DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

Draft Recommendations for relabeling of antihypertensive drugs for outcome claims as a follow up to the committee's meeting on June 15, 2005 where the committee discussed class labeling of antihypertensive drugs based on the proximity of their data to outcome trials

Wednesday, April 26, 2006

8 o'clock a.m.

The Ballrooms
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

Acting Chair: Thomas G. Pickering, M.D., D.Phil.
Executive Secretary: LCDR Cathy Groupe, B.S.N.

Voting Committee Members
David L. DeMets
Steven D. Findlay, MPH
Frederick J. Kaskel, M.D., Ph.D.
Ronald J. Portman, M.D.
John R. Teerlink, M.D.
Lynn Warner-Stevenson, M.D.

Non-Voting Guest Speaker:
Stephen W. MacMahon, B.Sc., Ph.D., MPH, F.A.C.C.

Non-Voting FDA Participants
Robert J. Temple, M.D.
Norman L. Stockbridge, M.D., Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. PICKERING: Good morning, ladies and gentlemen. I would like to call the meeting to order. My name is Dr. Tom Pickering. I am from Columbia Medical Center. My specialty is in hypertension.

The agenda for this morning is a second discussion of possible revisions to the labeling of antihypertensive drugs. The first meeting, which I think you will hear about in a few minutes, was held last June which was also a public meeting.

Maybe we could begin by just having the committee members go round and introduce briefly who they are starting with Dr. DeMets.

DR. DeMETS: Dave DeMets, a biostatistician, University of Wisconsin, Madison.

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

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

DR. FINDLAY: Steve Findlay, the consumer

representative on this panel from Consumers Union, Washington, D.C.

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

LCDR GROUPE: Cathy Groupe, Executive Secretary for the Committee.

DR. TEERLINK: John Teerlink, cardiologist, University of California, San Francisco and San Francisco V.A. Medical Center.

DR. STOCKBRIDGE: I am Norman Stockbridge, the Director of the Division of Cardiovascular and Renal Products at FDA.

DR. TEMPLE: Bob Temple, Director of Office of Drug Evaluation I in which cardiorenal lives.

DR. PICKERING: Thank you. Cathy Groupe will read a conflict-of-interest statement next.

Conflict of Interest Statement

LCDR GROUPE: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting. Based on the

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

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to the following participants.

Dr. Thomas Pickering has been granted a waiver for his unrelated Speaker's Bureau activity for an affected firm. He receives less than $10,001 per year.

Dr. Frederick Kaskel has been granted a waiver for his employer's participation in a related study funded by an affected firm. His employer receives less than $100,000 per year.

Dr. Ronald Portman has been granted a waiver for his employer's participation in four related studies. His employer receives less than $100,000 per year from each firm. Dr. Portman has also been granted a waiver for his consulting for

four affected firms. Dr. Portman receives fees of less than $10,001 per year from two of the firms and between $10,001 to $50,000 from the other two firms. Finally, Dr. Portman has been granted a waiver for his role on an advisory board for an affected firm. He receives fees less than $10,001 per year.

Dr. John Teerlink has been granted a waiver for his unrelated consulting for two affected firms. He receives between $10,001 to $50,000 per year for each firm.

Dr. David DeMets has been granted a waiver for his unrelated consulting for two affected firms. He receives less than $10,001 per year from each firm. Dr. DeMets has also been granted a waiver for his role as a member of four Data Safety Monitoring Boards. He receives less than $10,001 per year for each firm.

Waiver documents are available at FDA's dockets web site. Specific instructions as to how the access the web page are available outside today's meeting room at the FDA information table.

In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, Drs. John Flack, William Hiatt, Robert Harrington and Michael Lincoff have been recused from participating in today's discussion and vote concerning relabeling of antihypertensive drugs for outcomes claims.

With respect to FDA's invited guest speaker, Dr. Stephen MacMahon reports that he has received research grants from Pfizer and Merck. He also receives occasional honoraria from Pfizer, Novartis, Boehringer Ingelheim and Merck.

In the event that discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address

any current or previous financial involvement with any firm whose product they wish to comment upon.

Also, I would like to add that Dr. John Neylan, the committee industry representative, was unable to attend at the last minute. Therefore, there will be no industry representative for the meeting today.

DR. PICKERING: Thank you very much. Now, I think Dr. Stockbridge is going to give us an introduction and background.

Introduction and Background

DR. STOCKBRIDGE: I have a few introductory comments. First, I want to thank you, Tom, for chairing today's session. I would also like to acknowledge that this is your last meeting before your term expires from the Cardiovascular Advisory Committee. I hope everybody here will join me in thanking you for your years of service on the committee.

(Applause.)

The Advisors and Consultants Staff will be forwarding to you some token of our appreciation

that is not here with us today. I don't remember whether it is a gold watch or a Porsche. (Laughter.) I can't remember exactly what it was.

I would also like to thank Dr. Stephen MacMahon for coming again to participate in this. Dr. MacMahon is here. There is no formal presentation from him but he is here to help remind us of some of the data behind what we are doing so he is available to answer questions through the session this morning.

I also wanted to sort of sketch for you what the process generally is with respect to the document we are discussing. This flows out of the meeting we held last June to discuss relabeling antihypertensive drugs for outcome claims. In the months since then, Dr. Temple and I have been passing this draft back and forth between us and it got to a place where we weren't making any further progress and it seemed like it was time to get you folks back involved and see whether or not it pretty well captures what the outcome of the previous meeting was.

Following this meeting, we will make adjustments as seem necessary. At some point, the next step in the process will be publishing this in draft form in the Federal Register. That will set off some public comment period where people who want to can contribute their thoughts to this.

Then, after that period closes, we will revise the document as seems appropriate again and publish a final version in the Federal Register with some discussion of the comments that we got. So that is sort of the introduction to this. The basic flow of the morning really is sort of going through this document, a section at a time, and getting comments from people around the table about whether or not they think it captures the spirit of what came out of the earlier meeting.

Thank you.

DR. PICKERING: Thank you very much. We now move on to the Open Public Hearing. Let me say, just before that, that the plan is, actually, to have this divided into two sections because some of the current committee members who are recused

from the formal procedure I think would like to make statements as members of the public later on.

Open Public Hearing

DR. PICKERING: So, before we move on to the first public hearing, I would like just to read this guidance document. "Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

"For this reason, FDA encourages you, the Open Pubic 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, 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."

I believe Mr. Goozner wishes to address the committee. Thank you.

MR. GOOZNER: Thank you for the opportunity to speak here this morning. Good morning. My name is Merrill Goozner and I am the Director of the Integrity in Science Project for the Center for Science in the Public Interest. That is my only conflict of interest. I guess you could say it is a structural conflict of interest because the Center for Science in the Public Interest has a long-standing interest in the issue of hypertension, although I must tell you that my own involvement in this particular issue was not driven by that but more about the concern of the structure of the committee. Then I got into some

of the issues which I have written about over the years.

But our concerns about the FDA's proposed guidance on labeling hypertension drugs are three-fold. First, the draft guidance ignores the National Institute of Health Seventh Report on the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure usually referred to as JNC7, especially the primary roll its recommendations give to lifestyle modifications.

Second, the draft guidance misrepresents the findings of JNC7 and the government-funded Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, commonly known as ALLHAT, both of which were conducted at great taxpayer expense and, if followed, could save taxpayers billions of dollars to the recently enacted Part D of Medicare, the senior citizen prescription-drug benefit, as well as Medicaid and other government programs.

Third, the labeling provision of the draft

guidance permits the use of claims that have not been submitted or reviewed by the FDA which, in combination with the previously mentioned flaws in the guidance, could result in less than optimal physician prescribing patterns and less efficacious healthcare outcomes.

The draft guidance points out that labels on the more than 60 drugs and seven or more classes that lower blood pressure are, "mute on the clinical benefits expected from blood-pressure reduction." The FDA is considering this guidance because it feels it would be in the best interest to physicians and patients to spell out those benefits, "to encourage appropriate use of these drugs."

But, as JNC7 points out, and, again, I am quoting here, "Adoption of healthy lifestyles by all persons is critical," and I underscore that, "for the prevention of high blood pressure and is," and I will underscore this, "an indispensable part of the management of those with hypertension."

Why doesn't the FDA put that on the label.

The draft guidance, the industry for labeling antihypertensive drugs represents a golden opportunity for the FDA to begin educating the public about the primary and cheapest way of treating this leading cause of heart disease.

The second issue involves the draft guidance's claim that "numerous single studies--e.g., ALLHAT--and pooled analyses have tested whether drugs given to achieve the same blood-pressure goals have the same clinical benefits. To date, such studies have not distinguished the effects of different treatments on the--and I emphasize that; that is not emphasized in the original--major hypertension-related outcomes, strokes, myocardial infarction and cardiovascular mortality.

By limiting the primary endpoints to strokes, myocardial infarction and cardiovascular mortality, this statement inaccurately represents the findings of ALLHAT and JNC7. There are several differences, but let me point out just one. It leaves out the higher rates of congestive heart

failure suffered by patients who take calcium channel blockers, one of the more popular and still expensive classes of antihypertensive drugs on the market.

The JNC7 specifically recommends against using calcium channel blockers as first-line therapy in patients with congestive heart failure. In the new guidance, heart failure should be considered a major cause of morbidity and mortality and the guidance should distinguish between drug classes and their effectiveness in treating this condition.

Finally, the draft guidance recommendations for labeling concludes, "Many antihypertensive agents have additional effects on angina, heart failure, diabetic kidney disease, for example, and these considerations may guide selection of therapy." The labeling guidance further allows companies to include, "a summary of placebo or active controlled trials showing the specific drug's outcome benefits in hypertension."

I look forward to your discussion on this

point because there is a possibility I misinterpreted here. But in case I have, I will stand corrected. But, in case I have understood it correctly, while this would be a positive thing if companies chose to apply it to drugs that are less effective in reducing heart failure or less effective when used in certain subgroups, like African Americans, it opens the door, in my view, to labeling abuse.

The medical literature is filled with studies that measure the antihypertensive effects of specific agents on patient subgroups with particular comorbidities. While those studies may show the drugs are effective in reducing the comorbidities as well as reducing high blood pressure, they are rarely tested against other agents to see if they are any more or less effective in reducing those comorbidities.

These trials, which are usually industry funded and sometimes referred to as seeding trials, are a way to broaden the use of a particular drug within a crowded field when there are other, often

cheaper, alternatives that may well be just as effective or more effective not just against high blood pressure and its primary effects but the comorbidity.

To allow these trials to be included on labels and, thus, fair game for mention to physicians by drug-industry marketing representatives would put the FDA stamp of approval on some of the most abusive sales tactics in today's pharmaceutical marketplace.

Combined with the earlier part of the guidance that did not distinguish between drugs on a primary outcome like congestive heart failure, the net effect of this guidance could be a huge setback for public health and, I might add, the public purse.

Finally, allow me to take a few moments to address the FDA staff about my concerns about this commission's balance. As you are well aware, the Federal Advisory Committee Act requires committees to be balanced. You have interpreted this to mean that the committee should have the specialties and

expertise needed to render a qualified judgment.

But, according to the Government Accountability Office, that provision also requires that committees be balanced regarding points of view especially when there is controversy in a field as there is in this case. This committee is singularly unbalanced in that regard. Specifically, it contains none of the eleven physicians associated with the National High Blood Pressure Education Program Coordination Committee that wrote JNC7 nor were any of the physicians who led the ALLHAT Trial asked to serve on this committee including the experts, non-conflicted, at the National Heart, Lung and Blood Institute.

This is an area where you could easily have found unconflicted, highly qualified, experts, yet you chose not to do so. In his testimony before the House Appropriates Subcommittee earlier this year, Acting Commissioner Andrew von Eschenbach said that the FDA should not be prohibited from including scientists with conflicts of interest from serving on FDA advisory panels

because they are frequently the best minds in a particular field.

But this appears to be a case where you excluded the best minds in the field whether they had conflicts or not.

Let me conclude by quoting from a study that appeared in this week's Journal of the American Medical Association which some are interpreting to suggest that conflicts of interest on FDA advisory committees do not matter. That study found a 10 percent greater likelihood that an advisory committee meeting would favor a drug if it contained a person with a conflict of interest.

Yet, the office concluded that such a level of bias would never be tolerated in a jury. Individual jurors are frequently dismissed simply for reading newspaper coverage of their trial. Decisions reached by advisory committees have a much greater social impact. I think it is time for the FDA to begin considering how it forms this advisory committee and ensuring that balance with regard to point of view be one of the

considerations you take into account.

Thank you very much.

DR. PICKERING: Thank you. Would you be willing to accept a question from Dr. Temple from the FDA?

MR. GOOZNER: Sure. Absolutely.

DR. TEMPLE: It is partly a comment and partly a question. The decision to write something like this was actually made at a previous meeting at which one of the members of JNC7 was present, Henry Black, and was enthusiastically in support of it as a general matter.

I guess the other thing is this is going to be put out for comment as a guidance so, if you don't think the statement in there that says, "Control of blood pressure should be part of a comprehensive cardiovascular risk-management including lipid control, diabetes, et cetera," is broad enough on the life-style changes that people ought to be encouraged to do, comments will be welcome. Maybe that should be expanded to include--

MR. GOOZNER: We actually provided some alternative labeling language. What the Executive Director of the Center for Science in the Public Interest, Dr. Michael Jacobson, calls a green-box as opposed to a black-box warning label that could be put on antihypertensive drugs.

So, yes, we would comment--I suppose we will comment at that time and we have already sent some information to the FDA in that regard.

DR. TEMPLE: But I am curious about a larger question. One of my questions always is how long do you try to get people to change their behavior because, as anybody who looks at the obesity epidemic can figure out, it is hard to get people to change their behavior.

How long should their blood pressure be allowed to stay high without medical treatment, do you think, while you encourage them to change their lifestyle?

MR. GOOZNER: That is obviously a choice between the physician and the patient and I wouldn't presume to--I am not a physician. I don't

presume to make recommendations in that regard. I think that we see labeling as an educational tool. I mean, that is what is at stake here. I can imagine, just speaking for myself, if somebody told me I had blood pressure and--I am fairly physically fit and I am kind of skinny and somebody told me, the best thing for you to do is to take a drug, I suppose I would take a drug.

DR. TEMPLE: Later in the day, there is going to be a discussion of how long it is safe to leave people hypertensive off therapy even for the purpose of studying them. While we conclude that short-term studies--well, some people conclude; we will see what everybody concludes--but maybe short-term studies don't pose a risk.

There certainly would be a view that you don't want to let people sit around very long with a markedly elevated blood pressure while you encourage them to lose weight, which is very difficult. The whole purpose of this, in the first place, the reason we thought about it, is that--and I attribute this to me, but I know the people from

JNC7 think so, too, that it is really terrible that the benefits of lowering blood pressure are not widely enough dispersed.

We have ways of doing it. We have lots of drugs. There are different views--the ALLHAT people all believe you should always start with a diuretic. That is perfectly reasonable to start with. Maybe this should say something about that. I don't know. That could be debated.

But everybody agrees that it really ought to be treated better than it is now, that people ought to be encouraged to stay on therapy and all that stuff. I just wondered, do you all have reservations about that or is this just a matter of how to do it best?

MR. GOOZNER: As I said, no; I don't. I don't have any particular reservation about that particular issue, but I think you open up another issue which is the fact is that these are labeling that are--this is a guidance about labels that are going on drugs. So people are receiving these drugs. So that portion of my comments is directed

to the fact that many people in this country don't get the message. I think that that is probably a fair statement, that the diet and exercise and reducing salt and all those other things that I am frankly not that expert in are primary ways, and some would argue, and, again, I don't say this from a scientific perspective--I am very cautious not to do that--but are better as a way of controlling blood pressure than medication.

But, beyond that, the important thing you addressed in your comments is that we have, perhaps, tens of millions of people in this country who are walking around with high blood pressure who are not addressing it through diet and life style and also are not addressing it through drug therapy.

One of the reasons why they are not addressing it through drug therapy gets to the economics of this whole situation. This was actually what drove my personal concern in noticing this issue and having written about it and thought about it for a number of years.

When you have to have insurance and your physician is primarily interested, for whatever reason, in saying, take this particular, say, calcium channel blocker which is a patented medicine that might cost $75 a month whereas, if somebody were to get the prescription for that diabetic where, even if there is no copay, would be very--because they don't have insurance, say.

If we understand the epidemiology of the hypertension epidemic in this country, then you understand that payment is an issue for many, many of those people. Then you get to what is in this guidance in order to maximize the number of people who, whether it is through diet and lifestyle, or, through drug therapy, are managing their hypertension and reducing all the negative effects that we know are associated with that.

So I would emphasize that it is not just--I asked someone from CSPI--CSPI has made many comments over the years and continues to and, frankly, the food side of the house is over there. I am the Integrity in Science Project and have

written and thought a lot about drugs over the years.

That is an issue in which science and medical economics are intimately intertwined. It seems to be that your labeling guidance--you should take into account some of those issues especially when the science supports it, which I think it does it this case.

DR. TEMPLE: Last question. You expressed some reservation about companies getting particular claims when they haven't shown that other members of the class, say, when it is generic already, doesn't do it. A good example is the result of the HOPE study, a study of rimipril, just as far as we know--we don't know whether it is different from other ACE inhibitors or not, that shows improved outcomes in high-risk patients.

I must say, I have always thought that desire for companies to have their place in the sun by doing really superb outcome studies--they are not seeding studies--that would be a misdesignation of these kinds of studies--is one of the benefits

of competition. They do that because they can claim it.

I don't know, and nobody knows, whether a cheaper generic ACE inhibitor would do the same thing but they went to the cost and expense of showing something important and they got it in the label. Are you saying you think that is an unfortunate practice? I have always thought of it as sort of a capitalistic benefit, if you like.

MR. GOOZNER: I am not familiar with the details of that trial. I mean, I have gone over it but I can't speak exactly to it. But I think you raise the important issue. If you got the same benefit a lot cheaper, yes, it is a fact that that company had an incentive because that particular medicine was still on patent to go out and conduct that trial.

So I think what you are raising is the larger issue of how do we really scientifically test whether or not this is different from other agents within that particular class not to mention difference between classes when you have a--like

this, which has so many classes.

DR. TEMPLE: Well, we don't. If somebody does a lipid-lowering trial in a particular population, they get that claim, if it is valid. That is sort of the way things have been going. This is probably a larger discussion, but if you discover something completely new, the first people who discovered that ACE inhibitors were good for heart failure, for example, they got claims for that.

We didn't give it to every other ACE inhibitor. We don't usually do class labeling. This is sort of an exception where we are thinking about--because you don't really know that something hasn't been studied as going to be the same.

But you seem to think that is sort of a bad thing. I just wondered if you would elaborate a little more on it.

MR. GOOZNER: I am not a moralist. I don't know about good and bad. I happen to know that it is an information flaw in the marketplace. People can take advantage of information flaws that

can work to the detriment of public health. I think that is a possible negative outcome in this case when people, for financial reasons, end up not taking drugs that they could be getting the same benefit from that are a lot cheaper than some of the other drugs. That is just also a fact.

I would turn the question around and say, what do you do about that?

DR. TEMPLE: You are at the podium. I only ask. Thanks.

MR. GOOZNER: Okay.

DR. PICKERING: Thank you. Maybe I could also comment about some of your major points. You said we should not ignore the JNC7 recommendations and this was discussed extensively at the last meeting and will come up at today's meeting. I think the consensus was that any recommendations that the FDA makes should, in general, be consonant with the JNC7 recommendations.

With regard to the lifestyle issues, the American Heart Association recently published dietary guidelines for the management of

hypertension in the journal Hypertension for which I wrote an editorial. My stance there was that we should certainly recommend lifestyle changes for everybody with hypertension but we shouldn't fool ourselves that people with significantly elevated blood pressures are going to have very much success in controlling blood pressure and its greatest use is probably in people with pre-hypertension who are not yet eligible for drugs.

I guess today we will probably discuss to what extent the guidelines should include things like lifestyles. My own feeling is that the issue here is the drugs and we shouldn't try and duplicate what is already out there in JNC7 and other recommendations.

You also mentioned ALLHAT. That, again, was discussed extensively at the last meeting and I am sure will come up today. So thank you for your comments.

Are there any other public comments at this stage? I think some of the committee members may want to talk later as members of the public.

If not, I guess we can go on to Dr. Stockbridge, again.

FDA Presentation

Guidance for Industry Labeling for Outcome Claims for Drugs to Treat Hypertension (Draft Guidance)

DR. STOCKBRIDGE: I thought, at this point, we would just sort of start going through the questions that have been posed to you. There are a few general questions up front and then it sort of marches paragraph-by-paragraph through the draft document. I was going to give people an opportunity to comment on those particular sections.

Committee Discussion

DR. PICKERING: Do you want us to start going through the specific questions, or should we have a sort of general discussion first?

DR. STOCKBRIDGE: You are the Chairman.

DR. PICKERING: Okay. Maybe I could just say a few introductory things. I think, at the last meeting, as had been said, there was general consensus that current labels are really rather

uninformative. One example is the archetypal antihypertensive drug chlorthaladone that was used in the SHIP and the ALLHAT study as the basic sort of drug.

There is no label for chlorthaladone in the Physician's Desk Reference. For the other drugs, it mostly just says they lower blood pressure and there is no information as to which drugs have been shown to have effects on preventing cardiovascular morbidity.

So I think what we are going to be talking about is the concept of class effects, to what extent are the effects of a particular drug consistent with other members of that class versus drug-specific effects. This is always a source of tension, but if you read guidelines such as JNC7, there is continual reference to starting with a drug of a particular class but no recommendations as to, within that class, which drug you should choose.

It has also become very relevant from a healthcare point of view because I think a lot of

the insurance companies now are substituting drugs of the same class but not for the prescription that was originally written. This habit has been condemned by organizations such as the American Medical Association and the American Heart Association, but it continues.

I think having more extensive labeling would help physicians to decide which is the most appropriate drug to choose. One example of just how complex this picture is is the story of calcium channel blockers and heart attacks. As people probably know, some years ago, there was a story that patients taking calcium channel blockers are at increased risk of heart attacks and that, subsequently, I think, it became apparent that it was one particular formulation of nifedapine, short-acting nifedapine, that was responsible and the longer formulation of nifedapine does not do this.

So, even with the same drug, the formulation may be critical as to what the effects are. So this is a very tricky subject.

Having said that, I think maybe we should just open it for general discussion to begin with before we get onto the detailed questions.

Actually, could I do one other thing and that is I had a slide which I thought might be helpful to look at. This was, actually, adapted from a publication in Circulation by Bruce Psaty and Kurt Furberg on the subject of ACE inhibitors.

(Slide.)

As you can see, there are ten that are approved by the FDA but all for the treatment of hypertension. I think the helpful thing is it shows what other indications there are. You can see that are some ACE inhibitors that are only approved for hypertension whereas others, like captopril, have several other FDA-approved information and it also shows which ones are available in generic form.

I think this type of information which, hopefully, wouldn't be too controversial or susceptible to manipulation is actually quite helpful, both for physicians in choosing within a

class which drug would be appropriate and, also, as a sort of prod to the pharmaceutical companies making it better known which drugs have been shown to reduce cardiovascular events as well as blood pressure.

DR. TEMPLE: That sort of goes to some of the questions that Mr. Goozner was raising. The general theme in here is that lowering blood pressure affects strike, M.I. and cardiovascular death. The particular things that some drugs do and other drugs do, like treat heart failure successfully, would not be a part of this general statement. That would be drug--by-drug just as it is now.

So the thought was, I think, that, because drugs of so many different classes have had favorable effects on those first three outcomes, we know that that is just the property of blood-pressure lowering. But, as ALLHAT suggests, but I must say doesn't quite prove, drugs can differ on other properties, on side effects and a wide variety of other things.

Nothing in the proposal would take those things out of labeling. So the LIFE study would still be there. The HOPE study would still be there. All of those specific things would still be existing.

Now, having people know this sort of thing is, indeed, very helpful but we hadn't thought of that as actually going into the label. The only thing we tried to surround was the things that they really all do and not, say, get into how good one drug is at heart failure. I mean, calcium channel blockers, or at least many of them, would probably warn about the possibility that they are bad for heart failure.

DR. PICKERING: Thank you. Any other comments at this stage?

DR. STOCKBRIDGE: Were you proposing that a table like that go into this document, or are you just illustrating that there are a variety of claims?

DR. PICKERING: Well, I think it is information that is not readily available and I

haven't seen it, the equivalent thing, for angiotensin receptor blockers. Personally, I think it is helpful to have. I don't know where it should appear but I think the more--the wider use of this type of thing would be helpful.

DR. STOCKBRIDGE: You have already got a sense of what the lags are associated with trying to get a document like this published. It just seems like, if it got class-level, claim-level, information in it, it is going to be out of date and irreparable pretty quickly compared to the life cycle of it.

DR. PICKERING: Yes. I think any of the labeling we are talking about is going to have to be updated on a fairly regular basis, isn't it, because a lot of these things may change.

DR. TEMPLE: It would be for the individual. I mean, all the drugs have appropriate warnings and precautions and other claims. That would be business as usual. What would be novel would be a general statement applying to all antihypertensives that everybody is comfortable

applies to all antihypertensives.

I realize, based on ALLHAT, people can argue about which drugs are better for heart failure, or which ones prevent it better, et cetera, et cetera, et cetera, but nobody, I don't think, is prepared to doubt that blood-pressure drugs lower stroke rates because that seems to have turned up over and over and over again.

To the extent that is true, our thought has been that that could go in labeling to remind everybody that the first thing you should think about is getting your blood pressure down. Whether you do it with lifestyle or other methods is almost not so important. You just have to get it down.

And, as Norm said, the particular choice of therapy could be affected by whether you have angina also, so you might want to start with an antianginal, or whether you have heart failure, also, in which case, you might want to use something that is good for heart failure as opposed to something that isn't, or whether you have diabetic renal disease, in which case you want to

use something that is known to do that.

So all of those choices would be left to people to make as they ordinarily do but there would be a basis for clear promotion of all antihypertensives as something that will help you not have a stroke, not have a heart attack, not die.

DR. PICKERING: I guess the thing is--one of the questions is you have a statement that Drug X is a member of Class Y. I think it is helpful to give sort of background information about other members of the class.

DR. TEMPLE: That is an important component, too, but that, again, was intended only to apply to those three major outcomes that we agree are characteristic of blood-pressure lowering.

So it would say, oh, I don't know, for diuretics--well, for chlorthaladone, it would say there are specific studies showing chlorthaladone is good for you and, for some other diuretic, it would say there are lots of studies of diuretics

that show that they have this desirable effect and for ACE inhibitors, I guess there aren't any really, for ACE inhibitors. But there is one calcium channel blocker, placebo-controlled study.

So it would say those things but only about those three major claims. And it would characterize the evidence related to a drug or the class for the three things that we think are common to all antihypertensives. Just it is sort of in the interest of greater truth. It tells you whether there is actual data or whether it is a sort of class effect.

Specific claims on specific things would be as usual. The labeling would have a heart-failure claim if they have a heart-failure claim. And the labeling would have a diabetic nephropathy claim if they have a diabetic nephropathy claim, or whatever.

DR. STOCKBRIDGE: I was just going to point out one of the--it may be the only useful general consideration question that was offered had to do with the fact that we don't, in fact, propose

at this point naming the classes of antihypertensive drugs and what we think the sustainable claims for that class are.

The document does not do that now. So one of the things we are asking you at this point is should we name the classes we recognize and, in here, put our proposal about what claims we think are sustained there.

DR. PICKERING: The label already has something--an ACE inhibitor, doesn't it?

DR. TEMPLE: The new labeling guidance will require that even if it currently doesn't.

DR. PICKERING: Does anybody else have comments or questions or should we go on to the questions

DR. KASKEL: Can I add something? I understand the limitations and why you don't want to add too much to the table or include a table, but we have another health issue regarding 30 million Americans who have elevated creatinines above normal that may not even know it and may have some proteinuria. When we start talking about

classes of drugs that may have a protective effect on progression of renal disease, whether it is diabetic nephropathy or other causes, we shouldn't eliminate that from information to the public or to industry.

So, if you are going to make any changes, one can think about a class-related beneficial effect of some drugs on other organ systems in more detail that what is mentioned here.

DR. TEMPLE: Again, we have evidence that two drugs are good for Type II diabetic nephropathy. We have, historically, but this could be discussed, perhaps not now but another time, we have historically shrunk from class labeling because, while you are pretty sure, maybe, any ARB is going to do that, you don't really know.

So we generally haven't done that. But that is a good example of something that we would not include in the general statement because it doesn't seem to be a property of all antihypertensives. The IDNT Study had an amlodipine group and it didn't do anything. So it

looks like that seems to have been, in those studies, the property of the ARB that was studied not of just lowering blood pressure.

So those would be in the label appropriate to the drug that won, but wouldn't be part of any general statement because we don't know that it is a general property of antihypertensive drugs. I mean, we all probably believe that renal disease is probably improved by having your blood pressure lowered, but that is not the same as actually knowing. Most of the trials didn't really have much to say about that.

DR. PORTMAN: I think your first question, 1.1, is whether or not the labeling should also be guidance. I guess you have to ask who is the labeling for. I am certain the public and companies use the labeling but, being a clinician, the way I see the labeling is that it is for the clinician mostly to advise or to--not to advise, even. But, when I look at a label, knowing the process that we go through to get an indication for a drug, I feel that, if it is in the label, it has

been proven to some degree.

I think that the guidance is not always so proof-related, unfortunately. I lot of it is common practice. A lot of it is based on studies that may not reach the level of evidence that you need for labeling but it is still important. The whole area of renal disease is one. I don't think you can find a nephrologist who wouldn't say that an ACE inhibitor is important for a patient who has proteinuria and hypertension.

I think you would get almost universal agreement that that is the drug that should be used in that case. Yet, you know, how many drugs have that--how many ACE inhibitors have that in the label.

DR. TEMPLE: Only one.

DR. PORTMAN: Only one; okay. So the labeling, I think, is something where I think I would not want to stray from having it be kind of a testament to the proof that a drug says what the label says it will do.

DR. TEMPLE: This was a question,

actually, about the guidance document and pointing out that it is not written as a scholarly document, which is true. It presents conclusions we have reached but doesn't site the data and stuff like that.

The objective in the labeling change is to put down only--and, really, the last time a committee met on this, it thought that these were well-established, that all antihypertensives can be expected to lower your rate of stroke M.I., cardiovascular death, because drugs from many different classes, from diuretics to reserpine to--you know, a lot of drugs--have done the same thing and it fits with the epidemiology and it seems to be a property of lowering blood pressure.

Most of the other things that might be done, we don't put in that category and would not include in this because it is not so clear yet whether everybody's renal function benefits from having their blood pressure lowered. Maybe yes, maybe no, but we wouldn't propose to put that in.

But that first question really is about

the style of the guidance not so much what the words in the labeling should say.

DR. WARNER-STEVENSON: I have a related question. There must be information, in fact, on who actually uses the labels and what their impact was. I see basically four potential audiences. One is patients through their own initiative. One is patients through targeted marketing with claims that are made. One is physicians, through their own initiative, as Dr. Portman said. And then physicians through targeted marketing.

There must be information currently on how the labels are generally used and how they would be used if this were made a more dramatic claim. For instance, I think it would be unfortunate if the advantage went to the company with the largest marketing budget who said, "Our drug makes you live longer, prevents strokes and M.I.s," and it were inferred that that drug does it more than some other drug who has a lower marketing budget but could make the same claims.

DR. TEMPLE: The statements that are

proposed, and you can comment on this, are going to be general statements about lowering blood pressure. They are not going to say one drug does this.

DR. WARNER-STEVENSON: Right.

DR. TEMPLE: They are written broadly. Labeling affects promotion. So the contents of an ad, whether it is a direct-to-consumer ad or to a physician, are likely to reflect what is in labeling and will be able to say certain things that they cannot, really, now say because they are not in labeling. I mean, you don't see promotion of antihypertensives directed at outcomes because it is not in any of the labeling with one or two minor exceptions.

So I think one of the things we hoped is that, in a lot of ways that people get reminded of things, they will be reminded lowering blood pressure matters to you.

Now, if someone were to observe that it is very unlikely that anybody is going to promote chlorthaladone, a drug that costs, what, $10 a

year, very heavily to patients, they are absolutely right. People don't promote, for the most part, generics and cheap alternatives. So you have got to hope that the rest of the community reminds people that those drugs are available. That is JNC7 does and that is what everybody does.

But there is no question that the things that get promoted are the ones that are more expensive and are often still on patent. As somebody--I guess, you--noticed, you won't even find some of these drugs in the PDR anymore. In fact, you can't find anything that is off patent and generic in the PDR--well, that is a lie. You find some things, but an awful lot of drugs cannot be found in the PDR anymore.

We have hopes that labeling will become widely accessible on the Internet through a program we are developing but it is not there yet.

DR. FINDLAY: Is there, in fact, precedent for referring to another class of drugs in the labeling for a drug; in other words, one of the things that is being contemplated here is to talk

about, and potentially name, a series of classes of drugs. What is the context of that in terms of other labeling? Is that a general practice, and forgive the naive nature of the question to some extent--is there a precedent for a drug or all the drugs in a class to refer to another class, either in an advantageous way or a disadvantageous way; in other words, stating that, perhaps, you ought to think, or you ought to know or be aware, of the research showing another class is better under certain circumstances.

DR. TEMPLE: There are, certainly, package inserts that say you should only use this after you fail on something else or you should think about other things. That is usually because of toxicity. We would not do that because something else is, say, cheaper. We shy away from anything like that.

So that is not unprecedented. What is unusual here is that the basis for the conclusion that all drugs that lower blood pressure are good for you comes from a wide variety of drugs. It is not that it comes from the data on ACE inhibitors.

It comes from the data on diuretics, the data on reserpine, the data on nidralazine, beta blockers. A lot of different sources lead to that conclusion.

So we would probably refer to the source of that conclusion in here. That is a little novel. I can't say I can think of an exact analogy to that.

DR. PICKERING: Dr. MacMahon, do you want to comment? By way of introduction, Dr. MacMahon is, I guess, the senior author on the Trialist Collaboration which has been doing meta-analyses on all the outcomes antihypertensive trials.

DR. MacMAHON: Thank you. Just two comments that basically relate to this initial level of labeling for all agents. I think, first, the comment would be that it is perfectly reasonable to say that any drug that lowers blood pressure can reasonably be expected to reduce stroke risk, coronary-disease risk and total cardiovascular risk.

That, of course, doesn't necessarily mean that every drug has precisely the same quantitative

cause-specific effects. So those two things are rather different and I don't think there is any intention to indicate that all drugs are the same or have cause-specific effects which are common.

I think the other thing, and it relates to the issue that was raised earlier by the presentation from the member of the public, and that is that the current situation, in terms of labeling, in terms of claims for morbidity/mortality protection, virtually exclusively favors high-cost drugs because they are the only ones who have been taken through a very specific commercial development program that has resulted in claims.

So we have the current situation that the cheapest drugs, for example, diuretics, have no claims for morbidity/mortality benefit. So the very issue, I think, that was being raised about the need to identify morbidity/mortality benefits for less expensive drugs is exactly what would be achieved by this broad general labeling that is being proposed.

Thank you.

DR. PICKERING: Thank you.

DR. WARNER-STEVENSON: I would actually just like to follow up on those comments, though. My concern is that there wouldn't be anyone to jump on advertising for those low-cost agents and that, in fact, one would end up, perhaps, with a greater disparity between the recognition of the mortality benefit for the low- and the high-cost agents because no one is promoting the low-cost agents. But, now, the high-cost agents can be promoted with, really, additional emphasis.

DR. TEMPLE: We are not going to be able to predict or know whether that is likely. If third-party payers can't figure out that they should encourage people to start with something that costs $10 a year and simply cannot get that message to anybody, we should replace them. I don't know what is the matter with them.

But it is a problem. I went shopping for a 12-and-a-half milligram, and I would have accepted 15-milligram, chlorthaladone and I

couldn't find one at my drugstore. So I took 25 every other day. But that is kind of funny. It is a bargain. It works very well. I mean, what ALLHAT showed was that they didn't find anything better--that is what ALLHAT really showed--and there you are, in a reasonably large city, and I can't find the dosage form I want.

We are hoping that some of this, improving the label, will encourage people to pay more attention to it. But there is no way to guarantee that. But there is some much--you would have thought, third parties would have an interest in having a virtually free drug be the start of an antihypertensive regimen. You would think they would encourage it. I don't know why they don't.

Places like the V.A. sure do. They know how to do that. So we are optimistic but we don't regulate that.

DR. PICKERING: Thank you.

Questions to the Committee

DR. PICKERING: I guess we are on Question 1.1 now which is the issue of should the guidance

be a scholarly review of the topic. I think what I am hearing is that it shouldn't be an exhaustive scholarly review. Is there any other discussion about that?

I guess that is the consensus, in which case maybe we could go on to 1.2; should we be trying to assess the impact of these labeling changes on public health and how might one do that.

DR. TEERLINK: Yes; I think, obviously, we should. It is an important thing. The question is who is "we." I don't think it should be the FDA. And then the question is how. That is partly a function of who is going to be doing it.

It certainly is wide open to the kind of projects that have been going on already in the Veterans Affairs group where we do very careful monitoring of how changes of different policies affect prescribing patterns within the V.A. That can certainly be done within healthcare systems individually. Obviously, it would be very interesting to look at the Medicare populations and the more centrally funded systems.

So those are methods to do it. But I don't necessarily think it should be a mandate that goes along with the labeling to the FDA to show this.

DR. PICKERING: Thank you. Yes; there was a recent publication from Canada showing that their education program--they were looking to see what effect it had on prescribing habits and it did show that there was a benefit. My impression is the pharmaceutical industry actually keep pretty close tabs on what prescriptions are being written.

My impression is that all the drugs are going up at the moment except with the possible exception of alpha blockers. But it will be quite difficult to see if the prescriptions are appropriate to the indications. I think that would be very difficult. But, certainly, seeing if, for instance, the use of chlorthaladone is showing any change, I think, would be of great interest.

DR. PORTMAN: Question to Bob or Norm. What kind of controls, if any, or approvals are required of pharmaceutical companies when they

market their particular medication? I mean, it has to be the indication to market it, but how do you know that that is what they are saying?

DR. TEMPLE: Companies have to submit all of their promotional pieces to the Division of Drug Marketing, Advertising and Communication. That is many tens of thousands and it won't surprise you to know that we don't necessarily read every one.

But, if they are all conspicuous, we do notice them. We are very attentive to direct-to-consumer advertising. In general, they are limited to claims that are compatible with their labeling. They are not supposed to claim any other use or any other advantage over another drug that they haven't established and, generally, that isn't in the labeling or that isn't supported by well-controlled studies that may not have gotten to the labeling. You can sometimes do that in some things.

They are not supposed to imply benefits that are not there, all the usual rules, and they are supposed to provide appropriate warnings,

precautions, et cetera, in a balanced way. Those are the rules. We send out a fair number of letters to people who we think violate that one way or another.

But we do not clear advertising as a general matter except that, under a voluntary proposal by PhRMA, direct-to-consumer advertising is being submitted to us for a look before it is being promulgated.

DR. PORTMAN: So maybe this is a stretch but one thing that the FDA could consider is that, if you are going to market an antihypertensive, that part of your marketing or the discussion is that all drugs that lower blood pressure have these beneficial effects and then our drug may be better, or may be whatever, because X, Y and Z, as noted in the label, or something along those line, but you can make them work for you, from that standpoint.

DR. TEMPLE: Well, the way to do that is to make sure the language in the labeling that we agree is a good idea captures that in a way that is reasonable and then, if you don't capture what is

in the labeling, your promotion might be considered misleading. So we should think about what it says in a general way and, ignoring that or suppressing it, might be considered misleading. I don't want to pre-judge the advertising rules but that is a possibility.

DR. FINDLAY: My answer to this question is yes. I would hope that FDA would be part of the how question, how to go about this, although I agree with Dr. Teerlink's comment that it shouldn't be the only group doing this but particularly in the context of the comment you made before that FDA hopes to make labeling, drug labeling and drug information, more transparent, more readily available to the public.

So I hope that there is an case going forward of how presenting this information to consumers directly through the web over the next decade and beyond can be improved and the impact that it has on consumers.

DR. TEMPLE: But we will need to think about how to measure it. We can certainly make

contact with the High Blood Pressure Education Program at NIH and see what they are doing. If I were the CDC, I would be interested in this, too. But I don't know. It will be a good question.

I think the goal we all have is to have a larger fraction of people who are hypertensive be under therapy or under lifestyle modifications or under something, anyway, and that it be better than the current, I don't know, something like 50 percent which isn't really good enough.

So that is helpful. We will try to think about that.

MR. FINDLAY: One question off the comment that was just made. Is it feasible to have some sort of crossover guidance to the folks who run the drug advertising--DDMAC, I guess is the name of the group--some guidance for them with respect to the promotion of future brand high-blood-pressure drugs with respect to this labeling? Or is that automatic? That is automatic or would it be useful to have a crossover kind of guidance for that, for the industry?

DR. TEMPLE: We will make they get this message. As it happens, they work for me, too.

MR. FINDLAY: Yes; I mis-spoke. I mean guidance for the industry that is not necessarily strictly in the context of the labeling but somehow--I think you get the drift.

DR. TEMPLE: We will need to think about what a balanced discussion of an antihypertensive has to have in it. I don't want to say without consulting internally, but if there is a general statement, maybe that really should appear most of the time. But we have to think about that.

DR. PICKERING: I guess one possible additional source of this data would be NHANES which, as far as I know, is still going on and gives the national statistics for the prevalence of hypertension and how many people are controlled. I am not sure how much detail they get about drugs or why people are on drugs.

DR. TEMPLE: I think that is where the somewhat depressing figures about treatment come from, that it is not as prevalent as you would like

for lipids and for that. So, you know, your dream is you see the percent treated go from 50 to 60 and then further.

DR. TEERLINK: I would like to reinforce something that has been said kind a bit here that I think this is an opportunity with this if we go ahead with this general labeling that, in the advertising, that if, up front, there is this statement along the lines of saying, you know, all agents that lower this blood pressure, that can actually, in some ways, leverage the higher-power-type newer agents to actually do some of the marketing of chlorthaladone for you, for example.

DR. TEMPLE: It is an interesting thought. There are a number of different kinds of advertising that you probably see. The are reminder ads which don't do anything because they don't name the drug. But, ignoring that for the moment, there is something called help-seeking ads which are sort of institutional statements about, say, why it is good to lower blood pressure.

You don't see a great many of those because they don't promote a particular drug and you have to believe that a rising tide lifts all boats to be enthusiastic about that. But even ads that are directed at a particular product can have help-seeking components. There have been some--I won't name them, but there have been some good ads for lipid lowering that almost did that, that sort of told you about why it is generally good to control your LDL cholesterol while they promoted their own particular drug as well.

There is nothing that says that couldn't be part of the way people promote antihypertensives. That would be a nice outcome, how much we can influence that. How attractive that will be isn't clear to me yet but it might be.

DR. PICKERING: Any additional comments on Question 1.2?

DR. DeMETS: Tom, I just have one thought. If you are going to make the labeling stuff available on the web, for example, accessible to the internet, which patients are now fairly

sophisticated in doing, it seems to me that it has to be somewhat clear and transparent about what it is it is saying and not coded in our usual scientific language. Patients do go to that and do rely on it a lot, and more and more and more.

So I think some general statements that give patients the context of what they are looking at would be helpful.

DR. WARNER-STEVENSON: I would like to second that. I think one of the most important things this could do for those patients who religiously go and read about absolutely everything is that, when they read the 79 potential side effects, if it starts out that this is why you take it, so you have fewer strokes, heart attacks and death, that, then, those other 79 look a little smaller. So, to me, that could be one of the biggest benefits of doing this change in labeling.

DR. TEMPLE: I think that was at least part of what we had in mind. There was very little explanation of why you should bother. But David's thought about how to make it both as accurate as

you can and also accessible is an interesting one.

We could also think about whether there ought to be patient labeling developed.

DR. PICKERING: One thing you could do is actually use a reasonably legible type. The current labels are in such small type that the average elderly patient can't read it anyway.

DR. STOCKBRIDGE: Certainly web-based labels will help alleviate that problem, too. In addition, new initiatives to reorganize labels, the format of labels, including a highlights section should help people with things like that, too.

DR. PORTMAN: With all the money our government spends on trying to educate the public, it would be nice to see that you go into the web site and you type in hypertension and the first thing that comes out on Yahoo is the FDA and it goes directly to a video with Norm or you or maybe some handsome actor basically telling--

DR. TEMPLE: You meant even more handsome, didn't you. (Laughter.)

DR. PORTMAN: Basically a five- or

ten-minute video that basically says, this is what hypertension is all about and you should have--the hallmark is, "Lose weight, will you? Watch your salts. Do some exercise. And, if that isn't enough, you and your physician should consider working toward having medication, and these are the benefits of these medication," and blah, blah.

That should be available instantly.

DR. TEMPLE: You raise an interesting question. We always get at least a little nervous when we become the enthusiasts for drugs. We regulate them. So we don't often do that. This proposal is sort of a step toward one of the areas that sort of everybody recognizes. I mean, who doesn't think you should lower your blood pressure. That is sort of easy.

If we are going to say about how depression is underdiagnosed, oh, there would be controversy all over the place. The scientologists would on it like--

DR. PORTMAN: Not to mention a few suicides in kids.

DR. TEMPLE: Right. So that is tricky even you actually believe that--no matter what you believe, but this is one where we felt quite comfortable saying, this is something we all know is under-treated, however it should best be treated and with whatever.

So we are pretty comfortable. We usually don't do a lot of promotion of treatment but maybe this one is one where we would be enthusiastic. But there are so many people who would like to make that point, I don't think it necessarily needs us to do it.

DR. TEERLINK: I think the thing that can be done is I do like the concept of a general patient--just as we have this guideline, draft guidance, for the labeling, maybe there should be some attention given to a draft patient guidance for patient labeling in regards to this class, in particular, just because--not so much as a promotional rah rah but in terms of educating and using the regulatory powers that the FDA has to reinforce the importance of these agents in terms

of addressing a public-health issue.

DR. TEMPLE: And emphasizing things like, don't stop without seeing your physician. If you are having trouble affording it, go talk to your doctor about something cheaper. Don't stop. There are a lot of things that we have not systematically done, but we will think about that

DR. KASKEL: There is a template, a recent initiative, by the National Kidney Disease Education Program from NIDDK which as a patient education website as well as primary care and specialist education website together with videos and information and suggestions. That was copied after the work with the hypertension. We used there a template for this so there is already something in place that might be worth looking at, NK-DEB, it is called.

DR. PICKERING: The National High Blood Pressure Education Program which is another federally funded program is already doing some of that so I guess you don't want to be sort of directly competing with them. But I don't think

that should be an issue in practice.

DR. TEMPLE: Presumably, this language will be useful to them. It will be something that shows up on all drugs and can be, at least part of it--I am sure they say things that are similar already.

DR. PORTMAN: Whether you like it or not, there is a certain power to having a statement coming from the FDA.

DR. TEMPLE: Yes; we are very conscious of that and we try to be modest.

DR. FINDLAY: Just to underscore what may seem like an obvious point, but, for physicians, it is not going to be news that there are multiple categories of drugs that equally treat high blood pressure but, for many consumers, and especially a large segment of probably the under-treated population, that is a very important message, that there are multiple categories and this creates complexity.

But that is just a single message. There are five or six categories of drugs that are all

capable of helping you in a major, major way. Just that piece of information will spark some conversation between patients/consumers and their doctors about, "Wait a minute; I heard there are some other things here, too." That is useful.

DR. TEMPLE: The other thing is, if we can bring it off, that it is both more complex, in that there are multiple classes, and less complex in that they break down into a rather small number of options. There are not as many modalities to treat high blood pressure as you wish. There are diuretics and there are CCBs and then you are off into other territory.

So I don't know whether we can bring it off but it is, in some ways, not as complicated. You just have to pick among them.

DR. STOCKBRIDGE: All right; fine. So that really is Question 1.3, can you enumerate the classes--should we be proposing what the classes are and what their members are.

DR. PICKERING: I think we are now getting into the nitty-gritty bit. I mean, my own feeling

is that you should be saying what classes a drug, an individual drug, belongs to because class effects, even though they are not officially condoned and defined, they are basically here to stay and they are referred to in all the guidelines such as JNC7. Just to make recommendations on an individual drug basis would be totally impractical.

So I think you have to have something about what class they belong to. With some of these, it is relatively easy such as angiotensin receptor blockers where there aren't huge differences between individual members. With calcium channel blocker and beta blockers, it gets more complicated because there are subclasses and it may be relevant to say whether, for instance, it is a dihydraperidine or one of the other calcium channel blockers. Obviously, with beta blockers, we have got the cardioselective ones and the ones that have vasodilator effects which I, personally, would favor including more rather than less information about this.

Any other comments?

DR. TEMPLE: Only that there is a tension between being complete and being reasonably terse, obviously. So we will be interested in specifics as this comes up.

DR. WARNER-STEVENSON: I think this gets back, again, to the ambiguity about who the audience is. Patients, right now, I don't think would want to be deciding whether or not they want vasodilatory properties of their beta blockers. So we want them to just get the big picture.

I am not really sure who the audience is that is unaware of these differences that we would want to make more aware in a general sense.

DR. TEMPLE: I guess one thing that helps is that, with respect to the treatment of blood pressure, a lot of those differences don't really matter as far as we know. The various classes of beta blockers--I mean, there is some debate about some of them, but they don't seem to be distinguished by whether they are--as far as their effectiveness goes as to whether they are cardioselective or not. That is an adverse effect

that goes in a different part. The vasodilatory properties are more related to heart failure and post-infarction, maybe, which is a different set of claims.

So when we get specific, it will be important to think how much complexity we need to put in.

DR. PORTMAN: I have kind of a general comment and it, in some way, relates to the imbalance of this committee and that is that we don't have an adult nephrologist on the Cardiorenal Committee. Yes; I am a nephrologist and so is my colleague. But we are pediatric nephrologists.

While we certainly understand the kidney well, all the studies that are related to these drugs and their effect on the kidney have not been done in children. They have been done in adults. The people who sat around the table and designed these studies and talked about these studies and interpreted these studies were not me and were not Dr. Kaskel.

I think that there are some of my

colleagues, I know, who, at the very mention of ALLHAT would be screaming because ALLHAT was a lovely study for essential hypertension but not necessarily if you have hypertension related to renal disease.

Particularly a problem is that the best combination of drug for treating a patient with renal disease in hypertension which is a combination of an ACE and a diuretic wasn't even allowed in ALLHAT. So that is a real problem and it addresses somewhat of this issue.

So I just wanted to bring that out for this discussion in that we don't have, I think, a major representation here for this discussions.

DR. TEMPLE: But, again, the relation of treatment to renal disease is something we are not proposing to discuss perhaps for the very reason you are describing it. Even in the limited number of studies that we have actually reviewed to consider labeling claims, it is perfectly clear some drugs with equal blood-pressure effects have different effects on renal outcomes.

So that doesn't seem to be a totally generalizable effect, at least not in Type II diabetes, anyway. That doesn't seem to be a generalizable effect of lowering blood pressure so that would not be part of this. That would be in the part of the label that goes to what you know about your drug.

DR. PORTMAN: No; I understand that. But, for instance, if Andy Levy were sitting here, he might be arguing that point with you. Okay? I will just leave it at that.

DR. TEMPLE: Oh; okay.

DR. PICKERING: I think we think it is a good idea but we haven't been very specific about the details. So maybe we can go on 1.3.2; if so, should the guidance name the pharmaceutical classes, their members and whether the outcomes data is adequate.

This, I guess, is the sort of equivalent to the table that I showed earlier which I would like to see somewhere. If it is not in the guidance, perhaps it could be posted on the web for

the individual classes because I think it is helpful information that is not sort of readily available in other places.

What do other people think?

DR. FINDLAY: I think the classes should be named. I don't know how much detail with reference to your points you can get into there. But I think the broad classes should be named and my rationale for that is that, in the labeling and the impact that has on promotion and everything else that we know about, I think it is important to have those drug classes named for the benefit of consumers.

DR. TEMPLE: Okay. So, basically, the concern here and the reason we are asking is we are trying to make a general statement about all blood pressure lowering. You want people to get the idea that lowering blood pressure with anything is good for you.

But it also seemed important to say where the evidence comes from, that there is lots of evidence on diuretics--there is a little on

reserpine. There is a little on this. There is a little on that--and that that seemed part of it. But we wouldn't want that to undermine the--I mean, there could be drugs for which there is no good outcome data. I would probably say that is true for ARBs that are just as likely to be effective as any of the others but, as it happens, there is no placebo-controlled outcome data and there aren't going to be any placebo-controlled outcome data for anything new because you can't do that trial.

But it seemed appropriate to tell people where the evidence comes from without undermining the general theme. I think you are saying that you agree with that.

DR. FINDLAY: I agree with that, your point being--one point being that, even if an individual drug in a class has no outcome data, that it gets to make the claim by virtue of being a member of that class.

DR. TEMPLE: You should still believe, in general, that lowering blood pressure is going to be good even with that member but you don't have

actual on it.

MR. FINDLAY: Right. And I agree with that.

DR. WARNER-STEVENSON: I would agree. I think it is important also to just have the general classes so that they can make sure whatever they are considering fits in one of those; for instance, garlic. We don't have data on it, but many people feel that it lowers blood pressure and might assume that that falls right in this general thing.

So I think you would like to have them listed.

DR. STOCKBRIDGE: Go ahead. Tell me what the classes are.

DR. WARNER-STEVENSON: I think they were--as Dr. Pickering indicated, it is ACE inhibitors, ARBs, beta blockers, calcium channel blockers, diuretics and I guess you have to put in alpha blockers.

DR. STOCKBRIDGE: So diuretics is one class and ACEs and ARBs are two?

DR. WARNER-STEVENSON: I think so. I will

defer to the--

DR. PICKERING: I think most of us would say yes. I mean, obviously, there are subdivisions particularly in the diuretics, the aldosterone antagonists are different from the loop diuretics and the thiazides. I think, if you are going to say it is a diuretic, you have to say which subtype of diuretic it is because that, obviously, has major implications. I think we should discourage the use of furosemide for the treatment of routine hypertension.

DR. PORTMAN: You also have central alpha agonists.

DR. TEERLINK: The other question that I have is there are two ways you can look at this. One is that you include the pharmacologic classes that have actually contributed to the outcome data. So that is one. Then the other is including pharmacologic classes that are known to lower blood pressure.

You are saying two different things. You may want to have a statement to that--there are

clearly, we hope, going to be new agents developed with new mechanisms of action for hypertension that will not have outcomes data.

DR. TEMPLE: Right.

DR. TEERLINK: Where, in this list, do you want to put the new whatever it is?

DR. TEMPLE: Labeling will, as it does now, for drugs that lower blood pressure, say that they lower blood pressure. It will say what their class is to the extent there is an agreed-upon term for the class.

What this says is that, where we describe the overall benefit of lowering blood pressure, we will try to make it reasonably clear where those data come from. The strongest data, obviously, is from placebo-controlled trials. There aren't going to be any more of those. Moderately strong data comes from things like ALLHAT, but only moderately for a number of reasons. You don't get to use the drugs the way they are supposed to be used and a bunch of limitations.

But it certainly contributes to the data.

And then there are meta-analyses that Dr. MacMahon was referring to that have many members of some of these classes but not all. There would be an attempt to characterize the source of the data.

For some new class, they wouldn't be characterized as having contributed to the data but they would still be listed as an antihypertensive in the general view that lowering blood pressure with them is good, we would still be there. But, I mean, there are no outcome data that I know of for clonodine or things like that.

But they lower blood pressure.

DR. TEERLINK: So you are asking two different questions. One is a list of the agents that have contributed to the data that supports our concept. The other is a list of agents that we believe kind of would fall under that. So the list you are asking for now is what do we believe the listed agents are that have contributed to the outcomes data. That is a relatively short list.

DR. TEMPLE: Yes. I think the proposal in here is to--for a drug that is a member of a

particular class, you know, that is a beta blocker, the labeling would say that this is a drug where there are some outcomes studies--sorry; it depends on the thing. If it is, say, atenolol where there are at least some actual studies, it would say there are some actual studies. You can decide whether you believe them or not. That is a different question.

Or for chlorthaladone, say. Let's take something everybody agrees on. There are specific studies of chlorthaladone and there are lots of studies of members of the class.

If you were going to label indapamide, though, you wouldn't be able to say there are specific outcome studies but you would be able to say they are members of the class. That is the proposal, that we would say that this is a member of a class that has been studied with outcome data or this is a drug that has outcome data. Many drugs would not be able to say that.

DR. TEERLINK: So the specific point you are referring to is, in our draft documents, there

is the beginning statement that starts out saying, there are these groups that have contributed to the outcomes data, and then the specific statement is what is listed on the last page of our draft document where you select from a number of things saying that this drug is a member of the drug class, dah, dah, dah.

DR. TEMPLE: That's right. That last--I mean, we wouldn't want that to undermine the idea that all drugs that lower blood pressure are good for you but it seemed right to tell people that this is a member of a class that actually has data or this is an actual drug that has data.

DR. PICKERING: Dr. MacMahon, you wanted to make a comment?

DR. MacMAHON: Just on the same issue, the idea, therefore, would be a general statement about reducing morbidity and mortality from stroke, then identification of the class from which a particular agent comes from, then a statement about that class in terms of the sorts of findings that there have been for the class, in general, or for other

members of the class.

So there might be something specifically about--summarizing the information about ACE inhibitors?

DR. STOCKBRIDGE: If you belong to a class that has data, your labeling won't have those studies cited in it. It will simply say, I belong to a class that has some data. The question that was really being asked was the guidance document now doesn't list the ten classes that people thought were the pertinent way to divide things up and does not say, I think there are adequate data for beta blockers and these are the studies that make me think that.

It doesn't say what the classes are and whether or not they qualify to get a statement like this.

DR. TEMPLE: So how would it be determined what they would say? They would make a submission and a proposal.

DR. STOCKBRIDGE: Well, the question is whether we, before we issue this as a draft, would

write in the guidance, here are the ten classes. You belong to one of these or you are another. Of the ten, here are the five that we think have adequate data to support an outcome claim.

DR. TEMPLE: As opposed to just having people read the guidance and decide whether they think their drug is such a member of the class and submit it which is the usual way labeling is--

DR. STOCKBRIDGE: That's true and we can do that. That is why I am asking the question here is which way that should go.

DR. TEMPLE: Right.

DR. STOCKBRIDGE: I will point out that if we merely invite people to say whether they think their drug belongs to a class, you will get a variety of opinions.

DR. TEMPLE: Okay. So just to be sure, the question is should we try, even if we haven't yet done it, to say, on the basis of Dr. MacMahon's summaries and a wide variety of other sources, which are the classes we are prepared to say have contributed to the outcome conclusions.

DR. PORTMAN: How often are you planning to update this document because it is a once-a-decade thing--than saying that blood-pressure lowering is good and it is an ACE inhibitor is probably as far as you should go.

But, if you are going to update it on a yearly basis, as new studies come out showing that now there is new data for this class or that class, then it would be appropriate.

DR. TEMPLE: A couple of things to say. One, this is guidance. A company that thinks it has persuasive data supporting including its drug among the class of drugs that have data can always make that submission and convince us, maybe we would come to the committee and maybe we wouldn't. So you can always do that.

Second, guidance is quite updatable if we get around to it. It is not a terrible prolonged process to do it although, given the press of other things, it often seems that way. But I think the question is--what Norm is saying, I think, is that if we don't say, then we are going to get a whole

bunch of individual proposals which we will have to evaluate with your help or on our own at least for things that are at the margin.

You are asking whether a little up-front time in reaching a consensus on which ones we are willing to say get that claim, subject to further discussion, rebuttal and all the rest, whether it would be worth doing that in advance. I think that is what is being asked.

DR. PICKERING: As I understand it, some of this guidance statement is going to be nonspecific that would be the same across all individual drugs and then there would be a component which refers to the individual drug; is that right?

DR. TEMPLE: That's right. There are questions about each of those sections coming.

DR. STOCKBRIDGE: To be clear, there are sort of three classes in a different sense. You either have data of your own, you belong to a class that has data or you are an antihypertensive.

DR. TEMPLE: With no data.

DR. STOCKBRIDGE: Right.

DR. TEMPLE: With no data in your class or in your drug.

DR. STOCKBRIDGE: Right.

DR. TEMPLE: And, after the initial general statements, the labeling would say which of those you are. That is the current proposal.

DR. STOCKBRIDGE: Right.

DR. PICKERING: Okay. Perhaps we could go on to Question 2; please comment on specific sections of the background and discussion. So this is the generic bit, I guess. With few exceptions, labeling for antihypertensive drug products says that they are indicated to reduce blood pressure but the labeling is mute on the clinical benefits expected from blood-pressure reduction.

Blood-pressure control, however, is very well established as beneficial and an adequate treatment of hypertension is acknowledged as a significant public-health problem. The agency believes that, by making the connection between lower blood pressure and improved outcomes more

explicit in labeling, it can encourage appropriate use of these drugs.

DR. TEMPLE: These are all pieces of the guidance document which are the background to specific labeling. This is our justification, rationale, and Norm is inviting you to comment on whether you think these statements are correct as part of the guidance document that will contain the labeling we want people to use.

DR. STOCKBRIDGE: Right. Later on, since the guidance document mentions the specific things that we will put in labeling, the proposal for labeling, that is here, too. But, right now, we are just sort of marching through this draft guidance document to seek advice about whether we have laid the right context out.

DR. TEMPLE: The questions labeled 3 are specific pieces of the labeling. So, first it is the background and whether you find this all credible. Then the specific labeling consequences of what we have written in the background.

DR. PICKERING: Does anybody disagree with

what has been written there in 2.1? Anybody want to comment? Okay. Then I guess we can go on to 2.2; on June 15, 2005, the advisory committee met to discuss class labeling for outcomes claims. The committee voiced a broad consensus in favor of labeling changes to describe briefly the clinical benefits expected.

So any disagreements or criticisms of that statement? I think we are comfortable with that, too.

2.3; actuarial data and later epidemiology studies such as Framingham have shown that the elevations in blood pressure, systolic or diastolic, are associated with an increased risk of cardiovascular events. These data show this relationship is monotonic--the higher the pressure, the higher the risk--and nonlinear--the higher the blood pressure, the steeper the absolute risk increase per millimeter of mercury.

Steve?

DR. MacMAHON: Unfortunately, I think that the last part of that statement is incorrect. I

mean, the association between both systolic and diastolic blood pressure with both coronary heart disease and with stroke is log-linear. To describe it as nonlinear and to say that the absolute risk per millimeter is different at the higher and lower ends is not consistent with the epidemiology evidence.

DR. STOCKBRIDGE: I guess I thought I had fixed our problem by clarifying that we are really talking about absolute risk, the absolute risk is greater if you move 1 millimeter above 90 compared--well, 1 millimeter above 110--then, 1 millimeter above 90. That is what you mean by the log-linear relationship.

DR. MacMAHON: I guess it is if you have diabetes and your systolic blood pressure is 90, and if you are 25 years old with no other risk factors--I'm sorry; your diastolic blood pressure is 95--then changing that 1 millimeter is actually going to be greater at the lower level than at the higher level in an absolute sense because you are changing--the blood pressure may be lower but, if

the absolute risk is higher than that 1 millimeter, whilst it will have the same proportional effect, will have different absolute effects. But the size of that absolute effect is not necessarily related to the level of blood pressure at which you start.

So the key thing is that blood pressure is related to risk in a relative way and, therefore, it is basically multiplying the background absolute risk. So the key thing is not so much to be concerned about what the level of blood pressure is, although it is one contributor to absolute risk. The key thing is to say that there are, in an epidemiological sense, constant proportional effects of blood-pressure differences the absolute effects of which are determined primarily by the overall absolute risk not the initial level of blood pressure.

DR. STOCKBRIDGE: One more time. If you keep the other risk factors the same, don't mess within--let's keep a one-dimensional analysis going here--it is your diastolic blood pressure. If your diastolic blood pressure is taken from 110 to 109,

or it is taken from 100 to 99, you get a bigger absolute level of benefit, a bigger risk reduction, absolute risk reduction, if your blood pressure was higher to start with.

DR. MacMAHON: That's correct; if everything else is constant.

DR. STOCKBRIDGE: That is what this says, I think. I think that is what this says.

DR. MacMAHON: I think, though, that it emphasizes the wrong aspect. You are absolutely right, in those situations, where all other risk factors are the same. But it is still emphasizing that--and this is, I think, a popular misconception right now in the U.S. and other places, and that is that the level of blood pressure is the most important determinant of the size of the absolute benefits.

In that situation, where absolutely everything is the same, then, yes, that is correct. But, for the most part, the absolute level of risk and, therefore, the determinant of the absolute benefit of treatment is going to be only

fractionally related to blood pressure and much more related to age, diabetes, medical history.

DR. TEMPLE: But isn't it true that--which is what this is trying to--this is just describing the effect of blood-pressure change. It can't deal whether you should lower your lipids, too. What that is saying is that, for a given person with a characteristic lipid profile, diabetes profile, obesity profile, exercise profile, you get more of an absolute change when you are higher than when you are lower.

That is what log-linear means. I mean, it is log-linear but absolute means that--

DR. MacMAHON: Absolute sense; yes.

DR. TEMPLE: --the effect is bigger. I think that is all that was intended to say. Maybe it needs an additional paragraph that says risk is also profoundly affected by other aspects of your risk. So it is also true that, if you are a higher risk because you are diabetic or because you have abnormal lipids, that is also true that there is a greater absolute benefit from lowering blood

pressure because anything that makes your risk higher makes a given millimeter effect more important.

So we could add that, too. Would that do it?

DR. MacMAHON: I guess I would just argue that that is the more important emphasis because it is that totality of absolute risk that really does determine the benefit in an absolute sense whereas the level of blood pressure is only one small factor that determines first absolute risk and, therefore, absolute benefit.

DR. TEMPLE: But, you know, the current recommendations to be more aggressive in people who are the higher risk go to that, too, in some ways; that is, the reason that recommendations are lower in diabetics are that, because their risk is higher because of their diabetes, you get a bigger bang for any millimeter-of-mercury buck.

DR. MacMAHON: Correct.

DR. TEMPLE: Okay. But I don't think we want to exclude one or the other, so we will look

to make sure that everybody agrees that this is right.

DR. PICKERING: I forget whether somewhere you have some statement about systolic being more important than diastolic, particularly in older patients. That is one additional thought.

DR. STOCKBRIDGE: Actually, I don't think it says that now.

DR. TEMPLE: Do you think it should say that?

DR. PICKERING: I think somewhere that would be worth saying. Most of my patients still think diastolic is more important.

DR. PORTMAN: You have got pulse-pressure issues.

DR. TEMPLE: Should it rebut the idea that systolic doesn't matter or actually say that systolic is more important, particularly in the elderly?

DR. PICKERING: Personally, I would vote for the latter. Pulse pressure is another issue which JNC7 actually avoids discussing. I think we

should probably do the same because it gets to be very sort of hairy.

DR. TEMPLE: And it is a lot like systolic pressure.

DR. TEERLINK: I would like to support Tom's suggestion of including that aspect of systolic pressure but, in so doing, I would like to have this be the exception that proves the rule. There is JNC7. There is AHA. There is ACC. I mean, there are a lot of information out there in terms of hypertension. I don't think we want to try to rewrite JNC7 in terms of our labeling.

That partly gets to the point as well about including all these different other risk factors and things like that. It is important to maybe make very concise pithy statements in regards to those aspects, but I think the focus of this labeling document should be in regards to antihypertensive agents.

So I agree with including the systolic blood pressure but I don't think we should put too much more in there.

DR. PICKERING: Okay. Can we go on to 2.4; placebo-controlled outcome studies have been conducted with drugs in numerous pharmaceutical classes--diuretics, beta blockers, vasodilators, calcium channel blockers--and large studies consistently have found reductions in the risk of cardiovascular events. The clearest effect has been reduction in the risk of stroke but there have also commonly been reductions in the risk of myocardial infarction and cardiovascular morality.

My comment on this is that it sort of downplays the reduction of myocardial infarction which was true in some studies but I think a lot of the studies in older patients, it has been a pretty robust effect.

DR. STOCKBRIDGE: We say we believe all three things and nothing more and the clearest effect is on stroke. Is there something more that should be there or do you think it is not worth being slightly more circumspect about M.I. and cardiovascular mortality than about stroke?

DR. PICKERING: I guess I would favor

being a little stronger about M.I. Steve, do you want to comment on that?

DR. MacMAHON: Is the intention here to emphasize that the sizes of the benefits are bigger for stroke which is certainly the case or that there is more uncertainty about whether or not agents reduce coronary heart disease and cardiovascular mortality?

DR. STOCKBRIDGE: Well, it doesn't say anything at all about the size of the effect. Maybe it should.

DR. MacMAHON: I would say, based on the totality of the available evidence, that our confidence that agents reduce myocardial infarction, cardiovascular disease, is now as great as reducing stroke but also we do absolutely know that the benefits for stroke, in a proportional sense, are bigger. Whether that needs to be said or not, I don't know.

DR. TEMPLE: Suppose it said the largest effect has been reduction in the risk of stroke but there have also been consistent reductions in the

risk of M.I. and cardiovascular morality.

DR. MacMAHON: Yes; that would be, I think--

DR. PICKERING: Yes; I would favor that.

DR. TEMPLE: Okay.

DR. PICKERING: Can we go on to 2.5; positively controlled studies with more recently developed drug classes, ACE inhibitors and ARBs appear to share these clinical benefits. So this gets into the fact that placebo-controlled trials were no longer ethical when these drugs were introduced so you had to do comparison trials.

Steve?

DR. MacMAHON: I guess the wording, therefore, makes the assumption that things like the HOPE study, which is a placebo-controlled trial of an ACE inhibitor with a large proportion of patients who are hypertensive, isn't contributing to the data? I am not sure whether or not that is really necessarily justifiable.

DR. TEMPLE: Hasn't there been a debate about whether there was a difference in

blood-pressure control in that study?

DR. MacMAHON: Well, there has been a debate about the magnitude of the size of the blood-pressure difference but there was no question, I don't believe, about whether or not blood pressure was reduced or not.

DR. TEMPLE: But it was reduced in both groups.

DR. MacMAHON: Not to the same degree.

DR. TEMPLE: But not to the same degree. The end-of-day blood-pressure difference might have been 1 or 2 millimeters of mercury which didn't seem big enough to account for it. Certainly, the company's view is that this is not related only to blood pressure, that it has got some property of another kind.

But, then, I guess the 24-hour data suggest that the blood-pressure effect might have been bigger. I guess I didn't know how or whether that was considered resolved.

DR. MacMAHON: I guess it comes back to the issue, though, of when--what are the data you

wish to refer to as making the case that these agents, this range of classes, lower risk particularly when you get into the area of what does one class do. It would seem sort of artificial, if you are writing a paragraph about ACE inhibitors, then, to entirely restrict consideration to the head-to-head comparisons when, clearly, much of what we know about what ACE inhibitors do comes from placebo-controlled trials albeit in populations that are not exclusively defined by hypertension.

DR. PICKERING: I guess the issue is whether HOPE was considered a trial in hypertensive patients. I know some of them were but I think most of them weren't.

DR. TEMPLE: That is clearly why we didn't include it. It wasn't thought of as a hypertension trial. But I realize that has been debated and that people have said, if you look at 24-hour blood-pressure control, there is a huge difference and that could account for it. I guess I feel we don't know whether that accounts for it fully. It

might be some other property.

DR. MacMAHON: I guess it just comes back to the issue, though, that if you wanted to inform physicians and patients about what do ACE inhibitors do, then you wouldn't necessarily wish to restrict that only to hypertension.

Certainly, our approach in the Blood Pressure Trials collaboration is that the best information about what ACE inhibitors do in terms of protecting against cardiovascular disease is likely to come from a very broad range of studies and a broad range of patients. We certainly haven't been able to detect for any drug that there are distinctive differences in their effects in diabetics or non-diabetics patients with or without cardiovascular disease, patients with higher or lower blood pressures. I mean, all of the drugs pretty much do the same in a proportional sense in a whole range of subgroups.

DR. TEMPLE: To the hypertension endpoints.

DR. MacMAHON: To the cardiovascular

endpoints.

DR. TEMPLE: There is a mountain of data on ACE inhibitors in post-infarction people and heart failure. But we, at least, have not considered those hypertension claims. They are unloading claims or they are something, and they are really important and the drugs all have heart-failure claims. But we have not thought of those as hypertension studies up to now, although, conceivably lowering the blood pressure is part of the way they work--although not in ALLHAT, oddly.

That is a good thought. I guess the question back to you is which of those trials are persuasively really antihypertension trials that should be considered part of the relevant evidence? We don't doubt that those drugs work in hypertension but there is not a lot of placebo-controlled data that is a relatively pure hypertension trial because nobody would let you do those trials.

That is sort of why it was possible to even do the HOPE trial. Nobody would have let you

leave hypertensives untreated at the time that trial was done.

DR. PICKERING: I don't think that statement is actually inaccurate, is it? I mean, it says they share the same properties.

DR. TEMPLE: But it doesn't identify them as having placebo-controlled trials that show the properties. We can talk about it more but that is clearly because we didn't think of the HOPE study as a hypertension trial. But I realize that is debatable.

DR. TEERLINK: Do we want to just delete the "positively controlled" and just say "studies with recently developed drug classes."

DR. PICKERING: More recent studies.

DR. TEMPLE: Well, certainly, the bulk of the data on those things is and is going to be positive controlled studies. ALLHAT contributes. They didn't really define a noninferiority margin the way we all would have liked because it was a trial for superiority. But, nonetheless, it is pretty persuasive that there aren't major

differences except in heart failure.

DR. PICKERING: Okay. Can we go on to 2.6; the decrease in blood pressure is very likely to be responsible for these benefits because the outcome studies involve a wide variety of drug classes sharing few properties other than the effect on blood pressure.

I would possibly add, "and the beneficial effects appear to be more closely related to the fall of blood pressure than the drugs used to achieve it."

Any other comments?

DR. WARNER-STEVENSON: I would agree with the addition of that statement. I might think about deleting the phrase, "of sharing few properties other than." I mean, one could debate that a little bit. I am not sure that that adds a lot. I think the point is that the more the blood pressure goes down, the more the effect is with a lot of different classes.

DR. TEMPLE: It is actually a crucial part of the thinking process. The reason--tell us if

you don't agree with this, though--the reason we think, if you like, "It is the blood pressure, stupid," is that drugs that have nothing in common, nothing in common, all have the same effect when you use them in blood pressure.

Reserpine is utterly unrelated to a diuretic but they both work. Hydralazine, beta blockers--they all work which makes the argument that it isn't their mechanism, it isn't their other properties. The only thing they have in common is that they lower blood pressure. So that is at the heart of the logic of this, of saying that anything that lowers the blood pressure is going to be good.

So, in some sense, that is a relatively crucial statement to the whole comparatively unusual thing we are doing here. We are saying anything that lowers blood pressure is good for you, if it isn't bad for you.

DR. TEERLINK: So how about including saying, "involved a wide variety of drug classes with disparate mechanisms of action," because, sharing properties, sharing a few properties--I

don't know. I concur with Lynn's--I don't know.

DR. TEMPLE: That was captured, I think.

DR. TEERLINK: Is that more comfortable?

DR. WARNER-STEVENSON: Yes; I am much more comfortable that they have disparate mechanisms of action. There may be a lot of things that are kind of common about them that we don't necessarily know all of them.

DR. TEMPLE: But let's get the wording exactly here; "The decrease is very likely responsible because the outcome studies involved," and say what your substitute was, again?

DR. TEERLINK: "A wide variety of drug classes with disparate mechanisms of action."

DR. TEMPLE: Okay; and you think the public will understand that--no; I'm just kidding.

DR. TEERLINK: Well, you can--

DR. TEMPLE: No; I am just teasing.

DR. TEERLINK: It is that liberal-arts education.

DR. TEMPLE: That certainly captures it.

DR. MacMAHON: I just wonder whether it

might be best to say, "The decrease in blood pressure is very likely to be largely responsible for these benefits." There is a sort of sense--the statement, at the moment, says that it is exclusively, and that probably--I mean, one may wish to leave open the possibility that there are other characteristics of blood-pressure-lowering drugs that have some minor effect and there is probably better evidence now than there was previously about that.

DR. PICKERING: Can we go on to 2.7; the outcome studies all involve treatment regimens using more than one agent to control blood pressure so the data cannot unequivocally distinguish the contributions of individual drugs or classes.

I guess we would agree with that. Seems to be okay.

2.8; numerous single studies such as ALLHAT and pooled analyses have tested whether drugs given to achieve the same blood-pressure goals have the same clinical benefits. To date, such studies have not distinguished the effects of

different treatments on the major hypertension-related outcomes--strokes, myocardial infarction and cardiovascular mortality.

DR. FINDLAY: Well, the issue was raised earlier today of heart failure. I am not versed in the clinical issues there but, perhaps, you could speak to that and whether that is a major--that should be included in this statement. It is referenced right below and this is not the technical part of it, the guidance yet or the suggested labeling language. But, for what it is worth.

DR. TEMPLE: There is a reason heart failure isn't in there because some of the drugs unequivocally treat heart failure and some of them unequivocally don't. We don't know whether the differences that show up in trials represent failure to treat or actually making it worse.

Then there are peculiarities. Even in ALLHAT, a drug that has been thoroughly tested--well, not thoroughly tested but a member of a class that has been thoroughly

tested--lisinopril, really didn't look very good.

Who knows why that is. I think it is because every single ACE inhibitor trial was done on top of a diuretic and you couldn't a diuretic in ALLHAT because that the design didn't permit it.

So we are sort of staying away from heart failure. But the individual labeling will point out that certain calcium channel blockers are bad for heart failure, that the ACE inhibitors, some of them, have claims for heart failure. Diuretics are part of every heart-failure regimen although I don't know of any outcome studies with diuretics because no one would let you.

Anyway, that is why it is docked because we didn't identify it as the major outcome. But, of course, heart failure is a major consequence of having--

DR. FINDLAY: Right.

DR. TEMPLE: Maybe we should say more, that the drugs seemed to differ in their effects on heart failure. We could add that.

DR. WARNER-STEVENSON: I would really like

to include that because the way this is stated, "the major hypertension-related outcomes," it implies that that is all of them. I think heart failure is a major one. The fact that, unfortunately, there isn't a consistent answer I don't think makes it less important.

DR. STOCKBRIDGE: The very next few lines, 2.9, specifically mentions heart failure.

DR. WARNER-STEVENSON: No; I see that but I do think, in 2.8, it says, "the major hypertension-related outcomes--strokes, myocardial infarction and cardiovascular morality," heart failure would be considered a hypertension-related outcome.

DR. TEERLINK: If you got rid of the word "the" would you be more comfortable with it?

DR. WARNER-STEVENSON: Yes; I would be more comfortable--if you just want to delete "the," I can accept that.

DR. TEERLINK: I share your concern because hypertension used to be the number-one cause of heart failure until we started treating

heart failure.

DR. PORTMAN: The same with progression of kidney disease.

DR. TEERLINK: Exactly. And that was the slippery slope that I was--because I was waiting for you guys to jump in there.

DR. PORTMAN: I was poised.

DR. WARNER-STEVENSON: Okay; a simple deletion has solved this problem.

DR. PICKERING: I guess we are discussing 2.8 and 2.9 which are sort of related. But I agree this would be something about prevention of kidney disease not just-- progression of kidney disease not just diabetic nephropathy.

DR. PORTMAN: I would use the term "chronic kidney disease," CKD.

DR. TEMPLE: Are there good data on differential effects on kidney disease--other than Type II diabetes?

DR. PORTMAN: I can't quote you the specific articles, but there have been--there are good studies in chronic kidney disease. Ed Lewis

did a study and there are actually several others. I could get them for you.

DR. TEMPLE: That show differences of classes unrelated to their blood-pressure effects.

DR. PORTMAN: I think so. Again--

DR. TEMPLE: Nobody has come to us with a claim, to my knowledge, other than the diabetic case where there are several drugs that have claims

DR. KASKEL: There are numerous experimental studies where, even keeping the blood pressure constant, one class of drugs would prevent progression in the glomerulus and remit the proteinuria. So it is an unrelated effect of the blood pressure. Then, if you do have a blood-pressure-lowering effect, it is enhanced. That is what the ACE or the ARBs apparently--

DR. STOCKBRIDGE: I don't think we have a drug that has got a claim--

DR. TEMPLE: We absolutely don't.

DR. STOCKBRIDGE: --for chronic kidney disease so I am a little uncomfortable with adding that into that list there.

DR. PICKERING: You could say that, "Since these studies have not distinguished the effects of different treatments on outcomes," and just include progression of kidney disease in there. That would be a safe statement, wouldn't it?

DR. TEMPLE: Where would you put that?

DR. PICKERING: In 2.8.

DR. STOCKBRIDGE: Well, no; 2.8 enumerates the things we think the antihypertensive drugs do in general. 2.9 enumerates some things that not all antihypertensive drugs do. That is where I thought we were talking about putting chronic kidney disease and where I was suggesting that was not a good idea.

DR. KASKEL: I think that, with an epidemic that we now have, it is appropriate to say CKD and educate industry and the lay people and professionals about chronic kidney disease. That is the goal of NK-DEP, that it is an unrecognized epidemic.

DR. TEMPLE: But are there actual outcome data, not just experimental things no proteinuria,

but actual outcome data?

DR. KASKEL: Yes; Ramuzzi in Italy has at least two major studies showing in patients with CKD treatment of the blood pressure will effectively improve outcome. There are published data. Ramuzzi would be one of the biggest ones.

DR. TEERLINK: What was the outcome, though? I share your concern and belief that chronic kidney disease--certainly, as a heart-failure doctor, we are becoming renal doctors because of this issue of chronic renal disease and it clearly is a major epidemic, a major issue, that needs to be addressed from a public-health standpoint.

That being said, in terms of this document which is trying to enumerate the clinical data, the clinical-trial data, that has been proven to have effects of certain drugs within specific indications, I also am not aware, and you are more--this is more your stick--but, in terms of true outcome data, I am not aware of these trials showing benefits, differential benefits.

DR. TEMPLE: We are aware of things that may or may not have effects on proteinuria, things like that. But the outcomes we are looking for which have, up to now, been at a minimum, slowing the rate of decline of creatinine. I don't think we have seen anything that has come to us that we have had a chance to review.

DR. PICKERING: There is the ASK study, also, which showed that the ACE-inhibitor hand beta-blocker group did better in terms of progression of azotemia prevention than the calcium channel blocker.

DR. STOCKBRIDGE: But wouldn't you agree that, if you are going to name that as a property associated with some antihypertensive drugs, we ought to get one of them, at least, labeled with that claim? We don't have those now.

DR. PORTMAN: From a semantic standpoint, diabetic nephropathy is chronic kidney disease, okay--at least as defined by the National Kidney--

DR. TEMPLE: That's okay. We have that and that is, I think, listed as something where

some drugs seem to work better than others. We don't have any reservations about that. It is the non-diabetic nephropathy that has been a tougher nut to crack--not that there aren't hints

DR. KASKEL: I think it is significant enough that we should think about investigating it further with a group of experts on this possibly and getting a report to you. But it is significant in the community and it is an epidemic and practitioners are treating it with this class of drugs very aggressively.

DR. WARNER-STEVENSON: This is a small point to the rest of you but in 2.9 I would suggest deleting "various" and putting "other important endpoints." It currently says, "on various other endpoints." I would like to change that to "other important endpoints."

DR. TEMPLE: Okay.

DR. WARNER-STEVENSON: Because there are probably a lot of various ones that are not as important as those.

DR. FINDLAY: In 2.9, it might be worth

considering, at the very end, it says, "will often be a reasonable basis for deciding which drugs to use or to use first." Perhaps it would just telegraph it a little bit strongly, instead of the word "reasonable," to say, "important," or "very important." That is just for your consideration. That is wordsmithing. But I think it strikes us all that it is fundamental.

DR. TEMPLE: Okay.

DR. MacMAHON: Just with respect to 2.8, I should just remind the committee that the data that we presented last time did suggest that ACE inhibitors probably do have an effect on coronary disease which cannot be explained entirely by its blood-pressure effect.

Therefore, I wonder, rather than necessarily claim that, whether there is some way to soften it. I mean, at the moment, it says, "To date, such studies have not distinguished the effects of different treatments," which is, perhaps, too bold.

DR. TEMPLE: Well, 2.8 raises interesting

questions. There have been studies that suggested that beta blockers may not do as well on strokes, also.

DR. MacMAHON: Yes.

DR. TEMPLE: I think the view there was that that wasn't solid enough yet to assert but I can imagine there could be discussion of that. The example you have goes, perhaps, the other way. So is there some way to say that in a slightly weaker way?

DR. FINDLAY: You could say "not fully distinguished."

DR. TEMPLE: Or, "generally not distinguished," "not fully distinguished," because we do believe that all of them have a favorable effect on those outcomes.

DR. FINDLAY: Correct.

DR. TEMPLE: But maybe some are better. We are sitting there with numerous analyses that sort of make ACE inhibitors--make CCBs look better on stroke, too.

DR. MacMAHON: I think that is exactly the

right thing that--it is not the right wording but, qualitatively, that is correct. But it doesn't necessarily assume that quantitatively they are all the same.

DR. TEMPLE: Should one say "convincingly" or are you convinced already on the ACE-inhibitor one? It could say, "consistently," "convincingly." There are a lot of hedges.

DR. MacMAHON: I think "consistently" is reasonable.

DR. TEERLINK: We want to say that these all have been shown to have a beneficial effect but the effect size may differ among classes; right? "May."

DR. TEMPLE: They may, but I think the--well, there are these straws in the wind, you know. It depends on what you are looking for but, because of the blast that CCBs have taken over the years, I find it amusing that they can fairly consistently look better on stroke. You know, just my problem. And maybe ACE inhibitors are a little better on the M.I. thing. I don't know.

2.8 is obviously one of the more troublesome parts because they are straws in the wind even if they are not done yet.

DR. TEERLINK: We need a way to say that they are equal but some are more equal than others.

DR. TEMPLE: Yes; something like that. We could certainly say "generally not distinguished." That would be true. And then you could also say, "but it remains possible that, for some endpoints, some drug classes may ultimately prove to be advantageous."

DR. FINDLAY: Yes, but this is a guidance. This is not the suggested wording. There is no really restriction on length, per se.

DR. TEMPLE: No.

DR. FINDLAY: There is no prohibition for adding another two or three sentences here that would clarify, that would create the context of the nuanced differences in the data.

DR. TEMPLE: So, even following that, if we had said, "such studies have generally not distinguished the effects," blah, blah, blah, blah,

it could say, "there are pooled analyses and individual studies that, in some cases, have suggested differences but this remains to be evaluated further," or something like that.

DR. FINDLAY: Your choice of words, or whatever.

DR. TEERLINK: Something along those lines but with the idea, though, that you don't want to cut back on the statement that, hey, we really see beneficial effects from all of these groups.

DR. TEMPLE: Right.

DR. FINDLAY: On blood pressure.

DR. TEERLINK: And that there may be subtle differences between which specific events you--

DR. TEMPLE: Right; and, besides, almost anybody with anything serious is going to be on more than one drug anyway, so they will get the advantage of all of them.

DR. PICKERING: We are, actually, overdue for our break so I think, perhaps, we could interrupt now for fifteen minutes and then return

and have further discussions about beta blockers. Thank you.

(Break.)

DR. PICKERING: We are up to Question 2.10. We are obviously jumping around a bit with topics but we do have several items to get through. Blood pressure is one of numerous risk factors for cardiovascular disease and disease management should address all risk factors. Most outcome trials in hypertension preceded current lipid-lowering therapy or wide use of aspirin so formal measures of their interaction are unavailable. It is clear, however, that these other therapies are effective in patients who are and who are not receiving antihypertensive therapy.

One comment I would have here is that maybe this came out subsequently but the ASCOT lipid-lowering trial certainly did demonstrate the benefit of taking statin drugs in patients with otherwise uncomplicated hypertension. So maybe that statement could be modified.

DR. STOCKBRIDGE: So tell me exactly what

you would want to do.

DR. PICKERING: Well, you say formal measures of their interaction are unavailable. I think that the ASCOT trial really--

DR. STOCKBRIDGE: I see.

DR. PICKERING: Contradicts that. I mean, it does support the wider use of lipid-lowering drugs in hypertensive patients.

DR. STOCKBRIDGE: So, "often unavailable?"

DR. PICKERING: Yes. Do we have any other comments on Question 2.10? Apparently not. Okay. Let's go on to--

DR. PORTMAN: Actually, I do.

DR. PICKERING: Okay.

DR. PORTMAN: I don't know if it goes here or elsewhere, but I think there is clear proof that kidney disease, or chronic kidney disease, is a major risk factor for cardiovascular disease. So somewhere, I think, a statement for education purposes needs to be made that early identification and treatment of renal disease is an important prevention for cardiovascular disease.

DR. PICKERING: I would underline that on the grounds that end-stage renal disease is still increasing and uncontrolled hypertension and, I guess, diabetes are the two major risk factors for that.

DR. PORTMAN: Correct.

DR. PICKERING: Moving on to 2.11; patients whose risk for cardiovascular events is high for reasons other than blood pressure, particularly patients with diabetes, receive a disproportionately larger absolute risk reduction per millimeter of blood-pressure reduction than patients without such additional risk factors. Therefore, the treatment goal for blood pressure should be lower in such high-risk patients.

My comment on that is that it is sort of two separate things. The greater slope, I don't think, necessarily, implies the lower threshold but I agree there is evidence for a lower treatment threshold for diabetes.

Dr. MacMahon, do you want to comment on that?

DR. MacMAHON: Yes; I would agree that they are sort of two separate points, the threshold and the size of the benefit. I think this goes to addressing the point that I was making earlier and I guess one question would be whether or not this could be moved up to sort of balance the earlier focus on the level of blood pressure.

But the only comment I would make is that you have got particularly patients with diabetes but, in fact, it could be extended to particularly patients with diabetes melitis or a history of stroke or coronary heart disease, both of which have been shown to benefit, in terms of cardiovascular events, to a larger degree than uncomplicated hypertension.

DR. PICKERING: Thank you. Anybody else? Okay. 2.12; what is missing from the background and discussion? Are there additional caveats or principles that should be included? I think one issue which some of us are concerned with is that these blanket recommendations should not be interpreted as meaning that companies with drugs

that don't have outcome data or drugs from new classes should be given sort of a free ride and have any disincentive to do outcome studies.

I know Dr. Teerlink would like to comment on that and I think, after that, we could have another public session because I think two of the committee members who are not on the committee this morning would also like to talk as members of the public.

DR. TEERLINK: I have been trying to figure out where the right place to fit this in was. So this seems to be it. I mean, obviously, the class labeling seems to try to balance two competing desires. One is to have this educational informative aspect of the labeling. But, secondly, we still need to preserve the responsibility of the FDA to ensure the safety and efficacy of drugs within these labels.

Part of the question is, well, how is this label actually going to be applied. I have great concern that a company might be able to present a trial in a relatively small number of patients that

just lowered blood pressure and say, okay, we should get this global labeling without having a satisfactory safety database.

So I understand the concept of lowering blood pressure is good. But, in addition, we need to make sure that the application of this label doesn't ignore other potential safety concerns that would possibly mitigate these positive effects on outcomes.

I know that is implied but I just wanted to make sure that that is made very explicit here in terms of my feelings in regards to this. I don't know how other committee members feel.

DR. TEMPLE: I guess I want to hear more about what you mean. A typical antihypertensive now to be marketed will have exposure in somewhere between 2-and-a-half and 3,000 people. That is what a new ACE inhibitor would do, presumably what a new drug of a new class would do. We would be looking for toxicity, obviously. There would be a certain amount of long-term data given that these drugs are intended for very long-term use.

There would be a demand for a reasonable amount of long-term data but I don't have any illusions the drug doesn't have a 10,000-patient-per-group comparison with anything. And I guess I hasten to add that the first angiotensin receptor blocker didn't have a database like that either nor did the first ACE inhibitor, although it was pretty big.

Say more. Or are you saying that maybe there should be something in that that says the experience with this drug in long-term use is limited or something. How do you want to manifest that? I understand the desire, once you think you have got a bunch of good drugs, not to mess it up. But, as an approval standard, where we would also worry about removing any incentive to develop a new drug, which seems to me new drugs are needed--I don't think we really have a lot of blood-pressure drugs even though it looks like there are a lot. They are all the same.

Say more.

DR. TEERLINK: I am not sure I am

proposing, necessarily, anything new compared to what I already consider to be a reasonable approval standard except, because I think four completely new classes of drugs, which we will be seeing coming down the pike, we need, as with all drugs, long-term safety data that gives us fair confidence that those long-term safety concerns are addressed.

It will depend on the agent, itself, obviously. There are some mechanisms of action, some biologic effects, that seem to raise more concerns than others. If they are an extension of already known mechanisms, then you need to look at kind of the biologic correlates to those effects.

If it is a completely new mechanism with which we have no experience, then I think that has a higher safety bar. We need to have longer-term safety data because we just don't know what these entities do when they affect whatever system it is that it affects in the long term. These are long-term trials.

Patients are on hypertensive therapy for the rest of their lives. So I think there would be

a different safety standard for those and I think that is consistent with what we usually do. I just don't want to--or I think it should be consistent with what is done.

DR. TEMPLE: Well, it depends on what you mean. The drugs that we are familiar with have studies going three, four, five, six years. They have collectively the capacity to find the most infinitesimal differences, and although the differences happen to go one way or the other from one study to another, they really do rule out major differences.

No new drug has data like that unless we impose a particular standard on it. We do that if there is a hint of a problem. Everybody knows that, because of concern about angioedema, omapatrilat was subjected to a not terribly long-term but long-enough 25,000-patient study. So you would certainly do that.

But I guess my question back to you is, in the absence of anything that looks funny, do you need what? An outcome study before approval or as

a condition of approval? We would probably bring these things to the committee for further discussion. But I can tell you what is--I am worried about removing any incentive to do it which, I think, is a problem and trying to fit it into the usual pattern.

Obviously, you can always say that when you are adding something new to the armamentarium, you are grabbing part of the unknown. That is invariably true and, as we have seen, sometimes these things come out in ways you don't expect.

The other thing that impresses me, you usually don't know what questions to ask until something turns up. So that is part of the problem; you have to decide on what population to do it in.

But I guess I would say, at this point, we note your concern and need to think about it but probably this should be manifested as each new drug comes by. I would say a new class of antihypertensive is almost surely going to go to the committee for review, and to consider that

question.

Norm?

DR. STOCKBRIDGE: That is not so easy, as you perfectly well know. We have a first-of-class drug under review right now. I may or may not be able to get it to a committee meeting. So it is not so clear it will come here. It will presumably have about the same kind of safety data that other recently approved drugs have to support it.

I think the expectation is that when we are ready to label drugs for outcome claims here, this drug will get a claim. It won't wait for studies yet to be done and we won't be relying much on the post-marketing data to assure us that this is a good decision.

DR. TEMPLE: Probably it is worth hearing some more discussion. It is possible for us to ask for additional studies after marketing. There is some debate about whether we can enforce that reliably. But I think it depends a little on how you write it and what you say. But, assuming that companies will behave properly when they agree to

something, that is certainly a possibility.

Asking for a four-year outcome study prior to approval would be a very big step. There are other things to think about which is to say that, in general, this should be reserved for other people, for people who don't respond to the others, a very onerous requirement for somebody hoping to become part of the hypertension game and something we usually reserve if we are worried specifically about something. Then, without hesitation, we would do that.

So a little more discussion here is probably in order. I would be interested in hearing other views.

DR. WARNER-STEVENSON: The precedent here seems to be that we are talking about assuming outcome benefits when we see an early surrogate. Certainly, we all recognize that blood-pressure lowering is a very acceptable surrogate. But the new step is to say, so we are assuming the outcome benefits for anything that meets this surrogate.

It seems to me, along with what John said,

that it would be appropriate to indicate that this does not mean that we will assume that the same outcome benefits would pertain to any new drug that reaches this same surrogate necessarily and that that would have to be examined on a case-by-case basis.

DR. TEMPLE: But the whole logic of what we are doing here says that, indeed, we would. That is why it says things like drugs as different as reserpine, beta blockers, ACE inhibitors, and all these things have had positive results. That is another way of saying, it is the blood-pressure lowering.

Now, that never means that it won't do something terrible to bite you. The best surrogate in the world will be undermined by an adverse effect of the drug. We have long accepted blood-pressure lowering as a surrogate which means we always believed that it would lead to a favorable outcome. But the labeling never said so.

But we must have believed that. Otherwise, we wouldn't have been responsible to

approve the drugs. So we always believed it.

I have to say this whole thing implies that we would believe it also about a new drug. Now, that doesn't mean you know everything you want to know about long-term safety. That is a totally different question.

DR. WARNER-STEVENSON: I think we would believe it if there are no other effects. But there could certainly be other effects that would affect the same outcomes we are talking about. There could be effects on coagulation that would affect M.I.--

DR. TEMPLE: Also true.

DR. WARNER-STEVENSON: --stroke, et cetera. So I think we can't assume the same outcome benefits would apply if there were some other unrecognized effect.

DR. STOCKBRIDGE: I think what Bob was saying was that, if we suspected somebody had adverse effects that would outweigh the expected benefits of lowering the blood pressure, we wouldn't have approved it.

DR. TEMPLE: Or would have asked for a long-term outcome study. It is in the absence of anything that points that finger although the logic of this is that we would believe that this drug--I mean, first of all, the logic of approving drugs that lower blood pressure is that you believe they are going to have favorable effects. Otherwise, why would you do it? It is not good for you to have your blood pressure lowered unless it corresponds to a better outcome.

What we are proposing here is put in labeling the conclusions that are the basis, actually, for relying on that surrogate about which labeling has been silent up to now. But I think an implication is that it applies to a new member of a drug. It can't rule out some safety thing that you haven't watched long enough to know about.

But it means that, other things being equal and no problems and no agranular cytosis and no liver injury, blah, blah, blah, we expect it to have the usual effects on those major outcomes.

DR. TEERLINK: Not to be problematic here,

but I think the original goal that I saw for this was to try to expand the use of agents that are already there that we think have the benefits that evolved in a time, kind of in parallel structure and where you see mechanisms of action that overlap, so within ACE inhibitors, within beta blockers, that kind of raise all ships to this outcomes level.

The jump that we are making, I am not sure why we want to expand it to new therapies because is it just to make it easy for the pharmaceutical companies to develop new drugs? We have been saying, hey, we have this need. But if we have shown that these agents already reduce outcomes, why do we need any new drugs unless they can be shown to reduce outcomes better or have better effects on side effects.

So I am not sure that we should extend this beneficial outcome to "me, too" things that don't have any demonstrated additional benefit.

DR. TEMPLE: First of all, you don't have outcome data on a large fraction of the drugs that

we approve and you are never going to get any.

DR. TEERLINK: But we do have within those classes.

DR. TEMPLE: Some of them. Not a lot of ARB data, for example. I mean, you have some conspicuous things that it does to but there is not of big outcome studies with those drugs because they were post-ALLHAT. That is sort of the last big outcome study.

What I would say is that it is an attempt to be candid about the reasons we approve drugs on the basis of lowering blood pressure. I suppose if we really thought that everything is hunky-dory and there is no need for anything else, we would say we are not going to approve any more drugs for long-term use unless you do the outcome study up-front.

One could do that. My concern would be that it would probably obliterate the desire to ever have any more drugs. Since I don't think there are enough drugs to treat people the way we now think they should be treated, that strikes me

as not a good thing. But, obviously, that is a matter that people could discuss.

DR. PICKERING: I would like to ask Dr. Hiatt and Dr. Flack if they would like to make public statements related to this at this time.

Open Public Hearing

DR. HIATT: I am William Hiatt from the University of Colorado and was excused from the morning session. So I just want to clarify if it is okay to make a comment. If so, I think this is the crux issue of the discussion. I think historically it is clear that these drugs were approved to treat a surrogate endpoint and that subsequently, with event-drive trials, we have learned that they were good for you to lower blood pressure.

The endpoint of interest has been clearly M.I., stroke and death. What I am not comfortable assuming is that a novel new class of drug would confer the same benefit. So the question, I think, really is whether you need to do a new event-driven trial to approve a new drug in a novel class or not

beyond just the safety concern.

The issue, I think, is significant because if you achieve a blood-pressure endpoint in a relatively low-risk hypertensive population, even if you study 2,000 patients, you won't gather enough M.I., strokes and death to ever have confidence in your point estimate of whether that is favorably going in one direction or another.

It could even, in fact, be adverse and you really wouldn't know that. So you are going to then approve a novel, new drug and the new class for which you will have no confidence about the point estimate around the benefit of M.I., stroke and death but it will achieve that labeling and not just blood-pressure-control labeling, because of the history we learned today.

I think we are very confident that current drug classes have this benefit although my concern is a little bit that alpha blockers really share that. Generally, the data today would support that for the currently classes but a really novel new drug that might be very good at lowering blood

pressure might have significant cardiovascular effects that you wouldn't know about until you exposed enough people.

So I think there must be some way to address that issue and maybe the answer is not event-drive trials that destroy the development of new drugs but maybe the answer is to gather enough data in high enough risk populations with the drug to satisfy yourself that at least the point estimate is going in the right direction.

Maybe that would be some kind of compromise where you might know that at least it is behaving the way you think it should to allow a novel new drug to receive a label of cardiovascular benefit without actually showing it.

DR. PICKERING: Thank you.

Dr. Flack?

DR. FLACK: John Flack. I was excused this morning so I am commenting as a normal citizen. I certainly support the notion that the FDA has put forward to be able to try to more explicitly link benefits across a range of drugs

that lower blood pressure appear to be within a reasonable range, and that is reducing things like stroke, cardiovascular events and, to some degree, myocardial infarction.

I would also, though, echo the concern about leaving heart failure out. That is a very pressure-sensitive complication and responds very nicely to blood pressure. I would offer the advice that we probably ought to look at primary and secondary prevention differently. Drugs like ACE inhibitors, for example, don't prevent heart failure as well as diuretics yet they are clear treatments and very effective in reduced risk once you develop heart failure, at least on top of diuretics.

So I would separate those out. I think even secondary stroke prevention is starting to show some data that maybe some of the drugs that are really good for primary stroke prevention may be not as good as secondary stroke prevention.

The issue of diabetic nephropathy is also something I would like to comment on and that is if

we actually look at what we are trying to prevent in people with diabetes, it is not just progressive kidney disease. I think what tends to happen, when you get a disease like diabetes, chronic kidney disease, is we develop sort of a nephrocentric view of what we are trying to prevent.

But if you actually look at what these people die of, the majority of what they die of are non-renal cardiovascular events. So you go back to trials like IDNT and you find that proteinuria is reduced more with herbasartin, that progressive renal failure and progressive loss of kidney function reduce better there but it doesn't do as well, for example, as the calcium channel blocker on M.I. and stroke prevention.

So I think those things at least have to be balanced and not just focused in on the kidney even though it was "a diabetic nephropathy trial."

I don't know of any real convincing evidence that lowering blood pressure is not good. So I would have no problem with a basic claim being able to be made, even with newer agents, that, if

you lower blood pressure, you at least can make a claim that it is likely you are going to reduce stroke, et cetera.

Hopefully, there is enough study that has been done with an agent before it gets to that point that you have some idea through some signal that this may not be true. I think that we have to trust our testing process to do that. But, I think, over and above the basic claim that you can't allow a drug to do that unless you get firm endpoint data.

But I don't see any real reason not to because, of all the trials we have done, by and large, you get risk reduction although it is to some greater or lesser degree with some of the agents.

I would take a little bit of issue with the notion that all these drugs lower risk the same. If you go to pooled data, the calcium blockers do a little bit better than diuretics. They are both excellent stroke drugs. But there is some pooled data there. The notion that in

non-diabetic nephropathy, we don't know what to do, there are some pooled data by Jaffee and others looking at renal endpoints that include mortality and it is very clear that the ACE inhibitor there is better than a non-ACE-inhibitor regimen. Paradoxically, in diabetic nephropathy, all the data is with ARBs.

So, again, I would just like to say that I support the notion of the basic labeling and I would include newer drugs in that. I feel very comfortable that a lot of this is linked to blood-pressure lowering and/or things that change in parallel with blood-pressure lowering that some we measure and some we don't.

DR. PICKERING: Thank you. This closes the public hearing. I think we should move on with the questions because we only have a limited amount of time left.

Questions to the Committee (Continued)

DR. PICKERING: Perhaps we could go on to Question 3; please comment on specific sections of the proposed Clinical Trials section of labeling as

reproduced below. 3.1; high systolic or diastolic pressure causes increased cardiovascular risk and the risk increase per millimeter of mercury is greater at higher pressures. I guess we discussed this before.

DR. PORTMAN: Tom, before we leave this--I'm sorry; I hate to set you back. I had my hand up as you were reading. I have two issues before we leave Section 2. One is whether or not we should make a statement about pediatrics in that statement, something related to the fact that hypertensive trials in children and adolescents are in progress and, in general, show similar antihypertensive effects. However, long-term beneficial effects on outcome have yet to be established, something along those lines.

I think it would be important to make a comment, an educational comment, that that is being done and where we are with that. Any comment about that?

DR. TEMPLE: Does one actually expect outcome effects that soon in a pediatric

population?

DR. PORTMAN: It depends. Again, our outcome is different than adults. You are not going to see effects on myocardial infarction because kids don't have myocardial infarction. But if we consider things such as left ventricular hypertrophy or microalbuminuria as surrogate endpoints, then, yes, we hope to be able to demonstrate beneficial effects there.

It hasn't been done yet but those studies are in progress with Norm's help.

DR. TEMPLE: I think we would be reluctant to say much before the data come along but afterward it would seem to be part of the general spirit of this if there were a consistent finding to add that.

DR. PORTMAN: Right.

DR. TEMPLE: Of course, one of the things we haven't gotten into at all is things like effects of all of these drugs on left ventricular hypertrophy and stuff like that probably readily documented. But they didn't seem as big as the

stroke, heart attack and death. So we didn't go to those.

DR. STOCKBRIDGE: But your suggestion about saying we don't know what happens with outcomes was really meant to incentivize people to do such trials.

DR. PORTMAN: Yes; correct. The other is a clarification statement and I just want to make sure I have got this right. So, in looking at the chronic kidney disease, nondiabetic chronic-kidney-disease issue, what you are saying is that the data hasn't been presented to the agency to suggest that one class of drugs or another is superior in prevention of progression of renal disease, for instance.

I mean, you are not familiar with that. I am referring, again, back to 2.9 where we talk about the selection of drugs, hypertensives for diabetic nephropathy but it doesn't mention nondiabetic kidney disease. You contend that that data has not been presented to you.

DR. STOCKBRIDGE: There is no drug with

that claim.

DR. PORTMAN: Okay. Thank you.

DR. PICKERING: If we could go back to 3.1 which is up there. My only comment is that I think we have already said that.

DR. STOCKBRIDGE: To be clear, Section 3 is different from Section 2. Section 2 was the background part of the guidance. These are paragraphs that are really intended--they are part of the guidance but they are also intended to be literally put into the label.

DR. PICKERING: Ron, do you have a comment?

DR. PORTMAN: No.

DR. PICKERING: Anybody else? Yes; Dr. MacMahon?

DR. MacMAHON: It is really just the comment that I made before that I think, whilst there are some very, very specific instances where this is correct, I think you are deriving the emphasis too much towards the importance of blood pressure and the importance of blood-pressure

reduction being directly related to the level of blood pressure when I think, certainly, if you look at the Guidelines Committee around the world including, although to a lesser degree JNC, the emphasis has been to try to get away from the level of blood pressure as being the primary determinant of benefit and to have a more holistic assessment of absolute risk.

That is true epidemiologically and it is true therapeutically. My own suggestion would be to move away from this sort of emphasis, if you can.

DR. TEERLINK: How about if it says how systolic or diastolic pressures contribute to increased cardiovascular risk and risk increases.

DR. MacMAHON: Look; I don't think there is any problem--

DR. TEMPLE: But it is an independent risk factor.

DR. MacMAHON: Sure. I don't think there is any issue about that. It is the bit that says the risk increase per millimeter of mercury is

greater at higher blood pressures.

DR. TEMPLE: How about if one added, as we talked about before, for people at any given risk--or that is not right; for people--well, we need to work on it.

DR. MacMAHON: The is question is why you want to emphasize that.

DR. TEMPLE: Because higher blood pressure--for any given person, higher blood pressure is bad.

DR. MacMAHON: That's true.

DR. TEMPLE: The higher it is, the worse you are.

DR. STOCKBRIDGE: I think the reason to emphasize it was if you have somebody with high blood pressure whom you actually can't control very well, it is still worth making an effort. And the higher the blood pressure is, the more it is worth making a few millimeters worth of effort.

DR. MacMAHON: Absolutely. That's true. The problem with that is, though, that that continues to emphasize that, if you like, the

greatest benefits are going to be at the highest blood pressures. That, I don't think, is true.

In diabetics and patients with cerebrovascular disease and a bunch of high-risk people, you can get big benefits at much lower levels.

DR. STOCKBRIDGE: Okay; right. But the only reason why you think it is not true is that you think other risk factors contribute more.

DR. MacMAHON: Correct.

DR. STOCKBRIDGE: We can certainly put something in that says that somebody's highest risk may not be attributable to blood pressure.

DR. MacMAHON: Correct.

DR. STOCKBRIDGE: Okay.

DR. PICKERING: Lynn has a comment about this.

DR. WARNER-STEVENSON: It looks to me that much of this is covered by 3.6 and maybe what we need to do is just to move that up to follow 3.1.

DR. PICKERING: That sounds reasonable. 3.2; numerous drugs from a variety of

pharmacological classes whose only common property is to reduce blood pressure have been shown to reduce cardiovascular morbidity and mortality and it can be concluded that the blood-pressure reduction is responsible for those benefits.

Again, I guess we had some of this discussion before.

DR. STOCKBRIDGE: Rather than have you re-edit that part, I think we can absorb the comments you made on 2.9 there, if that is okay.

DR. PICKERING: Okay. That, I think, would apply also to 3.3, wouldn't it, because we talked about that also.

DR. STOCKBRIDGE: Yes; that's true.

DR. PICKERING: 3.4, I think we haven't talked about; some antihypertensive agents have smaller blood-pressure effect as monotherapy in blacks and many antihypertensive agents have additional effects on angina, heart failure or diabetic kidney disease, for example, and these conditions may guide selection therapy.

Comment on the ethnic differences? I

think, as was mentioned yesterday, while there may be quantitative small differences in the response rate in different ethnic groups, there is such a bit overlap which is probably of relatively minor consequence.

DR. TEMPLE: Is that actually--I mean, we have, for a long time, insisted that people analyze data by demographic and subsets. With very few exceptions, there has been a consistently small, or sometimes very small, effect of ACE inhibitors and ARB in self-identified black populations.

Now, what always impressed me is that if you look at the combination of a diuretic with these drugs, it is all the same. That has been studied by the V.A. 30 years ago. Maybe that is something that everybody should note, too. But, as a single drug, it does seem to be quite a different effect with the effect being like 2 millimeters, on average, or something, pretty small in some people.

That seems moderately important as, for example, a choice of initial therapy. But it is true, there is overlap. There are people in each

population who get very good responses. That is certainly true, too.

But you think this is overemphasized?

DR. PICKERING: I guess it is a question of interpretation. I think the danger is that people say these drugs don't work in this particular group so we won't start it. I agree that, with the combination therapy, the differences absolutely disappear when you use them in combination with a diuretic.

DR. WARNER-STEVENSON: I think the order of wording and the choice of wording becomes absolutely critical here. I wouldn't want to start out a sentence with, "Some agents have smaller effects in blacks." I think that is needlessly negative. Perhaps what we want to say is, "Considerations that may guide selection of therapy include greater efficacy of some therapies compared to others in the African-American population.

I think I want to emphasize that some may be better not that some may be worse, which is the flip side of something. But we don't want that

sentence taken out of context.

DR. TEERLINK: I strongly support that approach.

DR. PICKERING: I agree. Do we have any other comments on 3.4?

DR. FINDLAY: Yes; just one. Would it be inappropriate to--instead of the wording "may guide selection of therapy," is it inappropriate or too strong to say "should?" That is what I had written here.

DR. STOCKBRIDGE: Of course, there are other things that are going to be factors that people think--

DR. PICKERING: You might refer to JNC7 here because they have a table with all this with recommendations.

DR. STOCKBRIDGE: And we do, eventually, even mention JNC7. But there will be things like economic factors that we can't even mention here.

DR. FINDLAY: And you are into the suggested language of the labeling which I realize constrains the number of words.

DR. PICKERING: Any more on 3.4? 3.5; many patients will require more than one drug to achieve blood-pressure goals. But the cardiovascular risks increase steeply with increased blood pressure so that even modest reductions of severe hypertension can provide substantial benefit.

My own feeling about this is that combination therapy, particularly with diuretics, should be encouraged. I know many of the combination drugs are not approved as first-line therapy but I think the increasing trend is to use--for instance, starting off patients with a low-dose ACE inhibitor and diuretic or low-dose ARB and diuretic is something that is beneficial.

DR. WARNER-STEVENSON: I agree with both these statements but it is not clear to me why they are put in the same sentence.

DR. FINDLAY: I concur with that. I wrote down, "non sequitur," and they don't necessarily follow.

DR. TEMPLE: I had the same comment as I

read it again. There is a certain disconnect in here. So we need to work on that. I think the point that we wanted to make was that, even if you don't get all the way, it is worth lowering it some. But that doesn't really relate immediately to the fact that you may need more than one drug. So I think that one needs thought.

DR. PICKERING: Steve, do you want to comment?

DR. MacMAHON: I guess the emphasis on part of this has been that even small blood-pressure reductions can be beneficial, which is important. But what is missing is maybe an emphasis that larger blood-pressure reductions confer larger benefits for which there is now unequivocal evidence.

DR. PICKERING: Thank you. Any other comments on 3.5?

DR. TEMPLE: What I heard you saying is that you think what it really ought to say is you may need more than one drug; do it--which is somewhat different. It seems absolutely right,

especially with the new blood-pressure goals for diabetics and stuff. Probably most people are going to need more than one.

DR. STOCKBRIDGE: We also got a specific recommendation that we should say, use diuretics early. Are you okay with that? That is sort of promoting one of various first-line classes.

DR. TEMPLE: Well, JNC7 certainly doesn't go all the way and say that that should be your first drug. I think we are short of that.

DR. TEERLINK: They don't?

DR. TEMPLE: No.

DR. TEERLINK: I would stay clear of recommending specific drug classes as well, just given the spirit of this document. Once again, there is JNC7. There are lots of other organizations to do that.

DR. TEMPLE: So I don't think we intended to recommend a particular drug as first-line. Part of the reason is, in one of the previous sentences, that there are pros and cons of various drugs for various things and you have got to decide.

DR. FINDLAY: So it wouldn't be appropriate anywhere to even hint at, in the population of patients who only have high blood pressure, with no other complicating illness, condition, disease, that monotherapy with diuretics is probably your first choice. There wouldn't be a way that we could get that in. It is not appropriate even though I think we all agree with that.

DR. TEMPLE: If the main reason is economic, we like to say that that is not our business.

DR. FINDLAY: That's right. I am not suggesting that we would state on the basis of--is it something that we clinically all believe? Not necessarily.

DR. TEMPLE: I am not sure everybody does believe that.

DR. FINDLAY: Okay.

DR. TEMPLE: There may be subtle advantages on kidney disease for some of the others--

DR. FINDLAY: The answer to that is no.

DR. TEMPLE: Right. But I must say my view is you are probably going to get the diuretic as the first or second and it makes a lot of sense probably to start with two drugs. But that is a different question.

DR. FINDLAY: Yes.

DR. TEMPLE: Just so you know, we have given--I don't know whether it is only one or more than one, drug, a combination first-line therapy for two reasons--three, but one of them doesn't matter. Ziac has a first-line therapy because the very lowest dose, 6.25 of hydrochlorothiazide and 2.5 of bisoprolol, had almost the same effect as the full dose of the bisoprolol at 40 milligrams and no side effects to speak of. It didn't change anything.

That seemed like a sensible thing for some people. At least that was one. We have also given another, but I don't remember what, first-line therapy in people with blood pressure over a certain level because they showed convincingly that

very few people were brought to goal by a single drug. So that is the second one.

Obviously, a lot of drugs could get that--a lot of combinations could get that claim.

DR. PICKERING: You mean a single pill.

DR. TEMPLE: That neither component alone got an appreciable fraction of people to goal. I forget, were they over 105, or whatever they were. Almost everybody needed two drugs so that is another first therapy claim. Of course, people can combine things on their own without it being in a fixed-dose combination.

DR. PICKERING: Okay. I guess we can go onto 3.6; relative-risk reduction from blood-pressure reduction is similar across populations with varying absolute risk so the absolute benefit is greater in patients like diabetics at higher risk independent of their hypertension and such patients will benefit from more aggressive treatment to a lower blood-pressure goal.

Again, I guess we sort of had this

discussion.

DR. TEMPLE: And it was suggested we move it up nearer to 3.1.

DR. PICKERING: So perhaps we could move on to 3.7; control of blood pressure should be part of comprehensive cardiovascular risk management including lipid control, diabetes management, appropriate use of aspirin, smoking cessation and exercise.

DR. PORTMAN: Once again, as we discussed in the previous section, I would add in the identification and treatment of chronic kidney disease.

DR. FINDLAY: And weight reduction and dietary modification.

DR. PICKERING: So we do say something about lifestyle.

DR. STOCKBRIDGE: Are there trials that show benefits of weight reduction?

DR. TEMPLE: On blood pressure.

DR. PICKERING: Yes; Dr. MacMahon, I think, did a trial. Didn't you do one showing that

it reduced left ventricular hypertrophy many years ago?

DR. MacMAHON: Yes.

DR. TEMPLE: And, also, since we believe blood pressure is the thing, you definitely lower blood pressure by losing weight. I mean, that is clear. I don't know whether you can get people who have trouble affording their drugs to eat a lot of green vegetables, which, as anybody who buys--who does the home shopping knows, are quite pricey. But maybe.

DR. PICKERING: Okay. Can we progress to 3.8; for specific advice on goals and management, see published guidelines such as those of the National High Blood Pressure Education Program, JNC7. I think we are all agreed about that.

DR. TEMPLE: Just to be clear. So this is, obviously, the not very lengthy brief discussion of why it is good to lower blood pressure. So if you think there is something grossly missing, now is the time to say it because then we are getting to the drug class or

drug-specific data. So this is the overall statement; it is good to treat and here is why.

DR. PICKERING: Now we get more specific. 3.9; there follows an opportunity to describe outcome trials involving the specific drug being labeled. In the absence of such data, one is supposed to insert one of the following. There are no studies of DRUGNAME of members of drug class demonstrating reductions in cardiovascular risk in patients with hypertension or there are no studies of DRUGNAME demonstrating reduction of risk in patients with hypertension but at least one pharmacologically similar drug has demonstrated such benefits.

Comments about that? I mean, it seems reasonable to me. Everybody is happy with that by the looks of it. Okay. 3.10; what is missing from the Clinical Trials section of labeling? Are there additional caveats or principles that should be included?

DR. WARNER-STEVENSON: I would like to suggest that right up in the up-front,

hit-em-in-the-face, of the reasons that we want to do this, that we would also include the fact that hypertension is associated with heart failure and chronic kidney disease. Even though we don't way that the therapy includes that, I think it is important, if we are trying to scare patients into paying attention, that they understand the bad things that are associated with hypertension.

That comes out as a relatively minor factor, right now, under additional considerations. I think we want to start out with, "High blood pressure is associated with increases in heart attack, stroke, death and development of heart failure and chronic kidney disease."

DR. STOCKBRIDGE: Even though we are not ready to say we think these drugs help with that.

DR. WARNER-STEVENSON: Then you move on very specifically to delineate what they are helpful for. I think all of us are thinking, again, about what the patient sees when he goes to read this and thinks, okay, why should I even take my blood pressure seriously. It is because

hypertension is a serious disease with serious outcomes and these are what they are.

DR. TEERLINK: I would agree with that. If you could have a 3.01.

DR. TEMPLE: It sounds like, one, you think that it ought to be mentioned that heart failure is a common outcome.

DR. WARNER-STEVENSON: And kidney disease, in deference to our colleagues.

DR. PORTMAN: It is true, not in deference.

DR. WARNER-STEVENSON: Right, but I am saying in deference.

DR. TEMPLE: Okay. So heart failure and kidney disease are also consequences, and then somehow say that the effects of various drugs--I mean, after saying that all of them seem to lower the heart attack, stroke and cardiovascular survival, say something that is it not as clear that all drugs are similar in their effects on heart failure and you sort of have to look at each specific drug--heart failure and kidney disease,

maybe--and that you need to look at each specific drug.

So that flags it as a consequence and says you should worry about it and also says that the drugs could differ. Is that sort of what you had in mind? We, obviously, have to write this part.

DR. WARNER-STEVENSON: Yes. I think you want to start out very strongly because that is what we want patients to see before they get to the 79 adverse effects of the drug they are taking.

DR. TEMPLE: In some ways, that is an important distinction. That is why you might choose one drug over another and is why you might want to more often start with a diuretic which seems to help that.

DR. FINDLAY: Are you proposing that as a--where would that go, for clarification?

DR. WARNER-STEVENSON: Right at the beginning of why hypertension is important and why we--

DR. FINDLAY: At the beginning of the guidance or the beginning of the actual suggested

labeling language.

DR. TEERLINK: I put it 3.0.1, here. Is that consistent with what you are saying, Lynn?

DR. WARNER-STEVENSON: Yes.

DR. FINDLAY: I agree.

DR. STOCKBRIDGE: Okay. So, following that, maybe would be what is now 3.7 which includes the sort of comprehensive risk-management business. Maybe that has aspects of it that address some of these things we don't think the drugs may do.

Then, 3.8--then what is now 3.1? Is that where we are going?

DR. TEMPLE: I thought there was something about earmarking kidney disease and heart failure as critical features of hypertensive cardiovascular and all that and then, after saying that all of the drugs from a variety of classes have favorable effects on stroke, heart attack and cardiovascular outcome, adding something that says, "the consistency of effects on heart failure and its consequences is not as clearly related solely to blood-pressure control and appears to differ from

one antihypertensive to another."

Maybe that is equally true for kidney disease.

DR. PICKERING: JNC7 have, right up front, a statement about heart failure and kidney disease as two complications where the incidence is increasing. It also talks about the risk reduction related to--of heart failure related to treating hypertension which I think they said was 50 percent reduction.

DR. TEMPLE: So what I said is not entirely what people would agree with, then. They would probably say that you probably--well, but the trouble is there isn't going to be data on this--you probably get an improvement from lowering blood pressure but drugs also differ among themselves by how well they either prevent or treat the disease.

I think we will have to try to come up with language about that. Do you all think there is enough data to say that every antihypertensive drug probably has a beneficial effect on heart failure but that some just have more?

DR. WARNER-STEVENSON: No.

DR. TEMPLE: So just lowering the blood pressure doesn't, by itself, improve heart failure?

DR. WARNER-STEVENSON: Not if you have a class of drugs that increases fluid retention so that it balances it out.

DR. TEERLINK: I agree.

DR. PICKERING: One issue that I would like to discuss is what, if anything, we are going to say about beta blockers in light of the recent meta-analyses that have suggested that beta blockers, in general, and atenolol, in particular, are less good than other antihypertensive drugs, particularly--well, I guess diuretics at preventing morbid events even though they lower blood pressure.

I think there are a lot of elderly patients on atenolol who probably should be switched to another drug. Steve, do you have any views about that?

DR. MacMAHON: I think probably my views would be a little more conservative as to how

strong the evidence really is. I mean, I think the analyses are highly retrospective identifying a few negative studies with atenolol and then doing a meta-analysis of those and then extending it further down. So whether it really has--whether it is really as convincing as some of the other evidence, I don't know. I would probably be attempted to de-emphasize that.

DR. TEMPLE: So let me propose that, for the moment, we put out guidance that says, on the whole, there aren't differences but maybe we will bring to the committee that question and take a look at those data. That would be absolutely critical so it really needs a close look.

DR. MacMAHON: I guess it comes back to that single issue of you are not trying to indicate, for beta blockers or for anything, that it will have quantitatively exactly the same effects. You were just making the statement that, in general, these drugs--and I think you can reasonably include--I don't believe there is substantive uncertainty as to whether or not beta

blockers reduce these events. It is more a question of whether they do it as well as other agents. I think those are two separate issues.

DR. TEERLINK: And that is a distinction that I should be included in the guidance as we have discussed already to say that all of these do have that effect. The extent of that effect, though, may be different.

DR. TEMPLE: We have some proposed language, when we were going through it, in 2.

DR. STOCKBRIDGE: As we were doing it in 2.8, I had penciled in, in that first sentence--I had amended my copy to say, "whether drugs given to achieve the same blood-pressure goals have about the same clinical benefits."

DR. PICKERING: So that doesn't include the mention of beta blockers specifically.

DR. STOCKBRIDGE: No; it doesn't do that.

DR. TEMPLE: We should look at that just to make it clear that we, obviously, couldn't have yet ruled out the possibility that there are differences for certain particular things. But

they all have the right direction. So I think that needs a look.

DR. PICKERING: I think having another review of it would be very good, actually, because there are a lot of people who have written a lot about this.

DR. WARNER-STEVENSON: I think it may also be appropriate as a phrase somewhere in one of these sections to say, "which may vary between populations," whether it is the elderly, it is people with baseline renal disease, it is by ethnicity, by gender, et cetera, it may well be that there are considerations there.

DR. PICKERING: I think we are onto Question 4; please comment on specific sections of the proposed Indications section of labeling as reproduced below. 4.1; DRUGNAME is indicated for the treatment of hypertension to reduce the risk of cardiovascular events primarily fatal and nonfatal strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of

classes including this drug or including the class and, in parentheses, there are no controlled trials demonstrating the risk reduction with DRUGNAME.

DR. WARNER-STEVENSON: Is it necessary to include both fatal and nonfatal? That is something that we are used to thinking when we look at endpoints but, I think, from a patient standpoint.

DR. PICKERING: I agree

DR. KASKEL: Do you want to say anything about diabetic nephropathy or chronic kidney disease here as well?

DR. TEMPLE: Remember, this is not directed at patients. This is for physicians. But you think, on the whole, just saying--I mean, you could reduce strokes and not reduce fatal strokes. That has been the results of some trials.

DR. PICKERING: It is sort of an esoteric detail, I think, for the average doctor or patient

DR. KASKEL: The problem identified by the NK-DEP is that primary-care physicians need to be reminded about some of the consequences of diabetic nephropathy early on in treatment. That is why I

mentioned it.

DR. STOCKBRIDGE: But, again, this is the class label and only some drugs have a claim for diabetic nephropathy. So that is why it is not part of this statement.

DR. PICKERING: But then only those drugs would get that in the statement.

DR. STOCKBRIDGE: It doesn't replace everybody's whole label. If you have got a claim for diabetic nephropathy, you have got that claim. It would be a separate paragraph. This would replace the paragraph that is now there that speaks to effects on blood pressure.

DR. DeMETS: When I read this sentence, my eyes scan, "DRUGNAME is indicated to reduce the risk of cardiovascular events." I read, "to treat hypertension," but then I forget about that and my mind focuses on the, "DRUGNAME is to reduce risk of cardiovascular events," and that is not necessarily what you are saying.

So I don't like the way that first sentence reads.

DR. TEERLINK: So would you suggest something along the lines of, "DRUGNAME is indicated for the treatment of hypertension--"

DR. DeMETS: Period.

DR. TEERLINK: Period.

DR. DeMETS: And then say something about--

DR. TEERLINK: "Treatment of hypertension has been shown to reduce--"

DR. DeMETS: Yes; something like that. It is correct in one sense, but yet you can easily read it the other way.

DR. TEERLINK: I hadn't been able to formulate a wordsmithing that was satisfactory to address that issue but I also was concerned about that.

DR. PICKERING: Again, yes; it does sort of imply that that drug has been shown to reduce the risk, which may or may not be the case. I agree.

DR. DeMETS: You later become more specific, but I only may remember the first

sentence.

DR. WARNER-STEVENSON: Additionally, when we think about marketing flyers and advertisements on t.v. with people gardening with their grandchildren, I think we will lose that intermediate phrase there.

DR. TEMPLE: So the proposed fix was, "DRUGNAME is indicated for the treatment of hypertension," and then you say, "Treatment of hypertension reduces the risk of--"

DR. DeMETS: Yes.

DR. TEMPLE: That is the proposed fix, David; right?

DR. DeMETS: Yes.

DR. PICKERING: Anything else on 4.1? In that case, we are down to 4.2; what is missing?

DR. TEERLINK: I would just reiterate the concern in the discussion that we are going to have, to continue to have, in terms of how we are actually going to approve these agents for this indication.

DR. TEMPLE: The proposal here is that

this is what every antihypertensive would say. Now, that doesn't mean you couldn't--

DR. STOCKBRIDGE: Including the next one.

DR. TEMPLE: Including the next one. That doesn't mean one couldn't decide to add a paragraph that says, "There is not a lot of long-term experience with this drug," or something like that, that has not been done to date, but that doesn't mean it couldn't.

DR. PICKERING: I sort of agree that now this blanket statement is in there, there should be some qualifier for new drugs to say that everything that is said in this statement cannot be assumed to apply to whatever this drug is.

DR. TEMPLE: I think if that is what everybody thought, I would abandon this effort. The whole premise of this is that each individual drug does not need its own data. Many drugs have no relevant data on this point at all. They may have a class member who does but, even there, some of the classes do not have a whole lot of data.

The whole underlying assumption here is

that we now know enough, from the multiple drugs with completely different properties, to believe that lowering blood pressure is good. That doesn't mean that it won't kill you by causing liver injury because that is a totally different question. Surrogates never protect you against unexpected toxicity.

But the premise here is that we know that lowering blood pressure is good for you. Some other bad thing you do might be bad for you but that is a different question.

DR. TEERLINK: I guess the message that I wanted to give, from at least this member of the advisory committee, to any pharmaceutical companies that might be taking this as the direction for future development programs is that I would not at all be comfortable with a 300-patient trial that shows that something lowers blood pressure and then submitting that for approval because there has to be a sufficient--and I have said this before--but there has to be a sufficient safety database and the safety database cannot ride the tails of this

efficacy.

While I believe in the concept, in general, that it is the blood-pressure dummy, I think there are lots of other options. To prove the negative is an impossible task. I don't know if we should set the bar that high and just have everybody have to do huge outcome trials.

But there has to be a much more robust safety database than the next ACE inhibitor has to have.

DR. TEMPLE: Okay. Let's talk generally. Any new drug for widespread and chronic use is going to need a substantial safety database. Much of it won't be terribly long-term. But, under ICH guidance, it suggests that 300 to 600 people, at least, ought to be studied for six months and 100 for a year, I think you won't see anything that small with any hypertension drug.

So the recent drugs have had, even though they have been members of familiar classes, have had a couple of thousand people at least. I don't have any doubt that we would ask for a similar

database in any new member, probably a little larger if it was quite novel.

That is, in no sense, the same as saying you have got half of ALLHAT. Those trials don't give you outcome data. They don't even--some of the data is open so it doesn't give you--it only finds really bad obvious things. But it is not going to give you really good comparative data unless we further impose the requirement for a certain number of people in a long-term study at the time of approval or afterward. I don't think that is being done yet.

DR. TEERLINK: I would suggest that we should probably have discussions along those lines saying that, for these kinds of--in order to get this kind of blanket statement, we have to have a higher confidence in terms of the safety and the implications of the outcome data probably moves in that direction.

So, before they embark on their development program in their early discussions with you, I would suggest that you state that there

needs to be long-term data in thousands of patients done in a right way. It doesn't need to be a 10,000-patient outcome trial, but we do need--anyway; that is my--

DR. TEMPLE: To have real outcome data, though, it actually does. ALLHAT wasn't big enough, was it, really? I don't know what size difference it rules out, but it leaves many questions uncertain. Having a trial with 4,000 people in it, given that they are all going to be getting other drugs to get to control and all that stuff, is probably not going to be very persuasive on outcomes. That is not even big enough for a placebo-controlled trial while you could still do placebo-controlled trials.

So, if you really wanted outcome data, you are talking about a very large trial. Maybe that is something you need. I am just trying to point out the numbers. If you want a reasonable safety database to exclude agranular cytosis and liver injury and all that, I think that is routine business and we would expect that.

But I think we are talking about two quite different things, one of which is sort of half verify the outcome results which, I think, is talking about an order-of-magnitude difference in data. So we need to know which of those things you are saying.

DR. WARNER-STEVENSON: I would feel very comfortable with this as listed but bearing in mind John's concern that this not be seen as a free license for a totally new drug. What concerns me specifically is not so much the hepatic failure or agranular cytosis but some unrecognized safety issue that, in fact, does impact on primary outcomes such as M.I. or stroke.

I don't think they would need to demonstrate benefit there, but we would want enough patients to see any sort of unusual trend emerging that is in the opposite direction. So it would be essentially thinking of it as safety but safety in relation to important primary endpoints.

DR. TEMPLE: We probably need to come back with you either in connection with a particular

drug or something else to talk about what a new antihypertensive drug needs to have and who it has to be in. I mean, if most of the people who get into trials are not particularly high-risk, you are not going to have a lot of events.

So we need to have a longer discussion, I think. Fair enough.

DR. FINDLAY: This is a guidance to the industry. Would it be possible to have a section that discusses this issue? It doesn't have to be at length but it raises the issue in the guidance, not in the suggested language for the labeling. We have basically agreed to that, or agreed on it. But, in the guidance, it could discuss the weight of the evidence with respect to a new class of antihypertensive agents and that you are basically not going to get an easy pass on this labeling unless you--

DR. TEMPLE: My problem with that are these. The whole logic of what we are doing says lowering blood pressure is good. If that is in doubt, then we should really rethink the whole

thing.

DR. FINDLAY: I don't think it is in doubt except for the guidance to the industry is a nuance of signalling to them that--what should be obviously, really, is that if you have an entirely new class ten years from now, or two years from now, or some are already, perhaps--or today--of any hypertension agent that it won't necessarily be so easy.

I don't know how to do this but I think we are all going down that path.

DR. TEMPLE: I wouldn't do it in this guidance which is about labeling. However, Norm can tell us how close we are--we are in the process of writing a guidance on antihypertensives which we sort of need. We have a not-very-useful one from the ICH that doesn't really get into the size of the database in any sophisticated way, I would say.

So how near are we to having a draft? Or don't you want to say?

DR. STOCKBRIDGE: Maybe I should ask somebody behind me who knows. We are working on a

revision to a fairly ancient set of guidelines for development of antihypertensive drugs. When that is further along, we will come back and see you.

DR. FINDLAY: So there is another venue to communicate this clearly to the industry.

DR. STOCKBRIDGE: Well, again, this is about labeling for outcome claims. There is a separate document for how you should work up an antihypertensive drug.

DR. TEMPLE: It is clearly a relevant question. We have had people writing in journals about how big an adverse outcome you should rule out, some of them even speaking today. The whole safety concern of new drugs raises this very issue, just how much data you need.

There is always the same questions. You want more assurance. It is actually hard to get perfect assurance. You have to really get huge sample sizes. But you want, perhaps, more assurance than we have. How do you get that without stifling development. Those are very good subjects for discussion.

DR. PICKERING: Thank you. Dave?

DR. DeMETS: I was confused for a while. I bought into the idea that the discussion this morning was to try and organize and convey more clearly what we do know and how to get better penetrance of what we know into the community and so we have better overall control.

So I could buy into what you are talking about but I must say I would share all of the concerns of my colleagues that, for the next new class of antihypertensive drugs, I would be really concerned about having this discussion, brief as it is this morning, to sort of set off something that may, in today's world--not yesterday's world by today's world--we may regret.

So I think it needs a lot more discussion, but I can buy into--everything you said so far that we talked about is to try and get more clear where we are and to get more people to use what we know.

DR. PICKERING: I think we have got some general agreement on this and it is reassuring to know that there is going to be another guideline

that deals with this.

Steve, do you want to have a last word?

DR. MacMAHON: It is just with relation to the same issue. I guess I am having a little trouble imagining a situation where you would consider approving a new drug or a new class for the treatment of hypertension without being prepared to say it was going to reduce the risk of stroke and coronary heart disease.

So I guess--I mean, I understand the concerns that people may have about what new classes do, but, surely, that should be part of the decision as to whether to register or not rather than to say whether or not it is going to reduce stroke or coronary heart disease because, otherwise, if you didn't believe that, why would you be registering it for blood-pressure lowering?

DR. TEMPLE: I completely agree. The issue of what a new drug has to show was present before we changed the label. Just the fact that we are using a surrogate raises the same question.

So we should have a discussion, I hope, in

the context of this guidance proposal on just what the safety data burden should be for a new antihypertensive. That is a perfectly good discussion and not dissimilar from discussions that are going on in a lot of places.

DR. PICKERING: Okay. Thank you very much. I think it is nearly noon which is our closing hour, so I would like to thank everybody and officially close this session.

[Whereupon, at 11:55 a.m., the meeting was recessed, to be resumed at 1:00 p.m.]

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