on the combination, you see something slightly less than additivity almost always. But what I heard is that people would be very interested in those results, and they would also be interested in seeing whether there was a price that you pay for starting with both, like regarding falling over or something like that.

So, one of the things that I am taking away is that you are going to watch what dose you start with, too, not for these drugs maybe, but for some drugs, if you gave everybody the maximum dose right off the bat, you might get into some trouble if you gave a lower dose. So, that is something to think about and know about, too.

DR. HARRINGTON: Yes, I took from the remarks that it was not just the specific drug, but how they were used, so I agree with you, Bob.

Norm, did you have other questions on this?

DR. STOCKBRIDGE: No.

DR. HARRINGTON: Question 2. There are enough parts of this that it may take a couple

minutes, but I would like to go through each one individually. You can certainly pass on specific parts if you choose to.

So, the general question is: Please comment on the following factors that might commend initial or early use of antihypertensive combinations.

The first part of it is: Treatment goals change. While a study may be designed around a specific goal, the practicing physician may be considering different goals.

Do you want to elaborate on that a bit, Norm, what are you trying to get at there?

DR. STOCKBRIDGE: I think the idea was just to sort of start generating some discussion about what things, not just the fact that treatment goals are not constant, but some general discussion about what factors you believe influence your--I am trying to say this without sounding prejudicial--what things favor early aggressive treatment.

One of the things that Dr. Weber talked

about isn't even on this list. It is this whole idea that if you fall behind, you probably won't catch up. So, this is a list of some of the things that had occurred to me, and it was intended to provoke some discussion about which ones you thought mattered and which other ones you think influence your thinking about this.

DR. TEMPLE: One other thing. I think part of the thinking was that for various ways, either because they are reading an algorithm, because of their own view, different people are going to have different goals in mind.

I mean some people say the lowest pressure you can get out of bed with is the pressure you should have, but not everybody would push for that. So, if you have data on where you get with the combination versus the other, you can incorporate or you can allow your own views to influence your choice, which is one of the reasons we keep wanting to show some of the data.

DR. HARRINGTON: Let's consider then this whole group of issues as the factors that might

influence your decision-making.

Treatment goals changing.

Even at the time of diagnosis, patients are going to require more than one, so the notion that two-thirds will require at least two drugs.

Lower blood pressure is associated with lower risk of events.

Drugs are, for the most part, well tolerated.

Some drugs have minimal dose-dependent and dose-independent adverse effects.

Other factors.

John, why don't we start on your side of the table now and go around.

DR. TEERLINK: I think that one of the reasons we are here is because of the use of actually a surrogate here with millimeters of mercury being a surrogate for what we believe is reducing that route, all of our cardiovascular endpoints, and is a good surrogate, but it still is a surrogate, and because of that, people can interpret it in different ways.

Some people can look at systolic blood pressure as being the goal, diastolic blood pressure being the goal, or decreasing both of them.

I think from my standpoint, given the evidence base that we have so far, giving the drugs to the physicians in a way that they can use it with information on how the drugs have impacted those surrogates, how they have impacted blood pressure is probably enough for me right now.

We have already kind of done the legwork in terms of the background, and I would be willing to have physicians be able to make the choices. We have already had extensive safety experience with these specific agents.

I don't know if I would have other factors to consider. This is already a rather broad statement here in terms of factors that need to be considered.

DR. LINCOFF: I am struck by the idea, which I believe is true, that as low as your blood pressure can go and still get out of bed is

probably the right target.

You know, we think of these thresholds, but it is really not binary, and that become important I think because it is not like 20-some percent of people are only going to need a single agent and have no additional advantage from a combination.

Even those 20-X percent that would have reached goal on the single agent, may do even better in terms of their cardiovascular outcomes if they had been started on a combination agent.

So, once we predicate with the idea that our risk profile is very low, that the adverse events with the combination product are not substantially in any way worse with the single product, then, the question is for virtually everyone who falls into the group that we think there is going to be benefit, they may all benefit.

It is not like you are going to miss those people who could have gotten away with one drug. They could have gotten away by an arbitrary target, but they may still do better on the combination

drug.

So, I think that the integration of the fact that there really is no too low until you clearly become symptomatically too low, but that it is a gradual risk throughout the entire--there is no threshold, and that we are talking about drugs that have a good safety profile individually and together, I think that argues fairly strongly.

DR. HARRINGTON: I am trying to get a handle, Mike, because what you said is pretty broad. Are you saying that if combination therapy across the board would lower a person's blood pressure better than monotherapy, that even if they are within so-called JNC 7 goals, you would favor pushing it lower?

DR. LINCOFF: Yes.

DR. HARRINGTON: So, you are basing this largely on the epidemiology.

DR. LINCOFF: Yes. If I am not going to make them symptomatic, I am not going to make a larger proportion substantially dizzy, you know, and symptomatic, then, if you have two drugs, and

one drug lowers your blood pressure to a lower target in more patients than the other, even if a fair number on the first would have reached a target, I don't see a reason why not to give them the better drug, which in this case is a combination.

The only thing that limits that in my mind is if you begin to have too many falling below the threshold where you now have adverse events.

DR. HARRINGTON: So, you are really approaching this as your remarks before lunch. You are looking at this as Strategy A versus Strategy B, and if Strategy A wins, regardless of the starting blood pressure, you would go with Strategy A.

DR. LINCOFF: Yes, assuming again--

DR. HARRINGTON: Presuming that the adverse event profile across the starting points of blood pressure was consistent, so that you didn't have a different adverse event profile at the lower ends of starting blood pressure.

DR. LINCOFF: Yes.

DR. HARRINGTON: That is pretty broad.

Bob?

DR. TEMPLE: A somewhat less aggressive way to say that is that the practitioner should decide what blood pressure he or she would like to get the patient to, and then look at the graphics and see how likely you are to get there with a given approach.

Our labeling isn't going to try to settle broad questions like whether you should go for this drug or go for the lowest you can stand up with, but it is not unreasonable to think that the practitioner should be deciding that.

DR. HARRINGTON: I am pushing it a little bit, Bob, because one of the questions we are going to come back to is the labeling, and right now the proposal is for severe hypertension, and that is not what I am hearing from Dr. Lincoff, so I just wanted to make sure that I had clarified.

DR. LINCOFF: I am not really sure, Bob, that practitioners really have a rational target. They may have a target. They may want to get below

what a guideline says is appropriate practice, but how do we know if it's better to be 120/75 or if it's better to be 132/80. We don't; right? And yet all the data would suggest, that over the continuum, you continue to reduce cardiovascular risk.

I look at it as two strategies, one more effective than the other, as long as there is not more risk with that.

I don't know how you can rationalize a specific target. Many meds we use, we don't have a target. I mean many we do, but I don't know that hypertension is a rational target.

DR. TEMPLE: The thing we have data on here, though, isn't really going as low as possible. It is going, the main measurement we have is how many people got below 90, got below 80, or all of which are within the range of specific numbers that people have been advocating.

I am not unsympathetic to your view that lower is better, but one couldn't really say we have actual treatment data on that point even if we

do have epidemiologic data on that point.

Keep going.

DR. HARRINGTON: So, the other factor that I would add here in terms of what you might think about when you are talking about initial or early use of combination therapies is what other comorbidities this patient has.

So, if the patient has concomitant coronary disease or if the patient has concomitant heart failure, I think that those would be important things for the clinician to consider, chronic kidney disease, as Emil has brought up several times this morning. I think those are the kind of things I would think about, and I think the clinicians should think about, as they begin to consider potentially combination therapy.

In a sense, we are not yet at the era of personalized medicine of being able to figure out which specific medicines for specific patients. I still think we are playing the population game here, and the comorbidities would weigh heavily in that.

DR. PAGANINI: I would take the text of Michael's statement that we drop it all the way down until you drop, I think that is pretty foolish. There is a J curve to things and you have got to be careful that we have to perfuse organs here.

But apart from that, we already have somebody who is recommending. We have a recommendation for goals, and we have a recommendation for getting there, and so I would think that we would take into account that recommendation and try to follow that with our drug labeling.

The second thing I think is to reiterate what was said, and that is that underlying disease entities and drug classes should be considered, so that when you have somebody who is a diabetic with CKD, it probably is not a bad idea to have them on some sort of an ACE or an ARB, and also on a diuretic.

You have got I think certain subclassifications, subgroups of patients with

disease entities that may have a certain combination preferred over another combination, or may have a combination earlier preferred over single drug.

The third group besides disease would be patient-specific age, race. We have some inklings that perhaps age and race may respond better to one issue than to another issue, one combination than to another combination, so in considering combinations and whether they are front-line drugs, first-line drugs, perhaps age, race, and other issues, etiological issues, or specific issues may influence whether or not this particular drug might be better used in this subgroup of patients.

Whether you want to sort of apply, when people apply for these, to show the favored status of certain subgroups, or the favored status of certain chronic disease entities, compared to others may or may not be a question that you might want to ask in labeling.

DR. HARRINGTON: That is a very good point. I think the questions to come, we are going

to have you talk I think a bit about what should be the burden of proof, so to speak, in those separate subgroups and patient classifications, because it is going to be a critical issue.

Jason.

DR. HSU: My only comment is in regard to Item 1, the graphics showing probabilities achieving the goal ought to be useful.

DR. WARNER STEVENSON: I want to reinforce this concept of thinking about these different patient groups, the diabetics, the metabolic syndrome, chronic kidney disease, and as in the HOPE trial, people who have some vascular disease, but haven't yet, for instance, had a frank event.

I think clearly in these patients, we need to be thinking, first, about leaning towards drugs that inhibit the renin-angiotensin system and probably, in some cases, beta blockers.

Blood pressure is a bad thing, on the one hand, and, on the other hand, we have a certain amount of it and where are we going to spend it. You know, somebody who has only got mild

hypertension and is likely to need to be both on a renin-angiotensin system antagonist and a beta blocker. For instance, I would hate to see them put on a combination that gets their blood pressure too low for someone to be comfortable starting one of those. So, we have to bear in mind that.

In terms of the blood pressure issues being too low, I have considerable concern that, in fact, symptomatic hypotension is often neither immediate nor consistent.

You can see patients who do quite well for a month on something, and then develop postural hypotension, or who, in the setting of a little bit of decreased intake, or a hot day, or a viral illness, now have a very, at least quality of life-threatening event like a hip fracture from falling, et cetera.

So, I think we need to be very careful about looking at postural vital signs, and repeatedly assessing that in these patients in order to avoid going too low.

MR. FINDLAY: Just a general comment, not

necessarily specific to all these points, more specifically actually to the first question. From a patient and consumer perspective, this particular issue we are talking about today, and this particular drug, it seems like an expansion of options for patients and consumers and physicians.

Just from a pure, my role here perspective, that seems like a good thing, particularly the risk/benefit profile with this particular drug. That is just a general comment.

DR. HARRINGTON: Steven?

DR. RYDER: No, nothing to add.

DR. HARRINGTON: Let me see if I have captured the tone of the group and then ask Bob and Norm if they have any other questions.

I think there is general consensus again that achieving some sort of goal is important and that we all recognize that it is unlikely, in the majority of patients, that a single drug is going to get you there, so other options need to be considered.

Where there seems to be a little

disagreement is perhaps what that goal ought to be and that this is not the place to sort that out, as several people have pointed out.

But I like Emil's comment that there are goals and recommendations out there, and it does help to align the messages, that labeling, trying to get you to a goal that has been put forward by an organization might be helpful.

The other underlying theme in addition to what has been mentioned in the list here, as nicely I think articulated by Emil and Lynn, is try to pay attention to specifics about the patient, age, race, their diseases, and how specific drug classes might have more or less benefit by category or by indication. So, that seems to be something that clinicians might keep in mind.

Have I captured most of that?

DR. TEMPLE: Yes. With respect to the latter, it has been very hard to show that for the same blood pressure, different drug classes have different effects. I mean there are some debates about this, and there are exceptions if you have

Type 2 diabetes, you know, then, your renal function is deferentially affected, that we know, but on the stroke, heart attack stuff, and survival, it has been very difficult.

Now, we do have labeling that sort of suggests that losartan might have an advantage over atenolol, but whether everybody agrees with that or not, I don't know, and there is not a lot of data like that, although there is a lot of hoping I would say.

What I am taking from all this is that, yes, you should respect the fact that people have individualized goals and try to capture that in the instructions. I will tell you what I am writing as it's going along is maybe something like saying that the combination could be used in people who aren't likely enough to get to whatever goal you want on a single entity.

Maybe for people with severe blood pressure, a group with severe blood pressure is relatively unlikely to be controlled here, see this result from the study they did, but certain

moderate people might not be very likely, depending on your goal, and then you show some data from the moderate one about how likely they are, and people can use those pieces of information to make their judgment about what to do.

DR. HARRINGTON: I think the one thing I would add to that, Bob, is to use Emil's example of chronic kidney disease, that there may be specific groups of patients with moderate to severe hypertension who might preferentially benefit from certain things in that combination tablet.

So, for example, they may preferentially benefit from an ACE or an ARB plus a diuretic, for example.

DR. TEMPLE: That is true, but let me ask you about that. This is about a combination that somehow you have decided to use those two drugs on whatever basis you were. The only question here is whether to titrate them individually and then substitute or to perhaps start with the combination. But, presumably, anybody doing this has already made the decision to use an ARB with a

diuretic on whatever grounds they used to do that.

I would have said that choice, I mean not that that isn't relevant and maybe that should be somewhere else in labeling, but that is not the issue here. Here, you have already chosen your two drugs and the question is how to give them.

DR. HARRINGTON: Go ahead, John.

DR. TEERLINK: This is along the lines of what Lynn had said and something I had tried to get at, as well, is that there is an opportunity cost in terms of, when you start a double therapy, you may be precluding use of other medicines because you have spent all the millimeters of mercury that you want to spend.

While I think those are relatively rare cases probably, certainly in the severe and moderate hypertension that we are talking about, it is still a consideration I think.

DR. HARRINGTON: Certainly, I think it was Dr. Weber who made that point with regard to pushing the hydrochlorothiazide to its maximum point and then making it difficult to then add an

ARB at that point because of the volume depletion and the hypotension.

I think what you are hearing, Bob, is a little bit of an answer that was trying to take it to the broader category of question when you start to think about combination therapies, not just a specific drug.

Go ahead, Mike.

DR. LINCOFF: I would just like to clarify in case anyone like Dr. Paganini seems to be taking things literally, and sort of designed at the hyperbole, if we were talking about treating until they drop, we would be seeing it as side effects.

So, we are talking about strategies that treat to the same level of adverse events including dizziness and syncope, and things like that.

If you were presented with two therapies, one going to bring you to 120/70 in all likelihood, and one to 130/80, both of which would meet the JNC 7 goal, with no other consideration, would you pick the higher goal?

I mean that is the way I look at it, is as

long as these strategies bring you within a safe level of hypertension--a safe level of blood pressure, but one is likely do so more frequently, and also likely to bring you within the range of acceptable blood pressure to a lower level, then, that seems to me to be a superior strategy, if you know, as we seem to have from the safety data, that all the signals are the same, that there are no differences in side effects.

So, obviously, it would be people for whom maybe super vascular disease or other reasons why you might want to maintain a slightly higher blood pressure, but that is not really the majority. Most of the time we don't think in terms of I have got to keep the blood pressure up to a certain level. We try to get it within the range, as low as we can within what we consider the safe range.

DR. PAGANINI: The question was whether I now then go with the 120/80 versus a 130/85, I would go with the cheaper drug.

DR. HARRINGTON: Fortunately, we are not discussing the economics of hypertension care.

Other comments for Question 2 here? Bob and Norm, are you okay with Question 2?

DR. TEMPLE: Yes.

DR. HARRINGTON: Question 3.

What is the role of a study targeting a severely hypertensive population, like the one done with Avalide?

There is a series of subquestions to this.

Is it necessary? Would the usual factorial design have been sufficient?

In what population would it be most appropriate to assess the safety consequences of initiating therapy with more than one drug? Should it, for instance, be enriched in elderly patients, who, one might expect, would be less tolerant of excessive pharmacological effect?

So, trying to look at some of the study design issues and the evidence that might be required.

Why don't we start again over with you this time, Steven.

DR. RYDER: Thank you.

The Avalide program was very substantial and I think provides the committee with a great discussion platform for really I am going to try to ask you to please get into this as much as you feel would be helpful. I think the issue is what are the operational specifications, definitions, endpoints, issues of generalizability, many of the things that I have heard the committee discuss in the last couple of hours, how would you prioritize them, how would you ask sponsors in the future to work with the Agency and the investigative community to design these studies, what is important.

The more you can try to use the Avalide platform, because it does give you a great platform. It always helps in my mind to get real, and here you have a program that is very real, very tangible, but use it to discuss what is important to you.

MR. FINDLAY: Just a quick comment that it seemed from the presentations this morning that this was a highly useful study in a selected

population that gave us very useful data.

DR. WARNER STEVENSON: As I read the question, it is targeting a severely hypertensive population. I don't think it would have to be severely hypertensive. I think someone who had significant hypertension would be an adequate population for a study like this in the future.

Certainly, this one was very well done and very convincing, but I am not sure we would have to have the serious end, as well.

In terms of the drugs, I am not exactly sure what you mean by the factorial design. Certainly, I would want to know what the effects are of the components individually and what their effect is together, and whether those have to be in the same study or not, I don't think necessarily.

I do have significant concerns about the elderly population, which is the dominant population that we are treating. It will become even more dominant, and I do think that the issues of volume and a little bit of volume depletion may be much more important in the elderly in terms of

potential side effects, so I do think that, ideally, we would have more information about the elderly at least in post-marketing.

DR. STOCKBRIDGE: I was just going to point out that all of these combination products, including Avalide, got approved initially for second-line use based upon a trial which compared various combinations of the two drugs, had placebo and several doses of drug A and placebo, and several doses of drug B, usually, you know, 80 to 120 or so subjects per cell.

Many of these trials had every cell in that factorial design filled, a few studies have not quite filled that. They are usually in a mild to moderate hypertension population. The goal of that study, for the most part, is to look at the response surface for blood pressure as a function of the dose of the two components.

What is being asked here is whether you would get enough information out of a study like that, because everybody has got one, to address what you would need to know in order--and almost

all of those studies randomize people directly to the various doses in those studies.

So, you actually have quite a bit of information to assess. Again, it is not in the very elderly, it is not in the very hypertensive population, but you have got enough data to address some aspects of tolerability and response to therapy.

The question was whether you really needed a special study that targeted somebody with severe hypertension or something else to get more confidence about the safety data.

DR. HARRINGTON: Did you want add, Lynn?

DR. WARNER STEVENSON: Again, I think it would just depend on the extent of the information that you had about the different dose combinations in the different groups as to whether or not you feel comfortable, and I don't know enough about the earlier data banks to know what that provides.

DR. TEMPLE: Let's be specific. Every one of these drugs has one of these 12 compartment things where, as Norm said, there are four doses of

one drug, three doses of another, and all the combinations between unless a couple have been left out.

So, you can always draw those lines, say, that show if your starting blood pressure is this, what is your chance of getting to a particular goal, but most of them are truncated on the upper end, because you don't necessarily have a whole lot of people with diastolics of 110. That would be unusual.

Actually, because most of those studies entered people on the basis of diastolic, you actually will have a good range of systolic pressure, because nobody paid attention to that before. We have been sort of trying to change that.

In the future, probably you won't have a lot of people whose systolics are 180, so you won't be able to say specifically that if your systolic starting pressure is 180, you don't have a whole lot of chance of getting to goal, but you will have information about getting to goal from every other

blood pressure.

So, what Norm is asking is, I think, with that information, which qualitatively is going to be similar to what we have seen here, but lacks the more extreme components of it, be enough to reach the conclusion that this is a drug you should use when you don't have much chance of getting to goal.

But you won't able to say, as you can here, what your chance of getting to goal is if your starting blood pressure is 180 or 200, because there probably won't be too many people with 200.

So, it is a little bit of a problem to identify that with actual numbers.

DR. HSU: Thanks for the explanation. Actually, only now I understood why this question about factorial is specific to severely hypertensive. In this case, if I understand Bob's explanation, I am really not sure I know the answer to this one unless there is an analysis comparing both ways.

DR. TEMPLE: I want to add one other thing. People would be nervous about having a

trial with a zero group with very severe people, and, of course, they didn't have one. They compared the combination to irbesartan alone, so it wasn't the complete factorial.

They presumed that the diuretic wouldn't be more anyway than the single entity, and they already knew that there was an additive effect of the two, so they were really just focusing on the severe hypertension, and you can hear that from their presentation.

That may be part of the answer of what it might be reasonable to ask people to do if they want a claim like this, and that is not ethically problematic, I don't think. Having a zero group in those people might very well.

DR. HARRINGTON: Is this the point, Norm or Bob, where you would also want the discussion about the 10 percent, the 33 percent? They set out to mimic the Hyzaar approach, but irbesartan performed much better than that.

If one of the things you are saying, Bob, is that to explore the outer range, the severe

hypertensives, it would be most appropriate to do an active control trial, as was done here.

If that is the case, to allow you to claim, okay, at 180, 190, whatever it is, you are going to have X percent get to goal on this combination versus monotherapy, do we need to have a discussion about the 10 versus 33?

DR. TEMPLE: Let me tell you what we have concluded. We have concluded that the 10 percent, which as you know is carefully derived from mounds of data--

DR. HARRINGTON: Previous leadership is what we have heard.

DR. TEMPLE: --what was arbitrary in that even within a study where much more than 10 percent got to goal, you could identify people whose starting blood pressure made them very unlikely to get to goal, and that is what we wanted to know.

We wanted to know--I mean you can define it as a whole entry population or you can define it as some component of the entry population, and I think we are satisfied that that's good enough,

that if you can identify within the population.

However, Study 176 did identify a subset of the population that really was very unlikely to get to a goal blood pressure. I don't know how unlikely is sufficiently unlikely. 10 percent? 20 percent? 30 percent? It depends on the drugs.

That is one of the things I would say we thought is part of the judgment that the clinician should make, how worried are you, how fast do you want to get there, how likely is the person going to come back to clinic blah-blah-blah.

I think our inclination was to show the data as long as there were a reasonable number of people that didn't get to goal, and let people make those choices and not set an arbitrary 10 percent, 30 percent. We would love to hear what you all think about it.

DR. PAGANINI: I frankly think that what was presented and the data that was presented, as it was presented, and the data responses to the questions from the committee, and the depth of that data, can serve as a wonderful template for anyone

who wants to do this type of combination therapy at whatever area or level of drug that you are talking about.

Every question that I had was answered. Every concern I had was put aside because of the strength of--

DR. TEMPLE: You are just going to get cocky.

DR. PAGANINI: Oh, no, I know that, and I am sorry to say that, because I am supposed to be conservative here; right? But I think they did do a wonderful job in setting up a template for how drugs should be, in combination, supplied and presented.

The one thing I would have liked to see is a little bit more of an analysis on subgroup. And some of the people that are allowed into these drugs are truncated at certain areas, so, having an interest in a smaller population, such as those with CKD, Stage 3, for example, Stage 4, which may have some major influence on progression of end-state renal disease and blood pressure control,

or combinations of drugs that might be effective in some of the underlying diseases, I would have liked to see expanded a bit more.

But for the generic population and the elderly population, I think Lynn is right, that is the bigger population we are seeing, I think they have done a nice job in looking at that, so I would use that as a template.

DR. STOCKBRIDGE: It's okay to say you appreciate the data they have, but there are four companies lined up outside my door, okay, who don't have this severe hypertension trial, and they are going to want to know whether or not they can get a similar sort of looking claim by mining the data from their factorial trial in a mild to moderate hypertension setting.

What am I supposed to tell them?

DR. PAGANINI: I don't sit in your chair.

[Laughter.]

DR. HARRINGTON: There was no "but" to come there?

DR. TEMPLE: Some of those trials

probably, but I don't really know this, do have people with very extreme systolic blood pressures. We don't know that yet, but they might, and if they had nobody like that, if everybody was down at 150, and the diastolics were just over 90, they may well not have identified a group that needs the combination even though it seems overwhelmingly likely that if they looked, they would find it.

DR. STOCKBRIDGE: You will still be able to draw a set of curves with a set of, you know, maybe over a somewhat more restricted range of blood pressures, baseline blood pressures. But so what? That is still informative.

DR. TEMPLE: So, then, you will be able to say that for any given goal, more people will reach it, but it might be 80 percent versus 70 percent.

DR. STOCKBRIDGE: It may be.

DR. TEMPLE: So, one question would be is if everybody is up in that range, do you still think it is sensible to try the combination in those people, because you are going to get 80 percent instead of 70 percent, or does that depend

on the cost?

DR. STOCKBRIDGE: All kinds of areas is described as full disclosure. That is what we are talking about is a display of the data that would inform you without making a judgment about whether, you know, you really shouldn't bother with somebody if you have got at least a 20 percent chance of getting to goal. It doesn't say anything like that, this is full disclosure, so you describe what data you had. That is the proposal that is on the table.

DR. TEMPLE: So, as long as more people get to whatever your goal is with the combination, which is likely to be true, heaven knows, you would point that out and say use your judgment to decide what to do, here is the date, that is what you are saying.

DR. STOCKBRIDGE: Correct.

DR. TEMPLE: So, we would be interested in knowing how you felt about that. Here, the didn't find a whole population that only had a 10 percent chance, but they found within the people they did

study, some subsets of the population that had very little chance basically, people with much higher pressures.

But Norman is saying, as long as you can describe for any group of patients, even if they are relatively milder, how much better you do on the combination, shouldn't you just lay that out and let people choose even if you don't really know that it is only 10 percent or 20 percent.

DR. WARNER STEVENSON: I am still trying to figure out why we are focusing on this issue of making sure that we have a severely hypertensive group, when the severely hypertensives, we already know aren't likely to respond even to two drugs.

So, I mean the question of whether 10 percent of the severe or 20 percent of the severe respond, it is probably not going to be enough. So it seems to me that the biggest focus of information we need is in the 140 to 180 group, not necessarily at the high end in order to make these decisions, because, I mean, unless they want to come up and say we are more effective in that

severe group than other things, it seems like that is not where we are going to be making our decision.

DR. TEMPLE: Just to follow up on what Norm was asking, if you now saw that in this moderately hypertensive group, you clearly got more people to goal, 50 percent versus 40 percent, 60 percent versus 50 percent, whatever, by using the combination, and there didn't seem to be any terrible consequence of it, which would also be looked at, then, you are saying that seems okay, that is the information people need to have to decide what to do.

I think that is what Norm is proposing.

DR. WARNER STEVENSON: I am agreeing with that. I guess my concern is that I would want to look very, very closely and make sure that in the boxes which we are going to actually use of those dose combinations, that we have enough information about potential side effects and toxicity, because, if this is a database that was generated seven to eight years ago, all sorts of other things may be

different in terms of concomitant medications and how often they drink grapefruit juice, and who knows what else.

I do want to make sure that there couldn't be a lot more toxicity than we think from the earlier data.

DR. TEMPLE: That would be exaggerated by the use in combination in particular.

DR. WARNER STEVENSON: Right.

DR. TEMPLE: Okay. The drugs we are looking at are mostly pretty familiar and have been approved over the last few years. But there are some older ones where that might not be true.

DR. HARRINGTON: So, in general, Norm, I am in favor of full disclosure, that you lay out the data as it is and create some ways of displaying it that can be helpful to the clinician, and let him or her choose what is important in terms of what they feel is important in terms of allowing them to achieve some goal in their patient.

But what I would add on this, so I am less

concerned that we have specific studies devoted to the high end of the blood pressure curve. I am, though, more concerned, I think as is Lynn, about the second subquestion here, the population.

I asked a series of questions this morning about generalizability. I was very struck by Bill Weintraub's description of his population of who actually are the patients with moderate to severe hypertension, and they don't look exactly like what was studied in the clinical trials.

Now, that is frequently the case, that the clinical trial population is a subset of the population you want to treat. But, in this particular case, with regard to the elderly, the CKD patients, the diabetics, patients with some comorbidities, I do think that it would be important to have more of those patients in these clinical trials to be able to more fairly generalize the results.

Now, with irbesartan, with hydrochlorothiazide, we have a long, long experience of these drugs in these patient

populations, which helps me extrapolate some of that.

But let's take the argument where people come up with a new drug that has not been well characterized in large population studies, and they want to stick that in the combination pill. I would be much, much more cautious. I want generalizable information in my clinical trials.

DR. STOCKBRIDGE: Including if it were monotherapy, right?

DR. HARRINGTON: Including if it were monotherapy, that's right. But I want generalizable information.

DR. TEMPLE: But your comments I would say go to knowing enough about the interaction of this new agent with the various things it is likely to be used with. That is independent of the fixed combination.

DR. HARRINGTON: That's right. But that helps you a great deal here, because of the extent of the amount of information you have on these two drugs.

DR. TEMPLE: But that is in some ways a problem for what to ask people when they are working up a new fixed combination, or for that matter, the drug in the first place since, as we know, most drugs are used with something else.

Just to tell you, what we usually have when we approve a new drug is a lot of data on the combination with a diuretic, because a lot of people use that first, and often not as much about the interaction with other things, although the most recent drug we looked at did have a fair amount of information with ARBs and ACE inhibitors.

DR. HSU: A quick question for Norm perhaps to make sure I understand. The mining of the factorial data is looking back at data already there for whatever purpose, without necessarily having another validation trial. Is that the intent?

DR. STOCKBRIDGE: That is the question.

DR. HARRINGTON: Do you want to comment on that?

DR. HSU: No further comment.

DR. HARRINGTON: I suspect I know the answer from your look.

DR. HSU: Without actually seeing how they come out, it is difficult to answer that question. Generally, mining data for subgroup statistically is tricky to make sure it is not looking at something that is not really there. That is my comment.

DR. TEMPLE: We are actually agonizing, we are having rounds called beyond the primary endpoint, so you can imagine what we are agonizing about.

All of the trials we are talking about unequivocally showed that there was an additive or slightly sub or slightly super additive effect of the two drugs when they were used together. That is, the combination was better than either of the two single entities. That was the primary endpoint.

When you translate that into how many people met goal, we have not worried too much for a drug that clearly showed that it had, for a

combination, it clearly showed it had an additive effect.

We have not worried too much about translating the continuous variable into the dichotomous variable. Maybe that is a mistake on our part, but we have, on the whole, not because they are in some sense measuring the same thing, more or less.

When you start breaking that down into subsets of the population, black, white, male, female, old, young, we are in an interesting quandary. We have a requirement in our regulations that you have to do those analyses, have to do them, and we agonize a lot about what you can then do with those data after you have done them.

Our rules for what to put in your application are very quiet about what analyses to do. That is the only analysis that you actually have to do. You have to do demographic analyses for dose response, for safety, and for effectiveness.

To say how to handle that statistically is

up in the air is the greatest understatement you could possibly make. It is usually done on pooled data, which is another unusual thing, you don't have enough within a given study to do it.

But we expect it, we think it is important, and how exactly to use it is one of those things we debate all the time.

DR. HSU: I agree, the understatement, with genetic profiling coming, I really wonder how we are going to go.

DR. HARRINGTON: Michael.

DR. LINCOFF: I agree. I think, as my previous comments have suggested, I agree with more of the full disclosure rather than the arbitrary goal, and if that is the sort of precedent that this meeting sets, then, I think the need for a very high blood pressure or severe hypertension group becomes less, because really the need for that group was to establish a group of patients for whom the likelihood of a success in whatever measurement arbitrary there was a success, that that likelihood is low with the standard therapy.

If instead we are going to say that across a breadth of blood pressures, you are going to have some advantage, and you, as a physician with full disclosure, will decide which you want to use, then, it becomes less important to have the severe, and more important to focus on what was an important part of this presentation, which was the moderate hypertension that I think provided the important safety information because then you want to look at the patients for whom you feel they are most vulnerable to the adverse effect of hypotension or others, because you really want to identify are these really equivalent in terms of safety.

The severely hypertensive patients are the ones that are least likely to become hypotensive on the combination, whereas the ones who are moderate are the ones that you really have the question.

I am concerned that a retrospective look at a database that has 80 patients per cell may not have enough safety information. So I think we would want to maybe have a move toward a moderate

hypertension as the sort of main confirmatory study that would provide us reassuring safety data in the vulnerable populations of the elderly, et cetera, to make sure that these really are equivalently safe therapies.

DR. TEERLINK: So, yes, I would reinforce that exact comment. By the time the drug is made, at this point, you have already had a lot of experience with the individual components.

My main emphasis is, is the severe population necessary, no, but I don't think the factorial design will typically be sufficient to give you the information of the interactions of the combination therapy in a patient population with comorbidities and to evaluate the safety and the adverse events of the combination.

Because of that, you actually need to purposely select a group of patients that is going to be perhaps a little more susceptible to those adverse events to see what happens.

I am not saying you have to target patients purposely to cause AEs, but rather you

need to target the population where it is going to be most likely to be used.

My only concern about the Avalide program in front of us now from the combination studies is that the patients were incredibly healthy patients. For a hypertensive population to have this lower rate of comorbidities is impressive that you were able to find that many patients who were that healthy with that severe of hypertension.

So, I am not sure how applicable that data is actually to some of the issues of the safety. But, because we have so much knowledge about these individual components, I think I am comforted by that, but not necessarily by the studies.

DR. TEMPLE: There is another source of data. The long-term follow-up--I mean patients who finished their initial trials for all of these drugs are often put into long-term follow-up studies at which point they get all kinds of other stuff, because that is not controlled.

So, there is a place to look for anything weird maybe. I mean these aren't controlled

observations.

DR. TEERLINK: [Inaudible comment.]

DR. TEMPLE: No, it won't get you that. There is no outcome data for any new antihypertensive at the time of approval. If we don't ask for it, we wouldn't know how to really get it, because you can't not treat anybody.

DR. TEERLINK: Right. As I was suggesting, it is more on the AEs. I think the other thing that you get from one study, or two studies, it's kind of a larger study, single, focusing on a combination agent, is you actually get to see physicians use the combination, see how it behaves together in that setting, in a more--still a clinical trial setting, but perhaps a little different than you get from the factorial design.

DR. WARNER STEVENSON: I would also like to emphasize that the duration of these studies is really optimal for looking at blood pressure control. It is not optimal for looking at safety.

So many different things can happen after

seven to eight weeks. In fact, I am amazed how well medicines are tolerated for their first couple of months. You know, Month 5, Month 6, they come back and now they have sort of had a couple of dizzy episodes and different things, so we need to emphasize that these are very short-term studies in terms of safety.

DR. TEMPLE: I just want to mention these aren't controlled, but the longer term database for all of the antihypertensives is considerable usually, and there is lots of use of multiple drugs. These aren't controlled trials in any sense, but for weird stuff, you know, that speaks for itself, you do get a shot at those, not for subtler.

DR. HARRINGTON: We had the meeting last spring where the recommendation from the panel was that we keep these trials on the shorter side, because of concerns of--particularly if you were going to have placebo-treated patients. So, there is a challenge.

DR. WARNER STEVENSON: But which these, by

and large, were not placebo controlled, this combination versus single.

DR. HARRINGTON: So, Norm, let's see if we helped you, as you said, if we were in your seat. My interpretation of the remarks is that the data that was presented us today was actually a pretty good template if one wanted to specifically study the severely hypertensive population, that people felt that the data were fairly presented and that there were a number of analyses that were available to us to look at.

But at least I am hearing a sense that people do not believe that you necessarily have to do just a population focused on the severely hypertensive group, that people would be willing to look at a broader array of patients, that would then be presented in a full disclosure manner.

But I think I am also hearing from several people that they would like to see in these studies some more high-risk patients, more patients with CKD, some more of the elderly, some more patients with comorbidities, so perhaps we helped you a

little bit.

The final one is that I think I have also heard, particularly from Jason and Mike and John, that there is a concern about people going back to data mine, that they would like to see what that data looks like. People wouldn't be averse to looking at it, as I am sure you are not, but if that was not the original intention of those studies, that there is some concern about how informative they actually might be.

DR. STOCKBRIDGE: I just want to point out that the use we are making of Avalide's pivotal study is not based on their primary endpoint either.

DR. TEMPLE: This really goes to the question, and we are still agonizing with it, too, I mean those trials all were designed to show the combination is better than single entity. That is what they were designed to do.

All we would be doing now is dichotomizing those data, and that is, instead of saying it was 4 mm of mercury better, the combination was 4 better

than either single entity, we would be saying it was this much more likely to get to goal than the single entity.

It is the same data, it is exactly the same data, and as I said, we are inclined to think that is not exactly multiplicity in the usual sense, and not too much correction is necessary.

But we are still having internal discussions of this, so I don't want to present that as final, but it really is the same data. They are mining it for the dichotomous component, but they have already got it. That is how they got approved in the first place.

DR. HARRINGTON: Fair enough. We actually are looking at Avalide's primary endpoint. It is just that the assumption that they made about the event rate in the monotreatment group was not what was observed ultimately.

They made the assumption that a much lower control would be achieved, but it is the difference between the two, as they have pointed out, is still highly significant. It is just a matter of whether

you accept that that much of a difference is important.

DR. TEMPLE: Right The other thing I guess I would say is that in hypertension and a lot of things where people worry about goals, implicitly or explicitly, the dichotomous variable is always a secondary endpoint, and they have always met their primary endpoint or we wouldn't be talking. So, it is not so bizarre to pay attention to those numbers without too much correction.

I had one other thing about making sure you look at high-risk people. It would help us to know what risks you are particularly interested in.

I understand orthostasis is one of them, you are worried about that. But what else are we looking for that we wouldn't know already from the single entity data, because single entity data, we have got a lot. There must be some interaction in a high-risk population that we are worried about.

Some high-risk populations, I am not quite sure what that is. Someone has a lipid abnormality, I am not sure I know what to worry

about in a person who has lipid abnormalities as opposed to someone who doesn't, from the combination as opposed to the single entities.

It would help to think about what exactly we would be looking for in these high-risk patients other than blood pressure. I understand that one.

DR. WARNER STEVENSON: I think it all revolves around that. As soon as you include something that alters volume status, with something alters vascular tone, those interactions become less predictable, not only the hypotension, but potentially renal function, as well, are the major things that I would be concerned about.

In the diabetic population, particularly in elderly diabetic population, more people with autonomic neuropathy who may be less able to keep their blood pressure up when you inhibit it, and decrease volume status slightly. So, those are the things, it is blood pressure and renal function I think I would be most worried about.

DR. HARRINGTON: Do you want to comment specifically on those CKD patients?

DR. PAGANINI: No, only that it is a large population, it has grown, it has been defined, and has been fairly well categorized now into stages. I think as the population gets older, you are going to find more and more people with that type of subclass, subclinical, if you will, renal dysfunction, and they should be represented in a lot of these combination or single drug studies.

DR. HARRINGTON: The one other thing that I might throw into that particularly for the elderly is the average Medicaid coronary disease patient takes between five and six medicines, so understanding adding yet another couple on is not trivial.

DR. TEMPLE: Only five or six?

DR. HARRINGTON: The average.

DR. TEMPLE: They must not have multiple diseases.

DR. HARRINGTON: We have probably exhausted Question 3 there.

Question 4. What findings would support a more cautious approach to combination therapy?

Symptomatic hypotension or syncope. Hypokalemia. Other adverse consequences to consider.

Do you feel that such findings have been adequately excluded for Avalide?

We will start over with you this time, John.

DR. TEERLINK: Starting out with the Avalide specific questions, I think you have outlined the major areas of concern. I would have added to this, and had down here as well, the issues of worsening renal function, because there was that potential that, especially if you took already low, relatively mild blood pressure patients, then started them on this type of agent, you could precipitate worsening of renal function.

In terms of specifically Avalide, I do believe that it has been adequately addressed by the entirety of the experience with that agent.

In terms of general approaches to new combination therapies, it really needs to be once again viewed in terms of the context of what is

known about those agents as individual therapies.

Precipitating heart failure, precipitating angina, precipitating worsening renal function are all things that I would want to know about in a number of agents that could be viewed as combination therapies. But, for this specific project, I am content with what has been shown.

DR. LINCOFF: I think again we have talked about the main issues, but again, I think Dr. Stevenson's point about the duration here, for the data we have here, it looks like hypertension, we are reassured.

Granted, the moderate hypertension study here was 12 weeks, which is a little better than the 5 or 7 for the first study, but if they are going to focus--if the future developmental efforts focus on a group at risk, it may also be worthwhile to focus on a longer period of follow up, particularly since this isn't placebo controlled.

I mean the previous discussions were placebo controlled, and only exposing patients to a relatively short perio. But this is a study

comparing a therapy that is effective, but not as effective, and I think that you could justify going longer particularly if you weren't in a severe hypertension population, but in a moderate hypertension.

It would just be nice to have some reassurance over a longer period of time as patients go through the vicissitudes of life, they don't develop dehydration and become more syncopal or more dizzy on the combination therapy.

DR. HARRINGTON: I like the idea of adding worsening renal function to this list. I felt that with Avalide specifically, seeing all the data, particularly the data we saw right before lunch, granted it is limited by being claims data, but that it was also useful to see a large experience with observational analyses suggesting a safety profile that was consistent with what we had seen in the trials.

Adding it all together, I do think that the final question has been reasonably answered, that these things have been adequately excluded.

DR. PAGANINI: I won't add much other than just the final question, I think they have been adequately excluded, and I would agree with everything that was said before.

DR. HSU: I have no comment on this.

DR. WARNER STEVENSON: I think they were adequately excluded for the population studied. I am not entirely sure that we might not see some in the more typical population.

I think going forward, it would be important with the combinations that include a diuretic particularly, but probably all the combinations, to actually report all the postural vital signs as one of the safety endpoints, not just having it cut off of a greater than 20 mm change, again as in full disclosure.

MR. FINDLAY: I would agree they were adequately excluded in the data we saw today, and I would just make a general comment since the question is would you support a more or what findings would support a more cautious approach to combination therapy, and just make a general

comment that there is economic incentive obviously driving combination drugs these days, and people are taking more and more medicines.

Therefore, I think there ought to be just a general consideration of--and Norm already spoke to this--getting more and more applications for combination drugs, that that has the potential to add to the polypharmacy problem we have among the elderly particularly.

DR. RYDER: I have nothing to add.

DR. HARRINGTON: Bob or Norm?

DR. TEMPLE: No, but I heard a lot of people advocating polypharmacy sufficient to get the blood pressure down. I think in hypertension, we are not so worried about that. I mean we want them to get to goal somehow.

MR. FINDLAY: It's a general comment. No, I agree with it totally in the treatment of high blood pressure, and obviously, we are talking about that today, so we are favorably inclined towards the combination therapy. But, in general, we are going to see more and more combo drugs, I mean I

think we all know that.

So, I think from a public health perspective, it just behooves us all to just think in the grand global scheme of things that we need more caution.

DR. TEMPLE: Make sure they are all useful.

MR. FINDLAY: Yes, make sure they are all useful before we get them out there, and the economic incentive, we are not here to talk about that, but that is a reality in our world.

DR. HARRINGTON: Other comments?

I think on Question 4, the summary would be that there were a couple of other things that were added to the list here, including worsening renal function, some concerns over the duration of recording of adverse events, and as Lynn brought up again, some of the subpopulation issues, but in general, the feeling around the table was that these have been reasonably adequately excluded for Avalide.

Question 5. Demonstrating blood pressure

effects in clinical trials requires many subjects, many replications, and carefully controlled conditions unlike clinical practice.

Is there a value in terms of expected clinical outcomes to reducing the number of titration steps a physician is expected to make?

That is an interesting question. Let's start with Steven.

DR. RYDER: Thank you. I would like to emphasize something that Bob Temple mentioned before, but it is worth repeating.

Controlled clinical trials are just that and, as the people around this table know, you know, in controlled clinical trials, you prespecify everything and you do everything possible to try to get physician investigators and patients to adhere to the conditions of the trial so you can make observations, you can have prespecified endpoints.

But your algorithms are pretty much defined.

It is incredibly difficult, I would hate to say impossible--with scientists I should never say impossible--but it is very, very difficult to

look at things in a controlled clinical trial where you are looking at something that is free ranging, whether it's Hawthorne effect or Schrodinger, when you observe, you perturb.

Even in relatively free ranging experiments where you allow physicians to treat as they would, you still find when you observe, you perturb, and it is not the same as all the behavior patterns are different. I think that that is something that this committee has recognized.

I know that in past discussions, and Dr. Lapuerta this morning did a review of the literature that is unfortunately inadequate. It is a very difficult topic. But I think it is important to have that recognized. It is a point Bob made before, but it is worth repeating.

MR. FINDLAY: In terms of the data we saw this morning, I think the demonstrated value to clinical outcomes by reducing the number of steps that a doctor had to take in a patient, too, and consumers, was there.

DR. WARNER STEVENSON: I think that is a

benefit that is going to be even larger in real world. It is very difficult to have sequential interventions made without something interrupting it along the way, and I think the faster you get there, the better.

DR. HSU: No comment.

DR. PAGANINI: I really don't have much to say beyond what was said already.

DR. HARRINGTON: Mike Weber showed us that in a variety of trials, it can be very difficult to get there in the best of situations, so in practice, we heard from Dr. Berlowitz how challenging it is.

So, to take the public health perspective here a strategy where more people would get there quicker, I think Dr. Weber put it very well, that if you fall behind, you may well not catch up even in the best of circumstances. Practice is much messier than the best of circumstances.

I would be inclined to say that there is absolutely a value in approving outcomes if we can get more people there, which is likely what a

strategy of combination therapy would do.

DR. LINCOFF: I agree. I think this is a real example where the effectiveness of a therapy is even more marked than the efficacy.

DR. TEERLINK: Nothing else to add.

DR. HARRINGTON: That one seemed reasonably clear, Norman and Bob. It sounds like we all agree that taking things out of the hands of the physician, or make it easier for him or her to achieve what they want to achieve seems to be important.

DR. STOCKBRIDGE: So, the next step is you tell people not to measure the blood pressure again after you have decided to treat them.

DR. HARRINGTON: I think we are going to come to that question.

DR. STOCKBRIDGE: Isn't that where you go?

DR. TEMPLE: Why say that?

DR. STOCKBRIDGE: Because the additional visits are opportunities to make the wrong decision. It's why people, even with severe hypertension, only 40 percent of them got treated.

DR. TEERLINK: But at least 40 percent are getting treated.

DR. TEMPLE: You have got to see how they are doing.

DR. PAGANINI: Let's not take medicine out of the hands of the physician. Christ, guys, what are we doing here now? Let's just put it in perspective. I think what we are talking about is the step approach versus a non-step approach, or a different combination approach, or a different method of looking at hypertension, not taking it out of the hands of the health care provider. I think that is the wrong message that we are sending.

So, what I would say is that we are putting into the hands of the health care provider more realistic tools and medicines to use in controlling that disease entity. We are not taking it out of his or her hands and having the companies decide how to treat. That's foolish.

DR. STOCKBRIDGE: I am not advocating taking it out of the physicians' hands. I am just

saying the blood pressure measurement is too noisy to contribute in any useful way to the decision-making process that you need to follow.

DR. PAGANINI: Well, I think, Norman, that is because there is a wide variety of taking blood pressures. Now, I was schooled in the Ray Gifford school of blood pressure. I don't know if any of you guys are old enough to remember Ray Gifford, but he was a superb clinician who would leave his patients in the room for 15 to 20 minutes before he would go in and do any type of blood pressure measurement, both sitting and standing and lying.

Now, in the modern clinical pathway where in 15 minutes, you already saw 15 patients.

DR. TEMPLE: That is 8 minutes too long.

DR. PAGANINI: That's correct. You can't get to it, so I think the problem is in how you take your blood pressure and what that represents compared to how it should be done. So, I am not sure it is anything other than that.

I will agree with you that maybe that is the fuzziness, but if you were to then standardize

how blood pressures are taken, not over a sleeve, with an appropriate cuff, et cetera, et cetera, et cetera, et cetera, I think you would see less of a standard deviation, a little bit more of a specific answer.

DR. TEMPLE: But also, you have to decide somehow whether you are going to add a third drug, which can only be done by monitoring the blood pressure and seeing how you are doing.

DR. STOCKBRIDGE: No, I am with Dr. Lincoff. You decide to raise the dose or to add a drug in anybody who isn't complaining about how many drugs they are already on.

[Laughter.]

DR. PAGANINI: So, if somebody doesn't show up for their visit, you say cut back?

DR. LINCOFF: Or if they could make it, you add a third drug regardless.

DR. TEMPLE: One observation. We all are critical of casual blood pressures, but all that epidemiology comes from those.

DR. HARRINGTON: Let's go to Lynn and then

John.

DR. WARNER STEVENSON: It seems to me that we have an artificial tracer about the stepped care thing. This is still stepped care. It is just a bigger first step. You still have to decide whether to up-titrate to the second dose of Avalide, so it is still stepped. It is just we start with a bigger first step, so we don't have to make as many subsequent ones.

DR. HARRINGTON: This is going to be unusual. Let me take Norm's position here. In the clinical trial, it was forced titration. In fact, I forget who presented it, but somebody said, well, we may have had fewer adverse events if it hadn't been forced titration, because those people were reasonably controlled already, the group of them were already 140/90 or something.

So, maybe Norman is not crazy. You know, should the package insert read that you if you have a blood pressure in some range, you get started on Avalide and you get force titrated a week later?

I mean to push you. If we leave it in the

hands of a physician, these are the same physicians that Dr. Berlowitz was telling us that 40 percent of the time, even when it is severe, they don't do anything. Maybe we have given away our right to adjust things, and we should just push the medicine.

DR. TEMPLE: So, if the low-dose combination is tolerated, you go on to the high-dose combination.

DR. HARRINGTON: I am asking the question. I think Norm brings up a really important point. That is what the trial did. The trial got a blood pressure, but it titrated you anyway.

DR. TEMPLE: Unless you were too low.

DR. WARNER STEVENSON: Unless it was too low.

DR. HARRINGTON: But even people who were at goal, they titrated.

DR. WARNER STEVENSON: But that is not too low.

DR. STOCKBRIDGE: Every one of these trials, that is a difference finding trial with a

drug, there are 30 patients per group at least. There are 3 measurements, not 1, but 3 measurements made a few minutes apart in a quiet, well-controlled setting, you don't have a prayer of making a reasonable decision about what the blood pressure is when you measure it in the clinic and you are looking for some evidence of a drug's effect.

DR. HARRINGTON: Drug effects that are--what did we hear, what did Mike Weber say--2 mm difference might be clinically important. I guarantee in my clinic, 2 mm would not be picked up.

Since we are not sitting in your seat, Norman, you are going to have to write the--

DR. TEMPLE: We will probably still write it as if you are measuring blood pressure, but it's worth thinking about.

[Laughter.]

DR. HARRINGTON: Let's go to Question 6.

Is there a quantitative risk-benefit assessment that provides credible support for the

initial use of Avalide? If so, should the initial use be limited to a specific population?

I guess we are on this side of the table this time.

DR. TEERLINK: I am not sure I understand the question entirely, but I think it requires a number of extrapolations. So, is the competing risk of delaying optimal effective whatever therapy for reducing blood pressure, and the number of events then occur in that whatever time period, it is to finally change the blood pressure to an equivalent rate, which in this trial, which is much better than it would be in the real world. It took 7 weeks or 6 weeks in the one study and 4 weeks in the other study.

I might have got the numbers wrong, but there is clearly an increased risk in the area under the curve for the risk of having those extra millimeters of mercury doing damage to you, and that is offset against whatever extra adverse events we have from using, jumping right away to the combination therapy.

In this specific case, given that the extra adverse events were so low, and we have epidemiologic and other data to try to impute that bad events can occur during that time that it takes to get the low pressure, I think there is that kind of data. But I am not sure how to quantitate it per se, quantify it per se.

Does that answer the question?

DR. HARRINGTON: Michael?

DR. LINCOFF: I agree. I assume we are referring to the sort of back of the envelope calculations that were provided in the sponsor's briefing.

Given that the magnitude of cardiovascular benefit for a relatively small difference in blood pressure is so large that in the absence of sizable side effects, it is a fairly persuasive story. Again, I don't know that it helps us, though, pick out a population aside from the fact that higher blood pressure to start with is more likely to benefit from the combination therapy.

But it looks like it's a pretty wide

benefit as compared to risk, and would encompass a fair number of patients, which is why my inclination is, and has been, to include the moderate hypertension, as well.

DR. HARRINGTON: I think you have said well what I was going to say, so I will pass on to Emil.

DR. PAGANINI: I agree with both statements. I would say that this would be probably a drug that could be first line in Stage 2, JNC 7 in Stage 2, which includes severe and moderate.

I would actually want to couch it in those terms since we are trying to unify our approach as opposed to keep defining severe, moderate, and mild, to couch it in terms of Stage 1, Stage 2.

DR. HSU: I have no comment.

DR. WARNER STEVENSON: I would agree. I don't really think we have seen actually a true quantitative risk-benefit, but I think we all agree that it would be there.

I would point out that if we look at the

discontinuation due to adverse events, that if we are going to play the relative risk game, it was actually increased by 80 percent by use of the combination versus the single agent. However, again, that is playing the numbers game, and I do think that there is support for this initial use.

I think it would be reasonable to indicate that there is limited experience in the elderly.

MR. FINDLAY: I agree there is support for an indication of initial use in moderate and severe.

DR. RYDER: Nothing to add.

DR. HARRINGTON: Norm, did you get what you need from that one?

DR. STOCKBRIDGE: That was fine.

DR. HARRINGTON: This next one is a voting question. Dr. Ryder is non-voting member today. You certainly could comment, but we will ask you not to vote.

The question is: On the basis of available data, should Avalide be approved for first-line use? Please vote. If you do not believe

that the data are adequate to support approval, describe what additional data would be needed.

So, if your vote is no, please describe what would be needed. You certainly could also vote yes with a qualification if you believe that some additional data might be encouraged as part of that.

Why don't we start with Steve.

MR. FINDLAY: The vote is yes. There is data to support the use of Avalide as a first-line treatment as we indicated in the last question for moderate and severe.

DR. WARNER STEVENSON: I would vote yes with the caveat that we would like to see more experience in the elderly and in patients who have more renal dysfunction that was indicated here.

DR. HSU: I cannot speak to clinical goal, but given the understanding I have now of how the medical 10 percent number came about, I will say 10/5, 5/3 may have clinical benefit. I vote yes.

DR. PAGANINI: I would vote yes, and I would also ask that we have some subgroup analysis

at some time with CKDs and elderly.

DR. HARRINGTON: I just want to clarify, Emil. Do you mean analyses of pre-existing data or encouragement to do more studies?

DR. PAGANINI: Just more studies, not necessarily for approval, but to focus on that population. I think this is a population that is growing, and we have got to study it. They been sort of the higher end, the Stage 2, late Stage 2, Stage 3, Stage 4.

CKDs have been excluded from any of the stuff that we have seen here, and the extreme elderly, you know, getting old, as I am, it does two things. It makes you appreciate people who are young, and it also gives you the opportunity to meet so many new people every day, that you probably have already met before, just forgot who they were.

So, I think getting older, we are talking about 75, 80, 85-year-old people, and those are not that small a group. It's a very large group with CKD underlying it. So, I would say that is a

subgroup that I would like to see in clinical, after-market type of stuff.

DR. HARRINGTON: I will also vote yes for approval for first-line use and would support the statements that have been made about future studies including particularly the elderly population to better characterize the drug amongst them.

DR. LINCOFF: I would vote yes for all the reasons I have discussed, as well as everyone on the panel.

DR. TEERLINK: I would vote yes, as well. I would like, with this particular combination, we do have the benefit of the IDNT trial and a number of other specific studies with irbesartan in the setting of chronic renal disease.

In addition to that, I don't know this data off the top of my head, but I imagine that a number of those patients were probably on diuretics, so many of them could have been on hydrochlorothiazide. So, in terms of requiring a new data specifically for the renal issue, for this specific agent, I am not as concerned.

DR. HARRINGTON: What about the elderly, are you comfortable?

DR. TEERLINK: The elderly is another issue, but that is an issue in every trial, so to hold them--so I would make a general statement encouraging sponsors to be more liberal in enrolling patients who are more representative of the patient population.

In cardiovascular disease, that is going to be patients who are over 75 years of age.

DR. TEMPLE: There is a mountain of experience in the elderly with the drugs individually and in undescribed combinations. I mean SHEP is a very impressive study, it's all over 70, it is aggressive use of chlorthalidone followed by the second drug that you got if you failed was a beta blocker, I think.

So, while that is not one of these, it is sort of a near relative.

There are also a lot of studies with ACE inhibitors in heart failure, which has a lot of old people. There is a lot.

DR. TEERLINK: [Inaudible comment.]

DR. TEMPLE: Both ACE inhibitors and ARBs have, oh, I don't know, upwards of 20- to 50,000 people in heart failure trials. We can go look and see what the elderly population in those is, but I know if you are doing heart failure, you have got to have a lot of people in their 60s and 70s, you do.

Over 75, that is another question. Those people have been hard to get into trials all together. But of all the categories of drugs that I would bet have data, we can look. These would be the ones, because they have been used for so many different things.

DR. WARNER STEVENSON: I would just clarify, though, in the heart failure trials, in fact, the diuretic doses are adjusted to maintain volume status in someone with elevated volume status. We would not be using them in people who start out looking euvolemic. So, the risk would be considerably different in that population of the combination compared to in a hypertension trial.

DR. TEMPLE: Yes, they are probably hypervolemic, but they are also getting aggressive treatment with furosemide and a wide variety of other volume-depleting things.

DR. WARNER STEVENSON: [Inaudible comment.]

DR. TEMPLE: Okay. But I am still interested. Before we start asking for stuff, I am not I understand what it is we are looking for. Is it more data on ARBs in the elderly, for which I would say the place to look is see what the total collection of data is. I don't think that is a drug-by-drug question. We could certainly look at that. I don't know what we have.

DR. HARRINGTON: I think that would be the first step. I mean when we described the elderly, I think John was saying in these analyses, we have seen the elderly described as greater than 65.

DR. TEMPLE: That is a terrible error, I made it. Thirty years ago, I would never say this.

DR. WARNER STEVENSON: But that is just because people are older now. That was the age

they were old back then.

DR. HARRINGTON: So, we would like to see information, and it may exist in the pre-existing data sets. What you are talking about here, Bob, is combination therapy in a broad array of what I will call elderly, above the age of 75, who are commonly seen in clinical practice, and what the experience of ARBs plus diuretic therapy is in that group of patients.

I suspect it is relatively limited, because as you have also pointed out, it has been exceedingly difficult for a variety of reasons to enroll these patients in clinical trials, largely because the comorbidities usually exclude them.

DR. TEMPLE: We can look at the heart failure stuff. That might not entirely answer your question--

DR. HARRINGTON: No, it's different.

DR. TEMPLE: --because they are volume expanded, not volume depleted.

DR. HARRINGTON: Where you would have more luck is probably the coronary disease trials that

have looked at ARBs and ACE inhibitors, the post-MI studies, et cetera, where you typically would get 12, 15 percent above the age of 75, and those data sets are large.

DR. WARNER STEVENSON: And I think that this is certainly something that could be post-market in terms of just looking at the first 500 people who are over 75 who get the combination. I don't think it is going to require a lot of difficult comparisons. I think we just want to get a general feeling for that group.

DR. TEMPLE: And it is to look particularly for volume problems like hypotension.

DR. WARNER STEVENSON: Hypotension and renal function.

DR. HARRINGTON: The vote is 7-0 in favor of first-line approval, but I note that the question didn't say first-line use for severe or moderate, which is what we are going to tease out in the next question.

Cathy, let's go to Question 8, which has a series of questions to it.

If Avalide were approved for first-line use, should it have an indication with constraints similar to that for Hyzaar or is it possible to give better advice? A major element of better advice is a better description of the expectations of using irbesartan alone and in combination.

The placebo effect observed in controlled clinical trials has at least two components. Please comment on whether either component is relevant to clinical practice; regression to the mean; and accommodation to the clinical setting.

Since this question is a little different than the following one, why don't we stop and address that. So, comment on whether the component is relevant to clinical practice meaning talking about regression to the mean and accommodation to the clinical setting.

Why don't we start over at your side now, John.

DR. TEERLINK: Both regression to the mean and accommodation to the clinical setting clearly play a role in the transfer of a new therapy or an

old therapy, for that matter, into the clinical setting, into practice, so both of those are relevant. However, I think the reason we use the clinical trials is to try to also explain that with placebo as being the control force of those effects.

I don't know if that is answering the gist of the question, Norm.

DR. STOCKBRIDGE: Let me take another stab at the question. We do placebo-controlled trials when you use cuff measurements of blood pressure to tease out from regression to the mean and accommodation to the clinical setting, how much of the effect you see is, in fact, attributable to the study drug itself.

If you think that regression to the mean happens because you have got in mind a cutoff below which you are not going to treat, if you think regression to the mean matters, or if you think that accommodation to the clinical setting matters in the regular clinical practice, then, you are going to see people's blood pressure go down for

both of those reasons as you make serial measurements.

So, the question is as we describe here, what effect you are going to see in practice, how likely are you to get to goal. It seems to me that the data you want to put in those displays is not the placebo subtracted data, it is, in fact, what you are likely to see in the clinic that is including some placebo effects.

DR. TEERLINK: I would take your exact reasoning and say that I think because of that, that is why you need to present the placebo-corrected data, because that is what you are going to see in clinic. That is what you can expect in clinic is the additional benefit of that drug in addition to just basically measuring serially blood pressures, so I actually would be in favor of placebo subtracted data.

DR. TEMPLE: Remember the severe study didn't have a placebo. The benefit you get from the combination does not require a placebo subtraction. That difference is present, so what

is wrong is where on the Y axis you are. That is wrong. But the difference is right even without placebo subtraction, which, by the way, has nothing to do with becoming acclimated to the environment or to regression to the mean. It is entirely digit preference, which occurs at the time of entry. You read high to get them into the study and then you don't care anymore, because you don't see it with automated cuffs.

There is no substantial placebo effect with automated cuffs, whereas, within the first week of measurement in a trial, there is 5 or 6 mm of mercury, it is completely bogus. You don't see it if you use random digit cuffs and stuff like that. We really know what it is, and it is not these other things.

But the trouble is the best data on severe isn't going to come with the placebo group, so even if you would like to subtract it, you can't.

DR. TEERLINK: Right. So, I was answering the ideal situation. If you have it, I think the placebo-subtracted data is the most useful, and

placebo-subtracted data obtained in a setting where you don't have those kind of biases is the most ideal.

In the absence of all that type of data, then, you present your best comparator and just give a definition of what the differences are between them.

DR. TEMPLE: It does look as if automated cuff data doesn't have that problem, but we don't have very large studies with automated cuffs usually.

DR. STOCKBRIDGE: To be clear, if you do an ABPM study, and you enroll based on the baseline blood pressure measurement with ABPM, you absolutely are guaranteed to see regression to the mean.

DR. TEMPLE: You have seen that?

DR. STOCKBRIDGE: Absolutely, you are guaranteed to do that. In fact, it has got nothing to do with the nature of the measurement. It has got to do with truncating a distribution where you have got a measurement that has got some biological

variability to it.

DR. TEMPLE: The thing you see in clinic pressure cuffs is that the major fall in the placebo group occurs within your first measurement. A gradual downward drift I find perfectly plausible as regression to the mean. That wouldn't surprise me at all, but this abrupt fall I think is just breathing funny.

DR. HARRINGTON: It is just a function of the measurement itself.

DR. TEMPLE: You read high because you have got to be over this to get in, you know, and you round off your blood pressure cuffs, and then you don't have to do that once they are in the trial.

Actually, Norm has the solution to that. This has come up in many, many settings, and that is, you enter patients based on their blood pressure, but you don't use that as the baseline.

You use as your baseline the zero time in the clinic, and it will probably be lower than the entry criteria, but you won't have this phenomenon

anymore, which we are trying to sell to people it's a very good idea once you are in the trial.

DR. HARRINGTON: Michael.

DR. LINCOFF: I am not sure what to add to that. Fortunately, in this setting, what we are looking at is the incremental value of one combination over another drug, so I think those issues aside, they neutralize out when you make your comparisons. I think the presentation of the incremental benefit of one to the other, especially since I don't think the real issue is the thresholds, it is really the difference.

DR. HARRINGTON: The difference between the two therapies.

DR. LINCOFF: Yes.

DR. HARRINGTON: Emil.

DR. PAGANINI: No comment.

DR. HARRINGTON: Jason.

DR. HSU: My original comment was going to be whatever the analyses was based on to go with that, but the explanation that Bob has of Norm's solution, that sounds pretty good to me.

DR. WARNER STEVENSON: I think the full disclosure basically covers this question, which is you want to tell the physician what is the chance that he is going to get down to a certain blood pressure on this therapy, which includes the placebo effect, but that is what you want to know clinically.

I actually have a question, which is has the FDA approved the placebo for hypertension, because if not, it is an irrelevant question.

DR. TEMPLE: We haven't approved it for anything.

DR. WARNER STEVENSON: That would be an interesting panel.

MR. FINDLAY: Nothing.

DR. RYDER: That sort of drifts into the next little tiny question, but I sort of believe that because of the dialogue that I heard Bob and Norman talk about, it is important to tell people what you did and to present both the placebo data.

This committee had discussion in the past I think about the use of placebo, which is still

pretty important. It gets into the whole issue of equivalence trials versus non-equivalence trials. Dr. Temple has written standard articles on that, and it is better to have superiority if you can.

Placebo still has a role. Tell people what you did. Tell people the measurement instruments that you used, ABPM, or office measurements, and then present the information.

DR. HARRINGTON: As you said, Steven, it gets into the next question, which is: Should the description take into consideration the likelihood of getting to goal on each component alone, or just the irbesartan?

Start the conversation on that, and we will go back around the table if people want to weigh in on it.

DR. RYDER: I don't really have a comment on that.

MR. FINDLAY: No comment.

DR. HARRINGTON: Lynn?

DR. WARNER STEVENSON: I think it is useful to have the three curves frankly. I don't

think many people are going to go with the thiazide alone, but I think it is reasonable to have them. I think we do do better with information contrary to some accusations.

DR. HARRINGTON: Jason.

DR. HSU: No comment.

DR. HARRINGTON: Emil.

DR. PAGANINI: Again, it depends on your population. We are just talking about Stage 2, I think the three would be fine. If you are talking about just severe, which I think it looks like we have taken off the table, then, just the irbesartan would be fine. But I think we have broadened our indication first use in all three, it probably would be a good combination.

DR. HARRINGTON: I would fall in that camp, that particularly as we broaden the conversation into thinking about this more moderate group of hypertensive patients, having all the available information, which would include the individual components, as well as the combination, would be valuable as a means of presentation to let

people be truly informed.

DR. TEMPLE: The Clinical Trial Section will have the mean effects of all three, and they will be placebo subtracted. That part is easy. This is about the display of how you are going to do, getting to goal and all that, but I must say if there is a diuretic-only group, I think it should be shown, but in the first study there wasn't.

DR. HARRINGTON: Correct. But in the second study it did have.

Mike.

DR. LINCOFF: I agree. The presentation would have to take into account that we don't have the data for the diuretic alone in the highest blood pressure group. But I think it is instructive to see sort of the incremental benefit of the combination over the other two components.

DR. HARRINGTON: John.

DR. TEERLINK: I agree.

DR. HARRINGTON: So, it sounds like, Norm, that what the group would be in favor of is all of the information being presented particularly since

the conversation has gotten into this moderate range group of hypertension patients.

Let's go to the next subquestion here to 8, which is: Did subgroup analyses show other factors--like age or race--that should be considered?

So, those analyses, as you rightly point out, Bob, had to have been done, so is the question specifically, when you say should be considered, should that be considered specifically in the labeling in terms of adding that information, is that your question, or Norm?

DR. STOCKBRIDGE: Yes, that was the question.

DR. HARRINGTON: Why don't we start with you then, John. Should that information--we have seen some of the subgroup analyses on age and race--should that be included in the labeling?

DR. TEERLINK: Isn't it always included in the labeling? Yes, then, it should.

DR. TEMPLE: Before you leave that, if there is a difference, then, it would be. If it is

generally in the close range, you may not add much detail.

DR. TEERLINK: I don't see, I don't recall there being a huge difference that was of concern one way or the other, so I think a general comment would be appropriate. I don't know if this would require an in-depth description of the subgroups and their responses, and I don't think that would be more informative.

DR. HARRINGTON: If I recall, John, and maybe the BMS people can correct me, I thought that one of the findings, although the group of black patients was small, they did not get a very good effect as might be expected to the monotherapy.

DR. TEERLINK: But we aren't talking about approval of the monotherapy.

DR. HARRINGTON: No, but what you would want to do is do you want to show that the difference is, you know, that you might make the case that the effect is particularly impressive in the combination therapy amongst black patients.

DR. TEERLINK: I wouldn't do that, because

you are not comparing to the hydrochlorothiazide component there, for one thing. Secondly, I think the main point is that there wasn't a difference in response to this combination therapy with regard to ethnicity or race.

DR. HARRINGTON: What do you mean there wasn't a difference?

DR. TEERLINK: They had the same relative response, the same percentage of patients on the combination responded to the combination therapy whether you were white or black.

DR. HARRINGTON: But the magnitude of that difference between combination versus mono was greater. He is going to show us the data I think just to maybe refresh my brain. Emil's age is wearing off on me here.

DR. LAPUERTA: If I may present these data. Slide 25-54, please.

[Slide.]

So, the response to the combination in blacks approached that of whites, but the response to irbesartan monotherapy was different.

DR. HARRINGTON: So, how do you interpret this, John?

DR. TEERLINK: The Avalide was as effective in blacks as it was in non-blacks at achieving the systolic and diastolic goals or the changes in blood pressure. There would be equivalent changes in blood pressure.

DR. HARRINGTON: So, you are happy not then necessarily showing the individual data, but just pointing out Bob's remark that if they are generally consistent, leave them lumped together?

DR. TEERLINK: Yes.

DR. HARRINGTON: Okay. Leave that up while we go around.

Michael.

DR. LINCOFF: We are all aware of the difficulties in drawing too much from subgroup analysis especially underpowered. As long as they are qualitatively the same, and even if they weren't, you would have to do it with caution. But certainly these mild differences, I would be very hesitant to do anything other than to say the

magnitude of benefit was similar, because I think you just invite misinterpretation and misuse of the agent.

I have seen no subgroup analysis presented that was at all compelling enough for me to believe that they should guide therapy or be individually cited.

DR. TEMPLE: What is interesting here is that the irbesartan monotherapy looks--I don't know, you can argue about how much meaningful--I mean the labeling already says that it doesn't work as well in blacks for irbesartan, and that is shown in the green stuff.

When you use them together, there is no or little difference, and that is the most informative thing about the combination.

DR. LINCOFF: But you didn't see the expected effect in the moderate blood pressure with the hydrochlorothiazide. I mean you would have expected that to have looked better than it did, and it didn't. These are small numbers.

DR. TEMPLE: Actually, I don't expect