it is one thing if you say lowering blood pressure is good, and it is another thing if you say to physicians if you can lower this blood pressure by X amount, you can reduce the risk of stroke by 25 percent in your patients. Da? I get it now. You know, even interventional cardiologists can understand that.

DR. TEMPLE: It is also slightly reassuring. You know, you see somebody with a very high blood pressure, you think to yourself I will never get him down 40, but you really don't have to, to make a big difference. A more modest effect does a lot.

DR. PROSCHAN: Last night I took some of the data from these papers and did my own meta-analysis and overlaid the results of the epidemiological studies, and it actually wasn't all

that different. The epidemiological studies did suggest more benefit than I saw in the meta-analysis, but not a lot more. It was fairly convincing.

DR. TEMPLE: For stroke.

DR. PROSCHAN: For stroke, right.

DR. NISSEN: In the Framingham risk calculation scheme, they make a big deal out of this, the fact that the number of points you get is not the same if you have a naturally occurring blood pressure of a value versus one that is achieved with a drug. So, I am just trying to be careful here.

I mean I am personally pretty uncomfortable with taking epi data and translate that into data related to a treatment effect, it makes me uncomfortable.

DR. TEMPLE: No, we are not proposing that. I am just saying that the observation people have made all along is that the stroke data look closer to the results data. You can think of reasons why. People skip their drug, you know,

lets them go during the night. There is a lot of reasons why it won't be quite as good, but it's closer. In heart attacks and cardiovascular death, the collection of data is much worse, and I attribute that to a large dose of diuretics, at least in part, but maybe there are other explanations.

DR. NISSEN: Maybe it has to do with the fact that the pathophysiology is not as driven by blood pressure, you know, it is another question.

DR. PICKERING: I would be concerned if there is too much emphasis on stroke at the expense of other endpoints. It would be a very bad public health message. I mean I think that you could say the absolute effect is greater on stroke, because it is more blood pressure dependent, but I certainly think you ought to say something about cardiovascular mortality, coronary events, and perhaps some qualified statement about progression of renal disease, which is of huge importance.

DR. SACKNER-BERNSTEIN: I think that it is also important to put it into perspective of the

frequency of the problems, because if you are looking at a public health issue, since myocardial infarction, coronary disease is going to occur much more frequently in hypertensives and stroke, the magnitude, the relative benefit doesn't have to be as great in order to have a bigger impact overall.

DR. NISSEN: It depends on how old they are.

DR. SACKNER-BERNSTEIN: And how hypertensive.

DR. NISSEN: Exactly. Let's keep going because obviously, our time is moving. I am not what you mean by 4.3, the relationship between blood pressure and risk.

DR. STOCKBRIDGE: 4.3 was an invitation to say something about the epidemiological data.

DR. NISSEN: I am not sure you want to have that in the label myself, but that is one person's opinion.

DR. FLEMING: I agree.

DR. NISSEN: That is for guideline writers and other people.

4.4. The interaction among cardiovascular risk factors.

This is actually a chance to really do some good here. It is very clear to those of us that treat a lot of patients that there is this multiplicative effect that goes on. You know, you look at some of the trials, you even begin to see it now, that if you have hyperlipidemia and hypertension, and diabetes, you know, watch out.

We need to be focused on the fact that these things tend to co-exist, and when they do, it is really bad for you. Maybe that doesn't belong in a label, and you can argue that it doesn't, but I wish physicians were more aware or more cognizant of the importance of treating global risk, treating all these factors.

DR. TEMPLE: But you would be inclined to think that if we can do it without getting lost in the noise, some statement about you should be also conscious of all other risk factors the patient has because they interact with blood pressure would be a good thing.

DR. NISSEN: I think so. I think it would be informative and I think it is the right thing to do, and i am sometimes appalled--you know, somebody was doing a public education campaign and they had a guy sitting on an exam table, and it said, "We will treat your lipids now, we will wait until you have your first stroke before we treat your blood pressure." That goes on.

DR. TEMPLE: That was ironic, right?

DR. NISSEN: Yeah, exactly, something like that. I think it was intended to be ironic, yes.

Are people comfortable with that? I mean again we are not going to say more than we know, but I think we do know that there are a couple of things that we can say. One is that there tends to be, that if you are hypertensive, there is a tendency to also be hyperlipidemic and vice versa, that there is a clustering of risk factors that seems to occur, and that people should be aware of that, and they should look for it, and they should consider treating it.

Anybody else?

4.5 is the specific drugs with a primary role in outcome trials. I am not sure I know what you mean by that.

DR. STOCKBRIDGE: I think the question was whether, you know, in any drug label, you name specific drugs that had outcome data.

DR. TEMPLE: Or do you mean you would be giving the source of most of your outcome data, so, for example, as part of your general statement, you could say the bulk of these data are based on studies with diuretics, reserpine, hydralazine, and a few other things that no one has ever heard of.

I think that is what he is asking.

DR. NISSEN: I think the compelling evidence here comes more from the analyses like what Steve MacMahon did, which are by pooling all the available data, and so if you really believe, as I think Tom is shaking his head yes, probably does, as well, if that is really the source for a lot of this, then, you don't have to do that, and I think that is the source.

I mean why are we so comfortable with this

blood pressure endpoint, is because we pooled a whole lot of studies together.

DR. TEMPLE: Right. The placebo control data, which is the easiest to understand, though, really, mostly does come from the things that you don't see a lot of, you know. A few drugs to into SHEP other than the diuretic, but a lot of the placebo-controlled data is old for obvious reasons.

DR. NISSEN: And given the legacy nature of the drugs involved, I am not sure how you inform people by doing that.

Anybody else want to comment?

DR. STOCKBRIDGE: I think that sort of leads to what you are going to do with 4.62.

DR. NISSEN: I guess that's right, but I am a little more comfortable actually, but not much more comfortable.

DR. TEMPLE: I think part of the thing we think gives strength to the whole idea that blood pressure matters is the wide range of drugs, old, new, and strange, that have all had the same kinds of effects. That is really where a lot of comes

from, everything from reserpine to hydralazine to diuretics.

DR. NISSEN: That is why you don't want to say too much about which classes contributed because again it is making a suggestion that we know more about class benefits than we really do know, so I think maybe it's better left unsaid.

Anybody else? Okay.

4.7, whether this specific drug has outcome data. I will let anybody who wants to comment on that, please.

DR. TEMPLE: That has been discussed. We will put the specific outcome data that any drug has, and say whether it doesn't, too.

DR. NISSEN: It is really important, because it is an incentive to do trials, and it is informative. It's how we learn, so I think you have got to make sure that is properly emphasized.

DR. TEMPLE: And that way, the committee will get to review a lot of active control non-inferiority studies.

DR. NISSEN: With 80,000 patients.

DR. TEMPLE: That will be good.

DR. FLEMING: That was an important addition you made, Bob. We would specifically indicate when there are data, but we would also specifically indicate when they are not, so that when you have a agent that doesn't have specific data, and you are giving these general conclusions, you would then add a statement that these conclusions are not based on specific trials that specifically used this intervention.

DR. NISSEN: It is interesting. I have noticed that in the DTC advertising for the lipid class is when there isn't outcome data. When they do the DC, and they say, well, it lowers cholesterol by X, Y, or Z, there is this disclaimer down there that says that this has not been shown to prevent heart attack or whatever, and I actually thought that was a pretty good thing that the Endocrine and Metabolism group, which says we think lowering cholesterol is really good, but for this specific drug, we don't have the outcome data to show that.

I think that is really very reasonable, so you might adopt a similar kind of a strategy in the label, which would then drive, if there is DTC advertising, would tend to be a warning to folks.

DR. TEMPLE: It, to some extent, reflects a different level of uncertainty. The very exercise we are engaged in here is partly based on the idea that you may not need outcome data so much, whereas, for lipids, we haven't gotten to that point yet, although who knows.

DR. McCLESKEY: Could I seek some clarification on this point? What I heard you say was you would put a class statement in there that the class generally does such and such if a particular drug has outcome data that are valid, that would be included.

For the myriad of other drugs for which no outcome data exists, there would be a statement that says that this specific agent in this label, there are no data to substantiate the claim for the class.

DR. TEMPLE: That is the proposal, right.

After the general statement, there would be something that would describe what studies are or are not available for the particular. They would still, I mean this was the proposal, they would still be credited with the view that because they lower blood pressure, they do the right thing for you, but this would acknowledge there are no trials.

DR. NISSEN: And, again, it creates an incentive to do such trials, which I think is good thing to be doing, and I think that is the right thing to do, because we are not so certain that we are never going to be wrong here, you know, we are sort of hedging our bets a little bit, but I think it is appropriate.

DR McCLESKEY: I don't know what the other corporate entities in the room might think, but to me, that sounds a little punitive and maybe a little bit more information than is ideal, for example, you put in the label now what is known. Are there other instances, say, in other drug classes, not even cardiology or whatever, where

things that are not known are specifically called out?

DR. NISSEN: You just heard one. I mean that is what said. I think this probably was a deliberate compromise. You know, the other surrogate you can get drugs approved for is lowering LDL by 15 percent, and drugs have been approved with that as the sole evidence, along with good safety, but you may not have outcome data to suggest that cholesterol lowering is beneficial, and I think it is appropriate to say that for this specific drug, that outcome has not yet been demonstrated.

Then, if you go on and demonstrate it, you can get that in your label, and I think that is great.

DR. TEMPLE: There are many other examples where the absence of survival data is mentioned in cardiovascular drugs.

DR. FLEMING: To me, it is even more motivated by the fact that what is happening today is a statement that we are going to say much more

about what is generally known, so I think by implying that this agent, that hasn't specifically had clinical endpoint studies done, can be presumed in general terms to be yielding this beneficial effect on the clinical outcome measures simply by showing that you have these biomarker effects. I think it is very appropriate that you are adding that implication, to then make it clear that this is not specifically known for this agent or verified for this agent.

DR. NISSEN: It is based upon the general impression that lowering blood pressure is a good thing, but not with regard to specific evidence for this agent. I think that is a very balanced approach that makes me comfortable with the more general statement, the fact that we can do that.

DR. PORTMAN: What about an issue where we have, what was it, gruntopril or something like that--gruntomycin, right, and let's say just for Bob's favorite course here that we find that gruntomycin's normal dose for lowering blood pressure is 10 mg, and we find that 80 mg lowers

proteinuria, a very important marker, and so we find out that you have agreed that it causes it to go away and we are going to allow this as an indication, what about the other five ACEs or gruntocillins, or whatever it is, that are out there, what are you going to say in their labeling about what has been proven with this one?

DR. TEMPLE: Current practice is that those other labels would be silent on that question. We don't take someone's ability to show something and then transfer it to other members of the class. You know, we might bring that issue to the committee sometime, but there is a perception that you take away any incentive to do any more.

Also, we are not sure. You know, you might be 90 percent sure the others will do it, but you don't really know, so there is fair reluctance to apply that. Now, I think third party payors and people like that, they just transfer the conclusions about one member of a class right to the others all the time.

DR. NISSEN: It is one of the reasons why

I was a little bit uncomfortable with what happened with ALLHAT, is because we then translated the lesson from ALLHAT, which is now being translated into clinical practice in the use of hydrochlorothiazide, an agent that was never studies in ALLHAT, and that is why I thought that the--I am just going to put this on the record that I thought that they went too far in promoting the results of ALLHAT given the fact that it was a specific diuretic and a specific dose, and one that is very different from some of the diuretics we use every day in some respects.

DR. TEMPLE: Let me ask you, not that we would change labeling this way, but if you have to study every member of a class to learn anything, you can't do it. I mean there were 40,000 people in ALLHAT, what do you want, another 40 with diuretic?

DR. NISSEN: No, I don't.

DR. TEMPLE: So, what should people do?

DR. NISSEN: I think it would have been good to have qualified it a little bit to say that

this diuretic, which happens to be a very potent member of the class with a very long duration of action, has these benefits, and I mean the implication was transferred publicly to the entire class, and I had a little trouble with that for reasons that you would have trouble with it.

DR. TEMPLE: I understand it perfectly, and yet the point was to find out about diuretics, that is why they did the study. You are right, they chose one. Someday we should think about that. Maybe the right thing to do is just have a random assortment of diuretics. We did that with topical nitrates once, and you weren't allowed to look at the individual data.

DR. FLEMING: That is not a bad thought, because you are right, you are not going to be able to do these studies for every specific member of the class, and if you are a believer that the class is the essential signal, then, why not randomize to the class?

DR. McCLESKEY: If I could just respond one more time, may I, on this topic? Again, I am

speaking sort of personally now.

It seems to me that if you do start naming the particular product where the label lies, as not having shown data is supportive of the class statement, I think most of the industry folks in the room will find that as a negative, and it certainly would be an incentive to do a study to show that your product is, in fact, consistent with what has been claimed for the class label.

However, from a business case point of view, depending upon the product itself, performing such a study may or may not make business sense, and may or may not be done, in which case that particular drug would probably take a hit as a result of being called out as not having satisfied whatever the criteria are needed in order for that drug to satisfy that class labeling, and, in fact, as we have heard today, it sounds like in order for these non-inferiority trials to meet that requirement, they are going to become bigger and more difficult, requiring greater and greater investment.

So, I don't know this for a fact, but I would assume that most companies would view that as a negative.

DR. NISSEN: You know, we are giving them a positive here. We are giving them a very important positive, let me make sure you understand this. Since it is almost impossible to do these studies now, those big non-inferiority trials, so you can just say nothing at all, or you can say that blood pressure lowering is a good thing, and you get that claim, but you don't get the specific claim.

So, I think the companies are getting a whole lot more than they would have gotten otherwise, which is they get some claims related to the fact that they lower blood pressure, and we think that is a good thing, and I think that is a step forward, guys.

DR. PROSCHAN: Maybe cosmetically, the way you could do this is say here are the members of this class that have been shown. Don't say this drug has not been shown.

DR. NISSEN: They would find that even less palatable. Here, use our competitor's drug. I don't think that would fly, Mike, but I am just a poor knuckle-dragging cardiologist.

Whether this specific drug's class has outcome data, that is a more challenging question, isn't it? I would like to hear some discussion of that for sure.

DR. TEERLINK: I actually would be in support of that in terms of the levels of evidence concept that I had tried to allude to earlier, because that is what we are really trying to get at a bit here in terms of saying, well, we think the blood pressure, in and of itself reducing is a good thing, and then we know that, for example, ACE inhibitors do have these effects on outcomes, such and such, gruntapril is an ACE inhibitor, however, it has not been specifically addressed in this, so you have the different levels. So, I would be in favor of looking at the class effect.

DR. NISSEN: Let me tell you where this is particularly useful. I hope there will be new

classes of antihypertensive drugs that will come along, and at least initially, those new classes won't have such evidence, and given what we saw with the alpha blockers where there may be a problem with a class that works by some other mechanism, we should be providing some distinction between classes where we have seen benefits and classes where we simply don't know.

So, this is an opportunity to do that, and I, for one, will probably, if a new class comes along, it is not going to be my first-line drug until it has some outcome data, and I think we need to tell people about that.

Anybody else?

DR. SACKNER-BERNSTEIN: I think that that kind of caveat is exactly what we should do. We talk about a lack of evidence. We talk about some classes having great consistency within that class, other classes having less consistency.

DR. FLEMING: I endorse all three of what you have said. It is kind of a truth in advertising here, you are recognizing, as I think

we have throughout the day, that there are levels of extrapolation here. The broadest level of extrapolation is what we are saying based on all antihypertensives. Less of an extrapolation is what we say about a specific product based on evidence from other agents in that class, and the least extrapolation is from that product itself.

It is simply reflecting that truth. You are being very specific about what it is that we know and the level of reliability of that.

DR. NISSEN: Okay. I think that is good. Is that helpful? Okay.

4.9 is another interesting one that I think would like to hear some discussion of. Factors to consider in choosing a drug class.

Anybody want to take that one on? I certainly have some thoughts.

DR. SACKNER-BERNSTEIN: The only problem I would have with saying yes to these and then also getting into a discussion of other considerations is the fact that a lot of these questions are ones which I think we need to say yes to, and all of a

sudden we are going to have product inserts that are so long that will start getting a problem where people will have a greater disincentive to read anything, so I want to say yes, but I am just worried about that yes, that we should include these issues, but i am just worried, that if I keep on saying yes to these things, which I think are very good points, that then there will be information overload in the insert.

DR. NISSEN: It is interesting, because I want to say no, and I want to tell you why I want to say no. I think this is exactly where we transition into what belongs in a guideline. This is where you get a bunch of people who are clinicians together and they look at the totality of the evidence and they say yes, if you have certain--this comorbidity, let's say, that we think that this particular class has benefits.

The ability to make that decision based upon robust data from a regulatory point of view is very likely not to be there. So, this is more opinion, and opinion I think belongs in the

guideline realm rather than in the regulatory realm, and the question is how many of these factors--Tom, as you look at the evidence, how many of these factors do we really have solid data to suggest that one class, with this factor present, is better than another class?

Well, you might argue for kidney, there is some, you know, but that is going to be in specific claims, you know, I mean those drugs that have been shown to have effects favorable, they are going to get that claim, that is not such a hard claim to get, and so I wouldn't go there. I would let the societies that write guidelines take care of this issue.

DR. PORTMAN: It depends on whether we are setting this section up in the labeling that clinicians are going to go there, you know, to read. They are going to say this is the area that I am going to read because it is going to have the most information for me.

If that is true, then added in things such as its use in chronic kidney disease should be

there. You can refer them for more information to another part, but it certainly should be mentioned there.

DR. TEERLINK: I believe we are already saying that the general statement, somewhere in here, is going to already give the reduction in stroke, cardiovascular disease, and probable progression of renal disease, so I think the general statement will probably contain some of those elements, maybe not all of them, but I would concur that most of these other elements, while I think are very important, are better left to the guidelines.

DR. TEMPLE: Just so you know what model this was thinking about. The last paragraph of the first version had what we had in mind here, and it is quite short and not very major, but it said things like certain antihypertensives are less likely to be effective in certain ethnic groups and are more likely to be preferable in certain settings like ACE inhibitors and betablockers for congestive heart failure, and selection of

particular agents should be individualized.

It is not a guidance says if this, then, do this; if this, then, do this. It is a general sort of thought process you should be going through.

I don't know whether that makes any difference in how you feel about it.

DR. NISSEN: It does, because I happen to think that the issue of African-American responsiveness is important and should be commented on where we have information, and I think we do, then, that should be there, but I think that the number of factors for which we have solid information is relatively limited. I would urge a very cautious approach to this, because I do think that we just don't know enough about which factors ought to drive it in one direction or the other.

I think that the guidelines can, in fact, address this very well. They don't have to be regulatory issues.

What about hypokalemia, though? That is another interesting question. The way it is asked,

I mean obviously risks of hypokalemia are going to be discussed elsewhere in the label, so tell me what you were envisioning here in this question.

DR. TEMPLE: Well, that reflects my obsession with the early failure to have cardiovascular benefit when the whole world overdosed everybody with diuretics, which I consider the worse adverse drug reaction there has ever been, that is, the difference between 30 percent and 15 percent.

So, that makes me want to remind people that you mustn't overdose with diuretics whenever I have any opportunity, but maybe I am obsessed, I don't know.

DR. NISSEN: Yeah, I think you are obsessed. I could say some other things about you, but I won't say them here.

[Laughter.]

DR. TEMPLE: By now, everybody is using doses that are too low anyway, so the problem has been fixed.

DR. NISSEN: The other thing is you have

got lots opportunity and warnings in other areas to comment about this, and I think that is the place that it belongs personally.

Anybody else want to comment?

4.10. Other elements of a cardiovascular risk reduction program, control lipids, stop smoking, lose weight, and get exercise. I do think this is the guidelines again, but I also want us to totally lose sight of the fact that hypertension control ought to be part of a multi-intervention strategy, and the question is, is that a regulatory, is that something you address in a regulatory agency or that we address as guideline writers.

I just wish physicians were more astute about recognizing this and treating the multiple factors that are so frequently present, because I am convinced that if yo do that, you get a huge, huge benefit for these patients.

DR. TEMPLE: We heard this, I think you discussed this earlier, and we will try to write something that does that. It does seem relevant to

the labeling to point out that these factors interact.

DR. NISSEN: I will tell you the other thing you see is, you see people who are on the highest dose of a lipid lowering agent, and they aren't on aspirin. It is just amazing to me that people don't recognize that as far as we know, in fact, there is pretty good evidence that you preserve the benefit of aspirin in the presence of maximum lipid treatment. It doesn't go away. Yet, people don't always do it.

DR. TEMPLE: That's because they haven't had a heart attack yet.

DR. NISSEN: I am serious, though, I mean these people, incredibly high risk where all the data would suggest aspirin is beneficial. No, no, I know, I know, I am with you, listen, I am with you on the primary prevention part of it, but we are talking about people who have angina, who have known coronary disease, they have had an angioplasty or two, and they have high lipids.

DR. SACKNER-BERNSTEIN: Steve, you ought

to go to Question 4.11. I think you are going to get yourself in trouble in this one, just to move on.

DR. NISSEN: Whatever you say. I guess I am on a soapbox today.

4.11. The importance of blood pressure control through the inter-dosing interval.

DR. HIATT: Tom Pickering is not here, but I tried to get some more information on this in the next question. I guess my modest impression is we don't know enough about it. The other thing that makes me a bit concerned, if you say that is important, you need to be able to measure it, and we don't really do that in clinical practice.

If that is the implication and there is not a lot of outcome data, I would leave both of those alone.

DR. NISSEN: That is interesting. I have an opposite view here, and I think it is very important and very informative, and, you know, you put this in now, and you talk about peak and trough effects and all that, but I think that these are

very relevant.

DR. TEMPLE: I think we meant shouldn't you get a morning pre-dose blood pressure to see if it's under control. The reason that is an issue is that while some drugs at any dose are going to cover you over the whole dosing interval, some of them with somewhat shorter action, you may have to adjust the dose until you get a satisfactory response at trough.

I think we thought that--everything we know says that is very important.

DR. HIATT: Is that true, though, because the pharmacodynamics of these drugs tend to be relatively long, not short. Is it true that you can take these studies and somehow cull out of them people that are losing blood pressure control dose interval are somehow having events and those that retain it are not having events?

DR. TEMPLE: No, no, no, not related to events, but you see for some drugs that the trough-to-peak ratio goes up with dose. That tells you that at the lower doses, you are escaping, and

you are right, it would vary by class. Some drugs last a long time, longer than the apparent pharmacokinetic survival, and others don't.

DR. PORTMAN: I completely agree, and I echo Tom's talk that we should be doing ambulatory monitoring more and home monitoring, and getting a better picture of the length of action of the drugs, and this would be a good place to put it, but also we have disease states that have different circadian rhythms, chronic kidney disease being one of them, other types where you have nocturnal hypertension. I think it is very important that we have this kind of data when it exists.

DR. HIATT: Where I am going with this is that if two-thirds of this country does not have blood pressure control, whether you believe that is important or not, and now you try and tell people that this interdosing interval matters a heck of a lot, to go after it, in the absence of a lot of outcome data, I am just not sure from a public health point of view that is the right message to send.

I think taking something beats taking nothing.

DR. NISSEN: I sort of understand where you are coming from. I interpreted the question a little differently. I do think that the more we can tell people about how to give the drugs in the optimal fashion, the better, when we know that.

Now, we don't know what that is for events, but we do know what that is for blood pressure, so I think it is something that is certainly relevant in certain cases. I mean if you have an agent that was particularly short acting, I think that that information would be relevant and should be discussed, and suggesting to people that maybe this is a drug where you might want to know what the pre-dose blood pressure is when making decisions about dose.

DR. STOCKBRIDGE: Just to be clear, the questions 4.11 and 4.12 really had to do with what you knew and what you thought was important about drugs, the actual instructions for use, guiding people for how they should measure blood pressure

and when relative to dose and stuff, that is really 5.4 and 5.5 coming up soon.

DR. NISSEN: So, the information related to drugs, you are already putting in there, right, you are telling them about peak to trough and all of that, right? So, they have got that information. I would pay attention to it as least.

Are there any other elements that people want to bring up, that we haven't talked about under this? 4.13 is an open-ended statement. Please chime in if you do.

Let's to down to 5. We are actually making reasonable progress.

Labeling for lipid-lowering drugs is quite explicit in recommending an approach to treatment, when to initiate treatment, what the goals are, et cetera. Currently, labels for antihypertensive drugs do not say whom or how to treat for hypertension.

How should physicians be instructed to assess blood pressure with respect to...what to measure, 5.1.

DR. CUNNINGHAM: I have got a question first. Since it is in the lipid-lowering labels, what do we know about how effective it has been?

DR. TEMPLE: Lipids are undertreated just like blood pressure, but I don't know that anybody knows. My reservation about any goal statement is that it evolves and it is a long time before you change the label and to fix it, so what is in one thing is probably not what everybody would agree, and there is arguing about it.

DR. CUNNINGHAM: Is there any reason not to put a reference to the guidelines, because it is getting longer and longer and longer here, and the guidelines change on a relatively frequent basis, and I think it would be really wonderful, although I don't know if people would do it, but it would be wonderful if they would actually go read the guidelines.

DR. TEMPLE: So, like mention one source of information, JNC, whatever the latest is. That's a thought.

DR. NISSEN: Bob, I don't think that what

is in the lipid labels contributes very much personally. I mean I know it is always there and to repeat it and all, in every one of the drugs it is repeated again, I am not sure it contributes very much.

Again, I do think that that is much more in the realm of guideline writing than it is label writing, and given what we have said about the fact that labels are kind of longish anyway, I am not so sure I mean that some dumb-down version of JNC VII belongs in the hypertension labels. I wouldn't go there personally.

DR. TEMPLE: How about referring to sources of information?

DR. NISSEN: I think that is just fine to reference it and say if you want to learn more, go read this, but I think that the dumb-down version of the lipid guidelines that is in the labels for the lipid-lowering drugs, I think is not contributing a great deal to their optimal use. That is one man's opinion.

So, what to measure, should we say

anything about what to measure, that is, we should be measuring systolic or diastolic or both? Do you want to say that?

DR. TEMPLE: Well, it would be an odd person who didn't measure both.

Do you know--I will tell one on us--do you know that the primary endpoint in most hypertension trials is still diastolic blood pressure? Can you believe that now? It is true, though, that is the primary endpoint. Then, they give you the other data, too.

So, one of the things I want to get in here is systolic counts, just in case you have been asleep for the last 10 years. I think it should say very clearly that both systolic and diastolic pressures predict risk.

DR. NISSEN: The place you might put it is in that earlier indication where you talk about how the data, you know, with respect to systolic pressure, shows blankety blank.

DR. TEMPLE: And these versions all do say that.

DR. NISSEN: Yes, I think you can say that in a way that is not quite as heavy handed. The other reason why it is actually helpful, what is actually helpful about this is that it is harder to achieve systolic goals. I mean every study shows that, so the more you emphasize that, the more you push people toward more effective treatment.

Diastolic is a lot easier to get to in every study I have seen. So, it is raising the bar a little bit, and I don't mind raising the bar.

How many times to make the measurements during a visit? I don't think so. Anybody?

DR. HIATT: This is anecdotal, but I always take blood pressures myself two or three times, and they don't agree at all with what the nurse got, and most physicians and most residents present to me use blood pressures that just aren't real, I don't think. So, if there is some way you can make a comment about the importance of taking that blood pressure yourself multiple times might be a good thing to do.

DR. NISSEN: As soon as the Federal

Government starts paying people to take blood pressures, they will start taking it themselves.

DR. STOCKBRIDGE: I just think you have to understand the trials are done with people in a very stylized way, waiting a certain number of minutes in a given position, and making several measurements over a period of a few minutes, and it is partly done to reduce the very large variance that is involved in making single measurements.

So, I think the reason to say something about it is you are fooling yourself if you only make a single measurement of blood pressure.

DR. HIATT: Norm, I want to support that. I think that you should say something about great care should be taken, multiple measurements should be made, that the measurement is so critical for decision-making that to base it on a very noisy estimate when someone just walks in and suddenly sits down, I actually strongly encourage that that kind of language get in there, because it is just not a casual thing, it is actually not a trivial measurement to make.

DR. NISSEN: I hate to say this, but I don't think you are going to fix this problem with the drug labels. Again, I think you are adding a lot of noise to something that should not necessarily be a regulatory issue.

Do we need to take blood pressure better? You bet. Do we need to educate physicians to take blood pressure better? You bet. The organization that I represent and a lot of others need to do a much better job of educating physicians about how to take blood pressure, but I don't think the FDA can do that in a drug label.

I am sorry to tell you that, but I think it is just going to be a lot of noise, and we are already making these labels, as several people have said, more complex.

Let's stick with those things that really get with what the regulatory role should be, and I don't think telling people or teaching people how to take blood pressure needs to be there or should be there.

DR. CUNNINGHAM: I think you are also

assuming that the blood pressure cuffs have been calibrated. My experience is that people haven't a clue about calibrating, and one of the things in those big trials, the cuffs are calibrated, everybody is taught exactly how to do blood pressure. I am not going to tell any anecdotes about how people don't calibrate.

DR. NISSEN: We have a huge problem here, but it is not one that the FDA can solve for us honestly, I think that is the problem. There are probably people that are putting blood pressure cuffs around their neck and taking the pressure in the carotic artery, and that doesn't work at all.

Let's 5.4 and 5.5. Timing. What time of day to make measurements? Again, I think it is all in the same vein. Most of the discussion we have had probably is applicable to those. What I don't understand is what you are getting for about the risk of developing a cardiovascular event over the next few years.

What is that all about?

DR. HIATT: Maybe that is the absolute

risk concept that could be put in here, risk assessment which has been alluded to in a variety of other ways about treating of the risk factors should be part of your decision-making, and talking about absolute versus relative risk.

DR. NISSEN: Is that what you were asking?

DR. STOCKBRIDGE: I think more or less that was the idea, how one adjusts one thinking about treatment with respect to other risk factors.

DR. NISSEN: Again, I do see that much more as a guideline issue as was done with Framingham for the lipid guidelines. I kind of wish that the blood pressure guidelines incorporated some global risk assessment as opposed to 140 is hypertension and 139 is not.

DR. TEMPLE: You need a little hand-held device to give it to you.

DR. NISSEN: In the lipid groups, they have got this. They have got these little Palm things that you can punch in the Framingham risk just like that, and they actually have at least 1 percent of physicians that actually do that, maybe

half a percent, but it can be done, but it is very difficult people to implement those, and I don't think it is going to help them to put it here.

What goals to seek? Are the goals lower in high-risk patients? I see the guideline issue, but others please disagree.

How closely to monitor during and after up-titration?

Now, there is an issue here that I would like to maybe have some discussion about, let's see what people have to say. That is, the time to maximum effect of regimens is somewhat different from drug to drug, that is, none of them are instantaneous. That does have an impact on how to do your titration. Anybody want to comment about that?

DR. HIATT: Some of the trials we obviously discussed earlier did show that controls achieved after multiple drugs were added, and there was a time difference, and that time difference seemed to matter.

So, again, maybe the concept of

introducing that and do a label, that one shouldn't be complacent and wait for an annual visit to control the blood pressure, and you might tie that into the concept of multiple drugs are necessary to achieve control.

DR. NISSEN: You can also get into trouble with this, and I am going to give you an example. If you take a drug that has a long time to steady state, a blood pressure effect, and you don't know that, so you give it and a couple days later your patient calls. It happens to me all the time. They call me up on the phone. I get them on a home blood pressure program and they say my blood pressure is still high, and you then add another drug and two days later you add a third drug, you can get into some significant trouble.

Certainly, the pharmacokinetic aspect, some of these drugs have very long half lives, several days, and those drugs take a while to get to full effect, and you could go up too fast if you are not careful.

DR. TEMPLE: But even if it's a couple of

days, you have reached pharmacokinetic steady state by the end of a week. It is not very long.

DR. NISSEN: Can anybody tell us more about--what do we know about the time to maximal blood pressure?

DR. TEMPLE: We see data on that. I am concerned that it's not very good, but the dominant impression I have is that most of the effect is pretty much there by a week or so, maybe not for reserpine or something, but for most of them it is there by a week, and then you may get another millimeter or something, but I would say I haven't seen anything where I wouldn't feel reasonably comfortable titrating it a week even though you might get a little more effect later, but you don't mind having a little more effect.

DR. HIATT: Tom and I discussed that issue over lunch. It was my impression it was a week for pharmacodynamic effects, and he confirmed that, so I would think that the risk is far more under treatment than over treatment.

DR. NISSEN: That's a good point. Do you

think it belongs on a label?

DR. HIATT: As much as any of this other stuff does.

DR. NISSEN: Just give me an idea of how you would say it.

DR. TEMPLE: One thing is you don't want to spend four months getting to the dose, because by then you can have events. I think it wouldn't be bad to say for most drugs, titrating at one-week intervals. That is worth thinking about, put that down and see what people think about it.

DR. HIATT: You might link that to the concept again that multiple drugs are often necessary to achieve control, and that decision of titrating can occur on approximately a weekly basis.

DR. NISSEN: Let's see what you can do with that. People have made some pretty persuasive arguments about that.

Which drug classes are appropriate for initial therapy and which should be used second or later? Isn't that an interesting question. Let's

hear some comment and discussion.

DR. FLEMING: Is that also related to Question 7?

DR. NISSEN: It sure is.

DR. HIATT: I mean the data would be compelling to start with diuretics, and I think that there is also a cost advantage, a societal benefit to starting with generics.

DR. NISSEN: That's not a regulatory issue.

DR. TEMPLE: We suppress our thoughts about such things.

DR. HIATT: The data would still support diuretics as first line and certainly the guidelines say that.

DR. SACKNER-BERNSTEIN: Diuretics or diuretic?

DR. NISSEN: Let's be careful here for a moment. Let's take the largest study we have, which is ALLHAT, and let's take the primary prespecified endpoint, and the hazard ratio for the three classes, three main classes that were studied

were indistinguishable fundamentally overall.

Some endpoints went in one direction, some went in the other, so isn't it true that at least with an initial strategy in ALLHAT, you could use any of three, and you could ultimately get the same effect on the primary endpoint, an ACE inhibitor, a calcium channel blocker, or diuretic.

I am taking off the hat here of the economics, which I think is what was driving the public pronouncements about that, which I am not saying are irrelevant, but they are not a regulatory issue. I would have a hard time arguing that any of those three classes were superior for first line, they are all pretty much first line, and frankly, you are going to need more than one class most of the time anyway.

DR. PORTMAN: First line in whom? I mean a patient with essential hypertension or a diabetic or a chronic kidney disease?

DR. NISSEN: We have already said that we are going to inform people about some of those specific issues elsewhere, but I certainly would

have a hard time labeling any of those as second line versus first line based upon a 42,000 patient trial, it is pretty hard to make that argument I think, isn't it?

DR. HIATT: Steve's publications support that concept.

DR. NISSEN: They really do. Now, alpha blockers, not a first line, I think, unless anybody disagrees with me.

DR. TEMPLE: Also, tricky to use. You titrate over a much larger range, there is the orthostatic hypotension early. They have clear disadvantages.

DR. NISSEN: It gets a little more interesting when you then take it to the beta blocker level, and the question is does that apply there as well, but I have a hard time labeling any of the three drug classes used in ALLHAT as one being first line over the already other two, recognizing that there were differences observed in some of the individual endpoints.

DR. TEMPLE: I mean there are drugs that

weren't in ALLHAT. There is no A2B in ALLHAT. So, the question is how much does one want to say about this or is this another guideline thing.

The one thing that comes out of ALLHAT, and we have been talking about is if the development of heart failure and symptoms of heart failure is a recognized problem in hypertension, does that mean you want to use one of the ones that treats it. That seems like a legitimate question. But you are right, you are going to get to two drugs eventually anyway.

DR. NISSEN: I guess the other problem I have is that again, when you look at a study like ALLHAT, where you really have the power, is around that primary pre-specified endpoint, you know, everybody wanted to know whether any of those three classes had a distinctive advantage looking at all of the important bad things that can happen to people with hypertension.

The answer is that it was the blood pressure, stupid, pretty much, and they all did very well, and I can't imagine that anybody would

consider any of them not to be first line.

DR. HIATT: Well, there is this meta-analysis in JAMA 2003 that says diuretics beat everything, and that included ALLHAT in the analysis.

DR. NISSEN: Again, meta-analysis, not randomized controlled trial.

DR. TEMPLE: And it did so because of any particular endpoint, or all of them?

DR. HIATT: It was driven by heart failure, CHD death, I don't know. You know, it is just worth looking into all these different publications to make that statement.

DR. NISSEN: From a regulatory point of view, I am not sure you want to codify that in a label.

DR. TEMPLE: And meta-analyses where we can't replicate it and do all the stuff ourselves make us nervous, too, I have to say, and then the meta-analyses tend to show an edge for some of them for stroke. Maybe that matters more than a little heart failure. I mean I don't know, these are hard

questions.

DR. PROSCHAN: Is the reason that you are saying that you don't know why you would distinguish one as first line, is that because you think there is a tradeoff, maybe diuretic is better for heart failure, but worse for diabetes? I am trying to understand the rationale.

DR. NISSEN: No, it's one thing when you are writing a guideline, it's another when you are writing a regulatory document. Here, what is the level of evidence that suggests that diuretics are superior, again, you have to listen even to the author's statement.

They kept saying diuretics are unsurpassed, and I think that is correct, they are unsurpassed. My view is that they are unsurpassed, and if I were writing a guideline, I might well say, for a variety of reasons, some of which are economic, that you ought to start with a diuretic because it is as good as anything else, and it's very inexpensive.

But can I say that there is compelling

evidence that diuretics are better than ACE inhibitors or better than calcium channel blockers, and I don't think I can say that, I just don't think that that meets any level of evidence that would have regulatory implications personally.

John.

DR. TEERLINK: I think we are kind of caught between two extremes here, as well, because we earlier were all in pretty much agreement, gee, therapy should kind of be tailored to the individual patient, to their underlying risk factors, and to those aspects, and then we are trying to make more sweeping statements in terms of what should be first line or second line.

So, I would be in favor of leaving this to the guideline committees, as well, where they can give those specific nuances greater weight that we could in the time given to a label.

DR. NISSEN: Except where we know that there is a real difference. I do think we think the alpha blockers are not as good, and I think that informing the prescribing physician that the

agent is not a first line agent is appropriate, you know, when we know that.

I just don't think for the bigger classes where we have got a lot of evidence that they are pretty similar, whether you can really make that statement.

DR. TEERLINK: So, then, would you label most of those big classes first line?

DR. NISSEN: Well, I mean again, or just not speak to it. That is the other thing you can decide to do.

DR. TEMPLE: At present, there isn't any statement--I mean there is a difference between labeling something as first line and labeling something else as second line. That means that second one has a problem.

DR. NISSEN: What did you guys end up putting in the doxazosin label after our last--what did you say?

DR. TEMPLE: I don't know. We don't remember.

DR. FLEMING: Bill, were you referring to

the JAMA meta-analysis that was published in 2003? Basically, it was meta-analysis of 42 trials with 200,000 people stating that the diuretics, first of all, had direct placebo-controlled assessments showing superiority on all of the measures, coronary heart disease, congestive heart failure, cardiovascular disease events, cardiovascular disease mortality.

Then, they go down agent, class by class, and basically, for calcium channel blockers, there is superiority relative to heart failure. To ACE inhibitors, it's cardiovascular death, MI. For beta blockers, it is superiority for cardiovascular disease events. For alpha blockers, heart failure events and cardiovascular disease events.

Their point is in no case are the diuretics inferior to anything, and yet for each of these classes, there is a measure for which they are superior.

DR. NISSEN: How would you view that? What is your opinion about this issue, Tom?

DR. FLEMING: Well, I think it certainly

provides significant evidence that they are a good choice. The question is are they the only proper choice, and clearly, not in all settings.

DR. NISSEN: The fact that they had data against placebo, of course, has to do with the fact that they were the first class to be introduced, so there is a chronological aspect to this that you can't get away from.

That is why I rely upon the best prospective randomized data available even though it may not be perfect, and that is ALLHAT, and it is big and it's direct comparison, first line, what did it give first, either diuretic and ACE inhibitor or calcium channel blocker, and at the end of the day, on the primary endpoint, they are indistinguishable. It is pretty hard to call any of those drugs second line in my view.

DR. HIATT: I think, harkening back to earlier conversations, that the message is that it is the control of the blood pressure that matters, and we realize you have to get there in multiple way. I am actually comfortable not trying to

declare any particular class as superior.

DR. NISSEN: Let's move forward. When to add a second drug? Note that labeling currently usually says to start a second drug only after a single drug has proven inadequate at its highest tolerated dose.

Anybody want to weigh in on that?

DR. HIATT: You almost have to like look at the methods around each of these trials and what the criteria were for up-titration. To me, the answer to that question is you have got to look at the methods used to achieve that.

DR. TEMPLE: I think everyone would have doubts about that. You don't want to give the highest possible dose of amlodipine before you add a diuretic, because everybody will be swollen, so that is silly.

If the drug doesn't have any dose-related side effects, which some of them don't, then, maybe you want to do that, or you want to get up to full dose. This needs revision. This is sort of the old, non-thinking version of step care, but I don't

think anybody really thinks that is the right thing to do anymore.

DR. NISSEN: You can't substitute for clinical judgment here. Some people get dose-limiting toxicities at lower doses than others. Some people will tolerate a medium-sized dose of an ACE inhibitor, but cough like crazy when you push the dose on up. Well, they might do very well by having a smaller dose of an ACE with a diuretic than they would by having a maximum dose of an ACE.

So, there is just a lot of nuance here in how you practice clinical medicine, it is very, very hard for you to tell people how to do this. It is hard for us in guidelines to tell people how to do this, let alone put into a label.

So, I think it is probably an area you don't want to go too far in.

DR. TEMPLE: I guess one question is whether there are people still doing old-fashioned step care, in which case you might want to tell them maybe that is not always the smartest thing to

do.

DR. NISSEN: How are you going to tell them that, Bob, because it is so agent-specific?

DR. TEMPLE: The first thing you say is many patients will need more than one drug to get to a reasonable goal. The decision about when to add a second drug is individualized, but you don't necessarily have to use the highest dose of the first drug. You might want to stop when intolerance develops or when side effects emerge or blah-blah-blah.

DR. STOCKBRIDGE: I would just like to point out that in most cases, the combination products do not have first line indication.

In general, the easiest way, the least interesting way you can get a first line indication for a combination is to show in some trial that you can use it safely as a combination and identify a population that is far enough from goal that they are quite likely to need two drugs.

Are we backing off from that, too, so that we should no longer say anything at all about

whether or not you should use combination products as initial therapy?

DR. NISSEN: Anybody? I can only speak for myself in terms of I do sometimes start combinations as the first agent. If I get somebody that comes in that is really quite hypertensive, and I am convinced that they are going to need more active therapy, I may give them a combination right out of the box, and that is because I am worried about them and I want to get their blood pressure down promptly, and I do believe that the speed with which you get control is important.

But to what extent do we want to say that as part of a regulatory policy as opposed to guidance towards good clinical practice and how we educate physicians? I am ambivalent about this one, because your problem here is that you have to start talking about thresholds.

Well, if you are above X, maybe you ought to start two drugs. Well, what is X, and what is our level of evidence that says that that--

DR. STOCKBRIDGE: You might say nothing at

all about what the goals are. They don't say anything with respect to the single agents. You just don't distinguish them whatsoever. They will not say you should go through a single drug before you pick up this one. Is that what you want?

DR. NISSEN: Again, I think that it depends a lot on--I mean if somebody is coming in and their blood pressure is close to goal, then, I am not so sure giving a two-drug regimen is the intelligent thing to do. It is not always right and it is not always wrong, it's a judgment call, and it is very hard to convey that in a label.

DR. FLEMING: If it were an African-American patient, you were labeling an ACE inhibitor, would you say you should start with a combination of diuretic and ACE inhibitor?

DR. NISSEN: Again, I think it is good clinical practice. The question is, is it--you know, do we know enough, do we have enough clinical trial evidence that has been reviewed by the agency to suggest that if you are African-American, you ought to get started on the combo rather than on

the ACE inhibitor alone.

I would argue that in data that you have reviewed or that we have reviewed, and it meets all of our standards, that we don't necessarily really know that.

DR. TEMPLE: What we have been getting some data on is identifying a group of people with a baseline pressure that is over a certain level, accompanied by evidence that one drug will not control those people in more than 5 or 10 percent of the time. In those people, we have considered it reasonable to start a combination.

It certainly seems worth telling people that it will often be necessary to use more than one drug to get to a reasonable goal, and that how to titrate and how rapidly to titrate is probably related to how high the blood pressure is.

I guess my question for you is do we want to remind people that you don't really always necessarily want to use the largest possible dose of the first drug before you move, which is old practice. Maybe it is not being done anymore, I

don't know, I don't treat anybody.

DR. NISSEN: It is obviously good thinking, the question is how do you convey that in a way that is appropriate. I would sure like to see how you are going to do that. What would you say? It is not going to apply equally to every drug.

See, that is the problem that I have, is that drugs that have very well-known dose-related toxicities, your need to add a second agent, and the desirability of adding a second agent earlier makes more sense.

In drugs that don't have very key dose-related toxicities, then, it might sometimes be best to go to the highest dose of a single agent. So, it is very dependent upon the situation that you are in, and I find it very difficult to come up with a uniform guidance for that.

No. 6. How, if at all, and in which labels should one describe the results of an active-controlled study in which the various regimens were not distinguished for their primary

endpoints?

Help me out here.

DR. STOCKBRIDGE: Which labels should have some mention of some description of the results of ALLHAT? Say, for example, pick one at random.

DR. FLEMING: I would argue we would follow the principle that we laid out earlier. ALLHAT contributes to the global understanding, so I don't know that I would be specific about describing ALLHAT when it is one of many trials that contribute to the global understanding.

But when I am licensing the specific products that were in that trial, you get I would be describing that, and I wouldn't, as this question would seem to suggest, only do so if I had highly precise estimates from the confidence interval. If I had 25,000 people from ALLHAT, obviously, for pairwise comparison, I am getting a very precise estimate of that relative risk, but even if you had 5,000 people, and the confidence interval would be twice as wide, that is still giving you considerable insight about the relative

efficacy on those clinical endpoints.

So, in general, I would follow the principle that we laid out earlier on, and that is, if I have substantive information about the efficacy of a specific product, I would like to include in the label a description of those results for that product.

DR. STOCKBRIDGE: So, for like lisinopril and amlodipine out of the ALLHAT trial, you would propose that we say something fairly terse and non-quantitative, that the data in ALLHAT were consistent with those drugs having the benefit you would expect out of chlorthalidone or other antihypertensive agents.

DR. NISSEN: There are two levels of evidence here that I think have to be considered. We heard a presentation this morning from the folks at Pfizer on methodology that they were proposing that should be applied for inputing the placebo effect.

You would follow that line of reasoning and do that for lisinopril and you could do that

for amlodipine, and if you felt that you were comfortable statistically with the methodology, you could say, well, imputing placebo, that this is equivalent to having a placebo or similar to having placebo-controlled data.

This is really a statistical question, Tom, and I would like to know what your thoughts are.

DR. FLEMING: I am comfortable with the first of the two analyses that Pfizer was doing today, I am comfortable with that, and if that analysis was carried out according to standards that the FDA would consider acceptable, I would be very comfortable with that being included.

But, in fact, if that analysis had not been carried out, certainly, there are still very important insight from ALLHAT about the overall relative efficacy of amlodipine, about calcium channel blockers, relative to the comparator agents that are in the trial.

So, having those relative risks and those confidence intervals on those outcome measures is

specifically very informative even if one didn't go through the next step to do a non-inferiority analysis.

Remember there are two types of critical insights that come from an active comparator trial. One of those insights is having the clinical insight about the direct relative efficacy of these agents that were in the trial, and that is already apparent from this analysis even without non-inferiority.

Then, an additional insight particularly of regulatory importance is whether or not these also allow you to conclude that you are maintaining, let's say, at least half the efficacy of the active comparator, and that is an additional analysis that might be possible, and if it is possible, then, that would be added insight, and if it were done in a rigorous way, then, that, too, could be included.

DR. PROSCHAN: I think non-inferiority, somehow that seems a lot thornier issue than showing superiority. I have given this example

before that I can show that holding 50 sheets of paper in my hand is just as good as a diuretic, because I am going to hold the paper in my hand.

If it doesn't lower blood pressure, I will increase the dose. I will add 100 sheets. Then, it still won't lower the blood pressure, so I will add a beta blocker, and now my pressure is lowered, and maybe I can show that that is equivalent, but I don't want to say--that it is equivalent to the diuretic--but I don't want to say that I have proven that holding paper in my hand is equivalent to the diuretic.

The fact that you are using these second line agents makes it a little more troubling for this non-inferiority.

DR. NISSEN: I can tell you that for non-inferiority, there is going to be no perfect level of evidence unless you want to do a 100,000 patient trial.

Now, somebody spent a lot of money and a lot of years to do the largest type retention trial in history, and it belongs in the label for the

drugs that were used. Now, the question is what do you say. That is the only question we are talking about, because it would be a terrible shame to do a trial of that size and scope, and not put that in the label for the drugs that were actually used in the trial.

So, now I am back to where Tom is, and I would say that one has to look carefully at the statistical evidence, the methodology, and I agree with you, Tom, that some of that analysis imputing placebo was pretty convincing particularly when the agent that you were using to compare to was chlorthalidone where we know an awful lot about the drug.

We knew a lot about chlorthalidone, we are pretty comfortable with its benefits based upon placebo-controlled trials, so you are not going to get any better than that in terms of being able to impute placebo, and if you use that methodology and you come up with an estimate that you think meets normal statistical standards, I think you put that in the label.

DR. FLEMING: To reiterate, that is a potential added aspect to what might be included. What we were saying is in general terms, and I think it is consistent with what Michael is saying, if you have done a quality trial that provides important insight about relative efficacy of this specific agent with other antihypertensives, whether or not it provides a highly precise estimate, it is still going to be informative about the relative efficacy, and there is no non-inferiority assessment that is required to be able to interpret the data in terms of relative efficacy.

So, it should be presented at least in the labels for those specific products that were studies in that trial.

DR. TEMPLE: The trouble with all that is if you have a good analysis that shows non-inferiority, I would agree that it is informative. If the study is too small, and really fails to show a significant difference, it really isn't informative at all, but many people will

think it is, and that is really troublesome.

Most of the world thinks if you don't show a significant difference, you are equivalent. We know that is not true, and it is really quite misleading, so I am a little worried about putting in the results of studies that don't have the power to show anything.

DR. FLEMING: There is certainly a continuum here, Bob, and obviously, there could be studies that are relative small and quite unreliable, but where I have trouble is the argument that the only studies that are worth reporting are those that are so highly powered, that you are going to have a high level of ability to distinguish between appropriate activity and inadequate activity. That is why I took the numbers I did.

I would ideally like to see a trial with 20- to 25,000 people in the pairwise comparison as ALLHAT had, but if you had a 5,000-person trial, that would be still very informative. The confidence intervals would be twice as wide, but it

is still going to be very informative, and I think we have to move beyond the point that a study that doesn't achieve in some sense statistical significance is a negative trial or is uninformative.

DR. TEMPLE: No, but aren't you concerned that that 5,000-patient trial would give the appearance of show equivalence when, in fact, it had not been shown?

DR. FLEMING: Am I concerned about that? Yes, I am, but I wouldn't advocate ignorance in the interest of avoiding misinterpretation. Here, I think there is important insight that would come from having the knowledge about the results of that trial, and I think we have to continue to work on educating the way to properly interpret trials that I might call screening trials or Phase II-B trials that can provide important insights even though they are not fully powered.

DR. TEMPLE: So, you would say no difference was seen, but, of course, this means nothing at all.

DR. FLEMING: No, I would say here is the point estimate and the confidence interval.

DR. NISSEN: I am going to talk about this in a minute.

DR. PROSCHAN: This seems like a very broad question, I am not sure you can say here is how you should do it, if the primary outcome doesn't come out significant, you know, here is how you should handle it, I mean because it depends on a lot of things.

In this particular case, primary didn't come out significant, secondary comes out extremely significant at least with one of the drugs. So, I don't think you can say here is what your policy should be. If the primary doesn't come out significant, forget it. You can't really have a blanket policy of how to handle that kind of situation.

DR. NISSEN: You know, I almost never disagree with Tom on statistical matters, but I am going to disagree with you here, Tom, and say that you get into this creeping problem of A is similar

to B, but you don't really have quite the power you need to say that, and then you do C, and it looks about like B, but it is a little bit worse, and then D is a little bit worse than C, and things can get very, very dicey here.

So, I actually liked the first statement that you made where you said, you know, we listened to the presentation on the imputing against placebo, and you say, well, you either decide that that is adequate from a regulatory point of view to say we are willing to give that claim, or it's not.

The problem with saying it when it is not really statistically adequate is that those labels are used in marketing and they are used for lots of purposes, and if you set that bar too low, but I will tell you, you are not going to have any better data than you are going to get from ALLHAT. I mean you have got a lot of patients, and if that isn't good enough, I don't know what is good enough.

I mean I think that it is there, and I think you can make that statement. Now, my guess is that if you did the same analysis for lisinopril

in ALLHAT, it might not make it. It would be close, but I think it might not quite make it, but I think you ought to do the formal exercise, and if they meet your standard of evidence that would ordinarily be used for a non-inferiority trial, then, I think you give that claim.

DR. STOCKBRIDGE: Don't your priors count for anything here? I think that was sort of what Tom was saying is that you are partway home before you even did ALLHAT.

DR. NISSEN: It is actually not only priors, but it is futures. In fact, we also have things like VALUE and we have other studies, so if you want to give a claim to an agent, you really want to look at the totality of data that is available for that agent, and if you see things going in different directions, that tends to weaken the argument.

You know, you don't like to do non-inferiority arguments under any circumstance, and so if that non-inferiority is weakened by some other modest-sized trials where point estimates

look not so good, that will be used as evidence that maybe you are not where you need to be.

If you have consistency, then, I think you are going to be much more comfortable that you can say that agent is really better than placebo.

DR. FLEMING: Absolutely, I don't want to overstate the evidence. I certainly don't want to weaken the standards that we have for what you should expect to have to show to establish a claim.

The context in which I am interpreting this is in the future, as we continue on, we will continue to get additional data from control trials. In all likelihood, there won't be a lot of additional ALLHAT studies, so the kinds of evidence that we are going to get will be less than what some of us would ideally like to have, which is a fully persuasive large-scale trial that is going to allow you to establish directly what the actual level of effect is on clinically relevant endpoints.

In fact, what we have said is we are willing to extrapolate at some level the totality

of the evidence to new agents, and yet I would argue that the formal claims that we would make should be based on what we are formally able to establish with the data, and I am guessing that in many instances, with products, that is going to mean we are going to formally establish what their effects are on surrogates like blood pressure lowering, and the studies will be fully powered to be able to address that measure.

Then, we are going to make these general statements about what we believe the implications of that would be, and I am accepting of all that, but by the way, if we have a 5,000-person trial that is actually providing what I am calling a screening or Phase IIB direct assessment of what this intervention is doing relative to other known antihypertensives on these clinical measures, do I want people to know about that? You bet I do.

I don't want them to be misled that this study is providing direct clinical proof that this agent affects those endpoints, but it is contributing some insight in addition to the

insight that you have from the other data from other agents that we are using in our extrapolation.

DR. NISSEN: You have heard both sides to the issue. We can argue this until we are blue in the face. I understand where you are coming from. You are saying that it is useful information to have if not over-interpreted in the label.

DR. FLEMING: Yes, and if you have already decided that you are going to, based on the data that exists, approve this agent for marketing, then, I am arguing I want truth in advertising. I want the caregivers and patients who are going to use this product to be aware of the substantive information that is available to provide the best insight possible about what this intervention is going to do.

DR. NISSEN: The three of us are not actually disagreeing because what you are saying, Bob, is but don't take that bar down so low that a clearly, horribly underpowered study would take it as evidence of non-inferiority, and, Tom, I know

you wouldn't want to do that either. Tom was saying that a study that is well sized and that the information belongs in the label even when you can't get a claim based upon that information.

DR. FLEMING: And, in fact, just to contrast this with what we heard this morning on the analysis done with ALLHAT, one would be limited in this setting with being able to say this is the point estimate and the confidence interval for what the relative efficacy is on these various outcome measures relative to the other interventions studied in this trial.

It is undoubtedly not going to provide you, unless your point estimates are in the positive direction, sufficient evidence to be able to do the kind of analysis we heard this morning to say in addition, we actually can do a formal non-inferiority analysis projecting we are preserving 60 percent of the efficacy on cardiovascular death MI.

DR. TEMPLE: I am still worried about putting in things that would look like equivalence

that aren't. We also are intending to look at whether the general approach to these are more conservative than they need to be in light of an awful lot of information about what lowering blood pressure does. I think there are a lot more priors here that could make the tests we apply to these somewhat less stringent and still be credible.

DR. FLEMING: Bob, just to pursue this, because I respect your concerns here greatly, I do not want people to over-interpret the data either. You are saying there isn't a way to enlighten people to what actually are the most substantive data here and do it in a way that minimizes the risk that they are going to over-interpret?

DR. TEMPLE: Well, comprehension about non-inferiority studies, despite very substantial efforts by a number of us, is really difficult. It is the hardest thing I have ever had to try to transmit. So, yes, I believe in labeling your chance of making it clear and understandable close to zero.

DR. FLEMING: I am very torn because

whereas as I feel strongly about what I have been saying, I am also very, very dismayed in what I have seen in the way non-inferiority trials have frequently been interpreted, where if the point estimate is the same, people are all too readily willing to conclude that this means it's the same.

But the point is do we address this by keeping people ignorant to the data or do we show them the data and work on enhancing their understanding about the limitations of the conclusions.

DR. TEMPLE: Right, you can say these are the data, but really, even though they look exactly the same, it doesn't mean a thing. I don't know, it's a hard problem, but I do think that maybe we are over conservative in that way, we do these in situations where we have a lot of prior information, and we are working on that sort of slowly.

DR. NISSEN: I don't think we are all that very far apart on all this. Let's move on because the hour is late.

DR. STOCKBRIDGE: Skip No. 7, we have already dealt with it.

DR. NISSEN: Consider the ramifications of revised labeling on pediatric studies. The agency can require studies of antihypertension drug in children prior to approval for use in adults. The agency can also promote studies in children by granting additional exclusivity for assessing the effects of antihypertensive drugs in children.

Should it do either of these?

DR. PORTMAN: I think I already addressed that.

DR. TEMPLE: You said no to the first, yes to the second.

DR. NISSEN: I feel strongly that additional exclusivity is the right--and it is working, the evidence is that it is working.

Anything else on 8.1 you want to hear?

DR. TEMPLE: No.

DR. NISSEN: 8.2. A drug for another indication also happens to reduce or increase blood pressure.

DR. TEMPLE: I am sorry, 8.1.2., this was discussed a little bit before, and the answer you gave was that you need more than just the blood pressure, but it remains somewhat unclear to me what, in a reasonable sized, reasonable length study, you can hope to get in the way of outcome. That seems like a major challenge, and we have not really mostly been asking for that, Norm, right?

DR. STOCKBRIDGE: Well, we have only asked one time for something more in a setting where we already had information for another drug in the class, and another drug came along and said what can we do, and I said not the same thing.

DR. TEMPLE: What did we ask for?

DR. FLEMING: Specifically, I asked you that question and you said, in my words, you could look at other biomarkers, as well, LVH, and microalbuminuria, and other measures, such as that.

DR. TEMPLE: And in a reasonable amount of time, expect to see an effect on those things, yes?

DR. PORTMAN: I believe so. I mean the one we chose was microalbuminuria in diabetics.

DR. NISSEN: I think we want to encourage these studies in children, so obviously, we don't want to make the bar so high that it's impossible.

DR. STOCKBRIDGE: The only thing I was concerned about is if you are not sure the outcome benefits apply to kids at all, then, do I have any business ever even if it's the first drug in a class, just asking for blood pressure data. That is what we do now when it's the first drug, you know, they pick the easiest age group, they pick blood pressure, and that's what we get.

The question is whether we had any business doing that at all if you don't know anything about outcomes.

DR. NISSEN: It is also going to be very, very hard in children to get that information.

DR. STOCKBRIDGE: Getting the blood pressure was impossible before we starting giving exclusivity away, so I don't know what is possible.

DR. KASKEL: Could I add something? There is this whole concept now called "transition," and what it is, is a term that applies to the children

that now have become teenagers, now become young adults, across the board in pediatrics, with chronic conditions that before they never made it to adulthood, and this opens up an area of study.

There are a lot of people looking at how to use transition both for studies and for preparation of internists who will be taking care of these patients, so here is an area of an age group, and you can define it with limits, that possibly should be targeted to be studies in this transition zone, so you would get outcome in five years.

You start studying someone at 16 or 14, by the time they are transitioned at 18 or 21, it depends on the center, we take care of patients until they are 21, and other places stop at 18, and then you have a population that is transitioned to adulthood and can be studied.

DR. TEMPLE: I guess what I don't quite follow is what the control group for all these things is. Pediatric studies are a big problem, and in hypertension, no one will let you do a

conventional randomized, placebo-controlled trial for more than a week, and what we get instead is everybody gets treated, and then you do a randomized withdrawal study, and as soon as the pressure goes up, they are out of the study. Everybody is reasonably comfortable with that.

That is not going to be terribly helpful for getting effects on renal function or even proteinuria, and certainly not cardiac outcomes. So, we probably need some work in thinking more about just what we can actually ask for.

DR. PORTMAN: Well, we do, and I agree with you, and I think the whole program has been in transition getting stronger and better as time goes on, and I think we need to continue doing that, and that is why I made the suggestion that we need to, in future studies, begin to look beyond blood pressure.

I disagree with you about the issue of placebo. I think that as we have learned more about hypertension in kids, that were I to design a study today, you know, a Model A is what I would

choose.

I think the randomized withdrawal hasn't been all that terribly successful, and I think that i feel comfortable with a month or two, or even three, of treating kids with a placebo who have essential hypertension, not, of course, who have chronic kidney disease or diabetes or something like that. But I really do, and I think most of us. So, I think we are ready to move on to some other types of studies.

DR. SACKNER-BERNSTEIN: Are you looking at all towards gathering data about physical growth, development, those kinds of issues, as well, in these kids, because there seems to be rather a paucity of information about a lot of these medicines in kids with respect to those factors?

DR. STOCKBRIDGE: Yes, recent written requests for pediatric studies have included--it's not real long term, it's a year or something, and sponsors fight us all the way, because they don't want to collect that data at all.

DR. SACKNER-BERNSTEIN: Is there a control

group?

DR. STOCKBRIDGE: No.

DR. TEMPLE: So, this is measured against various norms. The norm is pretty well established in pediatrics, but it is something of a limitation.

DR. NISSEN: Let's see if we can wind up here in the next few minutes. It is actually is an important issue, and we can't shortchange it.

8.2. A drug for another indication also happens to reduce or to increase blood pressure. Should class labeling extend to it? Does it matter?

Does anybody want to weigh in? I have some thoughts here.

DR. SACKNER-BERNSTEIN: Well, we have seen non-cardiovascular drugs that certainly affect blood pressure. There has been some attention to that. Some of the central nervous system active drugs do that, and I think there has been some disagreement as to how important those changes in blood pressure are.

If you have someone who is taking a

medicine in a trial for 4 or 8 weeks, and you see a 2- or 3-mm mercury change, is that the kind of thing that really should lead to another long-term study, because in a lot of those situations, people may take the drug in real life for a period of years.

So, I think this is a very, very important question even just looking at that subset of what is being asked here. Is that what you are looking for, to discuss?

DR. NISSEN: There is a lot of subtlety to this. First of all, I think it is different whether the drug increases or decreases. Why don't you go ahead and answer it, Norman, but I want to hear a separate discussion about the two directions.

DR. STOCKBRIDGE: Well, yes, I think actually it would be helpful if you addressed why you think there is a difference about which direction is which. It seems to me this whole discussion has to do with whether you buy into the blood pressure hypothesis. It is all predicted by what you are doing to the blood pressure.

The sign of that can't possibly be important except in determining what direction the effects are.

DR. NISSEN: How can you be so sure?

DR. HIATT: I think there is an example, maybe phenylpropanolamine, would that be an example of this, because that had an absolute increased risk of hemorrhagic stroke in women. It was extremely small. When that safety signal was called out, it was pulled from the market. So, I do think that those things might matter, and those are short-term uses for drugs for symptomatic indications that cause bad things.

DR. TEMPLE: That was a weird result, however. The effect of that drug lasted for about a day, and most of the events occurred in association with starting the drug.

It did something, I don't disbelieve it particularly, but it ain't what we usually would expect.

Just so you know, our attempt to remove ephedra products from the market was based on the

view that they caused a prolonged--well, a persistent 4-mm mercury increase in blood pressure. We said in the absence of any benefit, we didn't see any reason for a dietary supplement to have that liability.

That didn't rule out having drugs with benefit that might have the same--my reservation about this is that at least as a potential benefit is that we are thinking about use of antihypertensive agents as part of regimen observed continuous that is going to take the blood pressure from somewhere to somewhere else. I am not sure what that has to do with whether the drug you are on for a brief period of time has a small effect on your blood pressure.

So, giving a claim on that basis seems not quite in line with the way you are using the drug. We would always, I should say, warn about a drug that increases the blood pressure. When there are drugs that do that, there is language in there that says you have to watch.

Now, i have to say that mostly warns you

that the blood pressure may go up a lot, and the consequences of 2 or 3 mm of mercury, a subject that has come up in the context of the Cox-2s, I don't know how we deal with that, or whether we deal with that consistently.

DR. NISSEN: That is the problem I have, and let me be sure we don't go--we have got to be very careful here.

We have incredible amounts of data on what happens when you give a drug to lower blood pressure, and we have about 1/10,000ths as much data about what happens when you raise blood pressure.

Now, is it likely, could it be the same? Could the point estimates for what 2 mm-plus does versus 2 mm-minus, could they be exactly the same? Well, maybe not, and let me tell you why not.

If you give somebody with a blood pressure of 118, a drug that raises blood pressure to 120, it also counts, not just what the mean change is, but what the standard deviation is, because it is very unlikely, you know, how many people are there

that get extreme elevations?

Are the people that got the problem with phenylpropanolamine, it is because there were a few people that had extreme responses and bled into their heads, we just don't know. We have so little information about this. We know a lot about what happens when you lower blood pressure, not much when you raise it.

Now, what about birth control pills, how much do they increase blood pressure? Can anybody tell me? They do increase blood pressure, right? It's 2 or 3 mm of mercury, but it's in a low-risk population that has mean blood pressures that are pretty low most of the time.

I just think it's treacherous to try to extrapolate from what we know about antihypertensive agents to drugs that might have some effect in a positive direction about blood pressure, which is not to say that there may not be an issue here, but I just think it's very, very risky in doing that.

DR. PORTMAN: There are a slew of them, I

mean corticosteroids, cyclosporin, all the drugs we use for ADD in kids, Ritalin, you know, adderall, they all raise blood pressure, but we are aware of it, and we basically deal with it. It is a known phenomenon.

I think it is incumbent upon the agency to let people know that this is an issue, but I am not sure you need to do much more than that.

DR. TEMPLE: The part of it that makes me a little nervous, I am not sure what we should do with it either, is everybody knows that for the fraction of people whose blood pressure goes up a lot, you are supposed to do something about it, stop the drug, or treat it, or do something.

But if sort of everybody goes up 3 or 4 mm or mercury on average, and stays there for 3 years, that seems like it could be a problem, but I don't really know, because who would know.

Maybe there should be a recommendation to start a diuretic in those people, I don't know. It is very difficult.

DR. FLEMING: I thought I heard through a

lot of discussion today, a position being put forward that it is blood pressure, stupid, or something to that effect, it's not even so critical to know how we did it, it's what you do in terms of blood pressure.

So, what is the logic of saying if you drop 4, that is good, but if you raise 4, it is not, just as likely, bad, if it truly is? Now, I am not the person who is in the best position, and I am not the one who is most strongly advocating it's as simple as blood pressure, and yet I have heard a lot of support for something that is, in essence, consistent with that.

So, if that is the case, how can we argue that a 2 mm or 4 mm increase isn't of the same clinical relevance as a 2 mm or a 4 mm decrease?

DR. NISSEN: Because we don't know, Tom. I mean we have 137 trials that show what happens when you give drugs that lower blood pressure. Now, Jay Cohn took the position that they do so, not because they lower blood pressure. I mean I don't necessarily agree with that, but so you have

that.

How many randomized trials do we have where we compared a drug that doesn't lower blood pressure or raises it by less than one that raises by more, and that there is a difference in outcome?

I completely agree with you that it is absolutely biologically plausible, and it may well be true, but we don't have any evidence, there is no trial evidence. No one has ever done, say, a trial where half the people get ephedra and half the people don't, and you find out what happens when you give half the people ephedra.

It all depends on the population you do it with, what their mean blood pressure is, how big is the variance. I mean I think there is a lot we don't know here.

DR. FLEMING: When you take this position, logically, what you are acknowledging is it isn't just the blood pressure change. You can't logically argue it is just the blood pressure change and then argue that when you are increasing it, it is probably or potentially or likely not as

problematic.

DR. NISSEN: Again, I am not saying you are wrong, I am just saying we don't have any direct evidence of that.

DR. PROSCHAN: But in the absence of direct evidence, wouldn't a default position be that it is probably bad? You are right that there are no clinical trials that dealt with that, but the question then is what is the default position, is it that you can't make any conclusion or is it that logically, it should be bad.

DR. NISSEN: I am not saying you shouldn't describe it, I am not sure you shouldn't warn about it, but I am unwilling to say that a 3 mm increase in a particular population means X, Y, or Z. All I am saying is we just know a lot less about what happens when you go in the positive direction than when you go in the negative direction, and we have to be careful when we don't have direct evidence.

I am not saying it is not relevant, it is relevant, for sure, and I think you have to also look at the context. I mean it's to me a

nutraceutical that people can buy and self-medicate with. I think we made the right call on ephedra, as a matter of fact, for probably the right reasons, but I think we have got to be a little more careful when we don't have more direct evidence.

What do other people think? John.

DR. TEERLINK: I think part of the issue here is many of these drugs that increase blood pressure were being used in less at-risk patients, so your baseline risk is lower, so you may have the same relative risk increase, but a very small absolute increase in risk.

So, that is hard to tease out unless you do these multiple--in this case, probably hundreds of thousands of patient studies.

The other thing is I think there is some point here where we have to say, gee, maybe a blood pressure of 110, you know, the difference from 110 to 113, or 110 to 107, may not be as important. I think there is someplace where that levels off and this J-curve, even though we haven't found it down

to 115, may come into play.

I think the way I would kind of add the labeling or add wording is to say in the presence, you know, this is an additional increase in blood pressure that can add to the risk in the presence of other risk factors related to hypertension.

So, certainly, in the presence of hypertension, I think that is part of the labeling for birth control pills, as well, right, that there is an increased risk in the presence of--

DR. NISSEN: What have you done with these other agents like, let's say, birth control pills or estrogen or whatever that raise blood pressure, what do you usually say?

DR. TEMPLE: The ones I know about, it is pointed out, and some of them may even say the blood pressure should be monitored, but they don't say this can be expected to increase your risk of a heart attack, stroke, et cetera, over a long period of time. They don't do what we are talking about doing now.

DR. FLEMING: What was said for Vioxx when

it was on the market?

DR. TEMPLE: I think it said you are supposed to watch--Vioxx does two things. One, it raises the blood pressure, and it also can apparently interfere with the antihypertensive that you are on, and there was--I don't remember exactly--but there was language pointing that out.

DR. NISSEN: I think that is a good thing. I think absolutely, that that belongs--when you find a blood pressure raising effect of a drug, it belongs in the label. I don't have any argument about that one way or the other, but translating that into some estimation of calculation of risk is asking a lot more from the available data that we really have.

DR. FLEMING: I hear you and it is consistent with my own beliefs that surrogates, it is treacherous to extrapolate with surrogates, and yet it seems logically inconsistent, at least in part, even though I realize what you are saying is our data are on what you have when you have reductions, and yet the principle that I am hearing

is there is just a whole lot of evidence to indicate that it's intrinsically the blood pressure that is really representing the essence, 80, 90 percent, or whatever, of the change in these risks, and to argue that the increases are not symmetric in what that impact would be.

I certainly agree that it's a low-risk population probably, so the relative increase might be, in an absolute sense, relatively small, and yet if this is an agent that is being used for pain relief as opposed to something that is more significantly an irreversible morbidity or mortality outcome, the benefit-to-risk here is such that you wouldn't tolerate a very high increased risk at all.

So, I am very sympathetic to what you are saying, Steve, about this being a very uncertain circumstance, but I agree with Michael here, and that is, the default in the absence of any evidence here is that if we are going to take an increasingly strong position that the blood pressure change itself is intrinsically telling us

something really significant about these cardiovascular and supervascular risks, it seems illogical to not take a similar position when you have increases.

DR. NISSEN: Let me give you some evidence to suggest that we could be wrong about this. Let's taken naproxen. Naproxen raises blood pressure, but the totality of the evidence suggests that it is, at worse, neutral on the cardiovascular events.

I know, Bob, but I am trying to point out here that, you know, it is not as clear for me here given--

DR. FLEMING: The totality of the evidence says it's the best or among the best in the class of NSAIDs. Now, that just may mean that it has a trivial adverse effect, but that is a lot better than the competitors.

DR. NISSEN: This is maybe not the best example, but let me put it to you this way. There were some differences in the blood pressure effects in the NSAIDs, and you were there, as well as I

was, that didn't necessarily translate into predictable differences in morbidity and mortality.

So, I mean we just don't have the same kind of robust evidence that we have for blood pressure lowering drugs.

DR. FLEMING: But that is because there could be multiple mechanisms.

DR. NISSEN: Of courser.

DR. FLEMING: And blood pressure just be one.

DR. NISSEN: I hear you, I understand. I am saying it is just the clarity isn't there that we have when we have 30 years of clinical trials involving 100-plus studies that tell us what happens, and I am not saying you are wrong, but I am saying I would like to have at least one study that shows that if you randomize people to a strategy that raises blood pressure 3 mm versus not, that that has an adverse consequence that falls in line with what one might expect from a blood pressure lowering drug.

I would just like at least one pretty

solid piece of evidence before I would want to say we ought to say that about a drug in its label.

DR. PROSCHAN: It seems like there should be some animal studies like that. I don't know if there are any, but it seems logical to do, that show that increasing it--

DR. NISSEN: Can you shed any light on this? Do you guys have any data available here?

DR. TEMPLE: I will bet there are animal studies, and I bet they show that if you raise it enough, animals get into the same trouble spontaneously hypertensive that other animals get.

DR. KASKEL: I know in animal studies looking at the kidney where they impair renal autoregulation, so that the blood pressure effect is transmitted directly to the glomerulus, 3 mm of mercury is significant to cause damage and changes within the glomerulus acutely.

DR. NISSEN: I guess what I am trying to say is I don't think we know enough to be able to set a regulatory standard, so I would urge that in each drug that comes up--and you listed the issues

here--it is whether it is sustained, whether the drug is used for long-term purposes or not, I mean all those are relevant.

What I am trying to say here is that we don't have enough to be able to sit here and say this is what the standard ought to be if you have a blood pressure change of more than X, Y, or Z, that it means A, B, or C, but we think it is relevant.

DR. TEMPLE: It sounds like people think that that should be noted as part of the labeling, but that what you should not do is put in the Clinical Trials or Indication Section a big thing saying we know from a long history of treatment of hypertension blah-blah-blah, that is the obverse of what we are doing here.

DR. NISSEN: That is what I am saying.

DR. TEMPLE: But that it is relevant and that for a drug intended for long-term use, we probably need to figure out what to say and try to get people to pay attention to it.

DR. NISSEN: I am just trying to get us not to leap to conclusions that are not necessarily

yet warranted without saying by any means that it is irrelevant, it is relevant, and it belongs in the label, but I don't think you can translate that into hard numbers.

As uncomfortable as we are about surrogacy, at least in the case blood pressure lowering drugs, we have got the benefit of huge, you know, a million patients in trials and databases, and so on, and we just don't have that for going in the other direction.

DR. STOCKBRIDGE: So, we are we talking it goes somewhere in the Clinical Pharmacology Section, it just mentions, you know, if your blood pressure goes up 4 mm, are we talking it goes in Precautions? Are we talking about it goes in a boxed warning? Where in the spectrum of presence in the label are we talking?

DR. NISSEN: I think the magnitude of the problem and the type of use is very relevant here, so that the bigger the magnitude and the longer term the use is contemplated for the drug, the more likely it is to want it to appear in warning.

Let's say you had a drug that you had very good data that it increased blood pressure by 1 mm, and it was a drug you were going to use for two weeks, an antibiotic, let's say you were going to use for an infection, I mean I think you have to apply some reasonable logic here to the thinking process around this, and not have a cookie cutter approach.

DR. TEMPLE: I think that is what the plan has been. One of the--I can't remember the name--but one of the weight loss drugs raises blood pressure a little bit, and there is a lot of noise about it in the label.

DR. NISSEN: Don't most of the weight loss drugs, they are sympathomimetic drugs, don't they all raise blood pressure?

DR. TEMPLE: Yes, some of them work different ways.

DR. NISSEN: And some people are on weight loss drugs for a long time, too.

DR. TEMPLE: That is contemplated, if you succeed in losing weight, your blood pressure goes

down. It's a little tricky.

DR. NISSEN: Is that enough discussion for you on that topic? Okay.

Question 9. Are we done yet? I think the answer is that we are.

Everybody, thank you so much. This has been a long day, but I hope that, Bob and Norm, you got some help here in your thinking process. I certainly learned a lot.

DR. STOCKBRIDGE: That was very helpful. I appreciate everybody's work on this. Tomorrow will be just really easy.

[Whereupon, at 6:30 p.m., the proceedings were recessed, to reconvene on Thursday, June 16, 2005.]

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