that. I don't expect diuretics to work better in blacks. I expect the combination to work better, because probably they raise the renin levels. I don't know, that is arguably informative. You know, everybody sort of thinks you should use the renin-angiotensin drugs along with the diuretic as an addition because it makes people more renin sensitive, and this sort of supports that, doesn't it?

Let me just pursue this. It is not uniform because the data weren't uniform. But most ACE inhibitors and ARBs say we don't work as well in blacks but, since the early VA studies with diuretics and beta blockers, it looks as if, when you use the combination, it is sort of a wash between blacks and whites, and that seems be more or less suggested here for diastolic or systolic.

It looks like the combination is race-neutral.

DR. LINCOFF: So, if you just say Avalide is as effective in blacks as it is in non-blacks, that is what you are saying?

DR. TEMPLE: Yes.

DR. LINCOFF: I was in favor of that.

DR. TEMPLE: Oh, okay.

DR. LINCOFF: I just was not saying that you needed to go into this amount of detail to get into that.

DR. TEMPLE: The labeling already says that the monotherapy doesn't work very well in blacks.

DR. HARRINGTON: Bob, would you like to say further that the combination neutralizes the ineffectiveness of monotherapy, because that sounds like what you are suggesting, and I am not sure I disagree if I could believe the results and thought they were consistent.

Irbesartan and ACE and ARBs don't typically work as well in blacks. It looks like by adding the diuretic, you eliminate that differential.

DR. TEMPLE: That is what I think is of interest, and these findings go back into the '70s when the VA did the study with natalol where it was

also true. Beta blockers didn't work very well. I mean the combination worked about the same.

DR. HARRINGTON: How to word this is not a trivial consideration given what we saw from Bill Weintraub. I mean there are a lot of black patients who fall into the category of the severely hypertensives. I am inclined, Bob, given the small numbers, is to just say that there is consistency amongst the subgroups, and that would include blacks and whites.

DR. WACLAWSKI: Dr. Harrington, I could show you what is in the label already as a way to maybe--

DR. HARRINGTON: That would help, yes. Thank you.

DR. WACLAWSKI: 41-31.

[Slide.]

So, as Dr. Temple was referencing, there is a statement that irbesartan monotherapy was effective in reducing blood pressure regardless of race, but the effect was somewhat less in blacks. And then the second statement concerns that black

patients had an improved response with the addition of the low-dose diuretic. So it has both pieces in the Avalide labeling already for race. So I wanted to show this to let you know what the current status is of the labeling.

DR. HARRINGTON: Lynn, you had a comment?

DR. WARNER STEVENSON: I think this is ambiguous. It shows an "improved response with the addition"--improved compared to what? I think it would be fine to say that the benefit appeared to be equivalent regardless of race, period.

DR. TEMPLE: Perhaps in the place where the study is described in the Clinical Trials part.

DR. HARRINGTON: Emil.

DR. PAGANINI: Again, I will agree with what was said. It seems that the data presented seem to show that, but I am not sure of the strength of the subgroups, so I would go with Michael and say, you know, we are putting a lot of strength on perhaps underpowered subgroup analysis.

My concern is that this is going to be sort of genericized and generalized, and I am not

sure the strength in the data that was presented allows us to do that.

DR. HARRINGTON: Jason.

DR. HSU: Quite a few proposals on the table. I reiterate my general concern about subgroup analysis even though I understand the necessity for certain subgroup analysis.

My hesitation carries over to making a statement about equivalence, because there is a statement, so I have some hesitation to make a strong statement of any kind if the sample sizes are small.

DR. HARRINGTON: So, you would use the word, there was consistency across the subgroups. What wording would you, as a statistician, feel comfortable with other than there weren't enough patients?

DR. HSU: With the proviso not enough patients, I guess I would be more comfortable with consistency, because equivalence has--

DR. HARRINGTON: Has a specific meaning.

DR. HSU: Yes.

DR. HARRINGTON: Good point.

Lynn.

DR. WARNER STEVENSON: I would agree. Equivalence has too strict a definition. I think consistency or comparability might be better.

DR. TEMPLE: Remember, though, that the original thing in the labeling came from a subset analysis on pooled data, not exactly planned, but sort of required, and wasn't such a strong finding in the first place. As you can see from the language, it says it is a little less.

DR. TEERLINK: Bob, because that label gets put on, that kind of wording gets put on most of these, as you said--

DR. TEMPLE: Most of them.

DR. TEERLINK: Is that because consistently every time you do--there is something, too, every time you do a subgroup analysis, if it keeps popping up across 10 different agents--

DR. TEMPLE: Right. The answer is almost consistently, not absolutely every one has shown that, but they almost all do. When people have

looked, the difference goes away when you look at the combination with a diuretic, for reasons that we think we understand, too.

DR. HSU: You might even go with the not inconsistent.

MR. FINDLAY: I agree it should be a restrained statement.

DR. HARRINGTON: Steven.

DR. RYDER: Just caution when things are small numbers.

DR. HARRINGTON: I think that is a reasonably clear message from the committee.

Should the description take into consideration the dose of each component, or just the dosing strategy?

Norm, is this your question about should you measure blood pressure? Is this the forced titration, or what are you trying to get at here?

DR. STOCKBRIDGE: We have got a specific trial that was the basis for comparing the effects on one regimen versus another. The question is whether you want to know something, well, and, in

fact, it will become even more important if we are going to make a presentation that is based on the factorial trial, you know, what dose are you going to put into that.

In this case, we have got a specific trial we are focusing on that had one regimen versus one other regimen, one monotherapy regimen versus one combination regimen. So, you don't have any choice in effect about how you would describe the difference between getting to goal on one drug versus two.

You will with a factorial trial have a whole range of possible starting doses with a family of curves, and the question is what are you going to want to see there.

DR. HARRINGTON: So, in the Clinical Study Section, it will describe this trial and will talk about that there was a dose and then a forced titration, but then in the Dosage Section, you will indicate that there are multiple doses available of the drug, of the combination product.

Are you asking us should we say a more

specific statement that the dosing strategy was what was used, or should we just leave that in the Clinical Study Section, is that your question? I mean do you want us to pursue this issue of dosing strategy?

DR. STOCKBRIDGE: I guess the question is what do you want to put in the Dosing Recommendation Section as you, you know, show a set of curves that say if you follow some strategy, you will get this much more of a chance of getting to goal compared to some other strategy.

DR. HARRINGTON: Right, or do you say you start with the lowest dose and you titrate up, which we have already--the whole reason we are starting with combination therapy is because we don't believe titrating up is the most effective way of doing things with monotherapy.

DR. TEMPLE: Well, we don't believe that finishing one drug before you start the second is the most efficient thing, but we probably believe you should use whatever the starting dose of the combination was that they used and showed was

tolerable. But the figure you were going to show on who got to goal, that is going to be with the highest dose that was used.

DR. HARRINGTON: Correct.

DR. TEMPLE: But how to do it, my guess from all the previous conversation about worrying about hypotension and everything is that it would say start with this dose of the combination and go up if you choose to start with the combination.

DR. HARRINGTON: Let me go around the room just so we keep somewhat organized.

DR. RYDER: Yes, although that hasn't always been the case, I think. But my just general comment is that the regimens of this committee that I have followed for about 20 years now are that labeling recommendations regarding usage of an agent comes from direct evidence.

You study empirics, study specifically in that patients population, then, all the clinical evidence of that particular product, and then all the clinical evidence that is available about the pharmacology of the class itself.

It hasn't always been that in every time you have said, well, the study was done using this regimen, and therefore the best regimen, in our august opinion, is the following. I think that it is important for the committee to either agree or disagree that those are the sources of sort of the universe of information and all of it is put together.

DR. HARRINGTON: I agree with that statement.

MR. FINDLAY: Yes; in the section where you describe the clinical study, there should be full and clear disclosure, but I agree with that comment, I think in general.

DR. WARNER STEVENSON: I think maybe there are two questions here. One is for Avalide, and I think one says you start with the lower dose and the benefits observed were seen when 99 percent of people went to the second dose.

However, I think maybe part of the problem is for these other agents in whom we have these factorial designs with a lot of different boxes, we

have to decide whether there is an adequate amount of data in a given box to say what effect you are going to get with that dose.

I don't think you can add up doses under that necessarily when you come to this factorial design, and that is where you have to decide what numbers you need.

DR. HARRINGTON: Jason.

DR. HSU: No comment.

DR. HARRINGTON: Emil.

DR. PAGANINI: Again, I think the description of the study and the forced increase is important in the study. The reason I think behind the forced increase was to bring out the complications from the higher dose, maybe try to produce or induce some of these complications, and, since that is not the purpose of treatment, I am not sure I would sort of advocate that way of starting.

So, I would probably leave it blank and just describe what the dosing strategy was in the study as it is described and leave it to the reader

to understand that the 90 percent effectiveness was in the higher dose of whatever, because I don't think that was really what was being done.

I think the forced increased dose was to bring out complications, and not treatment focused is my understanding, although I could be wrong.

DR. HARRINGTON: There is a complex issue here, isn't there, that if you take beta blockers for heart failure, the clinical trials really pushed people to titrate up. In clinical practice, that is frequently not done, that people get put on lower doses of beta blockers for heart failure and sort of stay there.

The question always emerges as to are they getting the clinical effect that was observed in the clinical study. Here, at least, we have blood pressure as a measurement. I would be inclined, I think the way Lynn said it is my preference, that you very clearly state that in the clinical study, the benefit was seen.

These benefits, these probability curves were derived from a strategy whereby 90-plus

percent of the patients were titrated up after a week's worth of treatment, but, as Emil is saying, that not telling people that they have to force titrate patients, but making them aware of the fact that that was the strategy that was used, sort of a fine line.

DR. WARNER STEVENSON: One of the other things that we actually have no information at all on, or I am not aware of it, is if we would have gotten to that tolerability of the high dose had we not gone there through the low dose. In other words, if you had started everyone out on the high dose, maybe you would have had more people fall out.

So, I think in terms of we can only make our safety conclusions based on this titration strategy.

DR. TEMPLE: Although as Norm was pointing out, in the classic factorial studies, we are pretty sure they usually go right to whatever the assigned dose is without titrating, usually without any particular problem for these classes of drugs.

DR. LINCOFF: I agree with the idea that you make it clear that it was the higher dose. You encourage going to the higher dose unless intolerance or clearly at a very good target, supervenes at the lower dose.

DR. TEERLINK: I agree and I think this is where the proposal in terms of the general wavelength for hypertension in terms of agents can help, as well, because you can say this is how, you know, it started at a low dose, titrate up, and see below where we see that getting low blood pressure is a good idea, and that should be what drives your clinical decision.

DR. STOCKBRIDGE: So,if you are going to display something like the baseline blood pressure versus percent of getting to some kind of goal curves, if you are going to do something like that, it is going to have to say there what the strategy was, and that if you don't follow this strategy, you aren't even going to get what increment there appears to be, small as it is, between what it shows here is the one drug and two drug effects;

right?

DR. HARRINGTON: I think that is what you are hearing around the table, people want to be clear that the benefits that were measured in the trial, in this case on blood pressure, were derived from a strategy, and here are the curves; therefore, you have to know what the strategy was that got people there. I think that is what I am hearing. Okay.

Let's do the next two questions together. I think that they are related, because I think it is largely the data presentations around some of these graphs we have seen.

Should the description focus on systolic pressure, diastolic pressure, or both simultaneously?

Please identify any data presentation you saw that you felt best communicated the necessary information in a manner understandable by a practicing physician.

John.

DR. TEERLINK: So, I would say yes to all

the above. I included the systolic pressure, I included diastolic pressure, as was commented on by a sage individual to my right, that one could possibly put the systolic pressure and diastolic pressure on one graph to save space, but either way I present both of those.

In addition, I think I would encourage a presentation--and this is trying to provide the linkage of the messages--saying and in this context, this is what percent achieved JNC goals in each thing, just to give a sense of where that was or percent reaching some of the goals in the different groups.

DR. HARRINGTON: You liked the proposed graphs. You are a 2-dimensional graph guy.

DR. TEERLINK: I am actually personally, and I hate to admit this publicly, but actually a 3-dimensional kind of graph guy, but I think for the actual presentation, it should be a 2-dimensional graph.

DR. TEMPLE: We haven't up to now put specifically identified JNC or other goals. My

reservation about that is that different people have different goals, and they change, so we hope people will read all those things and form their own goals, or take somebody's word for it.

DR. TEERLINK: You don't have to label it JNC goal, but you can say the percent of patients who achieved a blood pressure less than 140/80 was, and the purpose being that that gives a chance for the clinician to say, okay, globally, this is the difference I am looking at.

DR. TEMPLE: So, you would show all the data for starting blood pressures and stuff, and then you would pull out one or two of interest.

DR. TEERLINK: Right.

DR. HARRINGTON: Michael.

DR. LINCOFF: I agree with you, the point about the goal being a moving target. On the other hand, you need some sort of measurement to graph it against the starting blood pressure to give them some sort of idea of whether or not they want to use this as the first-line therapy, whether an alternative might be, you know, we didn't see that

for the severe. But the change in blood pressure at different levels might be another way of looking at it although I think that may end up just being confusing.

I think in the absence of other clearly defined endpoints, having the 2-dimensional graph of the goals for both systolic and diastolic, people should recognize that their goal is to reduce both of those to target.

DR. HARRINGTON: Do you want to show some data?

DR. WACLAWSKI: As we might have some of these that are sort of suggested, we thought we would come up, and if they come up, we will pull them up, so the committee can look at them.

The one that was suggested was the reduction in blood pressure, baseline blood pressure. Dr Lapuerta will describe that.

DR. LAPUERTA: This will be the numeric reduction in blood pressure rather than the percent achieving goal. What we saw is that patients with higher baseline blood pressures had greater numeric

reductions in blood pressure.

So, the reduction in blood pressure, systolic pressure, in Study 176 was 31 mm of mercury, and those with a systolic blood pressure greater than 180 was 41, and those with a systolic blood pressure less than 180 at baseline, it was 27. That is something that we see commonly in hypertension studies. Slide 51-30, please.

[Slide.]

This does not have that simplified distinction, systolic blood pressure greater than 180, systolic blood pressure less than 180, but it has a range of systolic blood pressures and the blood pressure reduction seen in every category.

DR. LINCOFF: That, to me, is actually very helpful because this allows, you know, you have got a patient at 180, and you realize that if you can drop them by 42 or whatever it looks with the combination, you are pretty much at goal whereas there is little chance that you will do so, and with the error bars in particular, that you will do so with irbesartan alone.

This may be an alternative rather than reaching the goal if you wanted to avoid the arbitrariness of a goal.

DR. HARRINGTON: So, this provides the absolute, obviously, all of the data as opposed to just categorizing patients by goal.

DR. LINCOFF: And it also suggests that you may need to watch them later for the third agent, for the ones that, you know, instead of just I am there or not, but how close you are likely to get and how careful you want to be about following them up.

DR. HARRINGTON: Emil.

DR. PAGANINI: Notice the n across there before you make a big deal of it. Those n's are not tremendously large.

DR. LINCOFF: No, but the error bars are pretty small.

DR. PAGANINI: I am going to guess the error bar is the standard error of the mean, is that right, which always looks small?

DR. LAPUERTA: Yes, it is standard error

of the mean.

DR. PAGANINI: As opposed to the confidence intervals. That is an old basic science trick of using the standard error of the mean.

DR. LAPUERTA: Well, I will say one thing we have done is in our draft labeling to the FDA, rather than having all these categories, we have proposed text that describes just two groups, the group with systolic blood pressure greater than 180 at baseline, and a group with systolic blood pressure at less than 180 at baseline. So those are much richer numbers, and we had a 41 mm reduction in those greater than 180. It believe there was a 27 mm reduction in those less than 180.

DR. LINCOFF: But that data, I don't think is helpful to guide. That really doesn't help to guide therapy. In both cases, it shows you got a better outcome, but is your question is they need a practitioner to be fully informed to try to decide for his patient which one he would like to use, the sort of dichotomization at 180 I think is less useful.

DR. LAPUERTA: Slide 51-31, please.

[Slide.]

What our thought was, was that the overall mean reduction is at least useful, because if the mean reduction is 31 mm, then, you know, systolic, you know someone 40 or 50 mm away from goal will likely need even a third medication.

DR. HARRINGTON: Lynn would like you to go back to the previous slide.

DR. LAPUERTA: Could I have the previous slide, please, 51-30.

DR. WARNER STEVENSON: I can concerned about doing it this way, because when I first glanced at it, it looks like, gosh, no matter where they start out, they are going to get pretty close, and that is not the message we want to get.

I think the message we want to get is you are not likely to get there if you start out with a higher blood pressure. So I would prefer those other curves we had before, your declining likelihood of getting to a systolic of 140. I think the 3-D graph is only if you send out 3-D

glasses with it.

DR. HARRINGTON: Could you put up those slides of the patients getting to goal, the number of patients getting to goal?

DR. TEMPLE: The one that is on now just shows that you get a bigger bang the more deviant you are, which every antihypertensive I know of has shown. It is going down to, incidentally, zero when you are only 150. There was no irbesartan effect at all.

DR. LAPUERTA: Slide 39, please. I think this was requested.

DR. WARNER STEVENSON: I think I like this one because it emphasizes it is going to be tough if you start out high, and then just putting the thiazide on the bottom curve to this one.

DR. HARRINGTON: This, Mike, if I recall, makes your point that in the mid-range dose or the mid-range of blood pressure, you continue to have an effect, a benefit of the combined strategy. I like this, as well, with the caveat that the text again include that the strategy was with the dosing

strategy.

Emil, did you have--

DR. PAGANINI: This is superb. I think it does, however, will I think lower the blood pressure threshold for combination, because it seems that the baseline systolic blood pressures of 160 to 150 have a much better goal effect at 140, or not necessarily diastolics, but systolics, if you look at systolics, so that if you have a lower systolic, you might tend to use this more. So, it goes into the moderate range and allows you to use the moderate range.

As far as depiction is concerned, this is fine. I personally like 69, the Slide 69, which sort of looks at the same thing, but it was not from this particular study, so maybe set up in a different way. That was basically a 3-dimensional parameter with little boxes there and stuff. I thought that was sort of easy to understand.

DR. LAPUERTA: Slide 69, please.

[Slide.]

This was not from Study 176, it was from

the original NDA.

DR. PAGANINI: It was a totally different study, I know, but I just like the way it is depicted there. I thought that was a nice way of looking at things.

DR. TEMPLE: Those are hard to get actual numbers off.

DR. PAGANINI: I understand that. On the package insert, I am sure that would be very, very small, and you would have to have magnifying glass to figure out what is going on, and all that jazz, as opposed to those little lines that you can figure out. But I like the depiction of this a little bit better than the straight line.

DR. HARRINGTON: Jason.

DR. HSU: I like the curves that show probability of reaching target. In addition, to follow up on Dr. Harrington's suggestion, and to echo Dr. Stevenson's point, to present information about the magnitude of differences, I think there is opportunity there using graphs corresponding to your tables that actually show confidence intervals

or differences.

For example, for 185, the magnitude of difference estimated at 5/3, but the confidence intervals I believe are from 2 to 8 over 1 to 5, so it seems to me there is opportunity there to make a set of graphs for this other kind of endpoint, not probability of reaching goal, but magnitude of difference corresponding to your tables.

Of course, speaking as a statistician, whether you present graph or tables make my teaching job a lot easier seeing these drug labels.

DR. HARRINGTON: Lynn, you have commented you like this, and Steve?

DR. RYDER: I have nothing to add.

DR. HARRINGTON: Bob or Norm, have you had your question answered here?

DR. STOCKBRIDGE: [Nodding.]

DR. TEMPLE: [Nodding.]

DR. HARRINGTON: The final question is sort of what we have been building up to here is: Please comment on wording for possible indication statement. Some versions to consider, there are

three options which are proposed for us to consider.

The current Hyzaar indication statement: This fixed dose combination is not indicated for initial treatment of hypertension except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy.

Alternative proposal: Avalide is also indicated as initial treatment when hypertension is sufficiently severe that rapid control of blood pressure, within days to weeks, is of primary clinical importance.

Finally, the sponsor's proposal: Avalide is also indicated as initial treatment for severe hypertension.

DR. RYDER: I don't have any real comment.

DR. HARRINGTON: Steven.

DR. LINCOFF: Well, this is tough, because simplicity is always better and short is better, and so No. 3 is nice, but my gut feeling is with Alternative Proposal No. 2. Door No. 2.

DR. WARNER STEVENSON: I was hoping we would be on the last side of the table for this one. I guess one of the things I need to understand from the FDA standpoint is what you mean by "indicated." When we use this phrase in a guideline, if you say it is indicated it means that you have to do it. I am assuming it doesn't mean that in a product insert, so I have a little bit of two hats there but I think basically is indicated as initial treatment.

I mean what I would say in the guideline, can be considered as initial treatment for moderate to severe hypertension would be what I would say in a guideline, again trying to get away from this sort of mandatory feeling. I realize it's different for you.

DR. TEMPLE: We never mean mandatory, I mean it could be considered for this. A claim never requires that you do anything.

DR. WARNER STEVENSON: So, I think just for moderate to severe hypertension. I don't know that we need additional qualifications.

DR. HSU: I don't have any comment.

DR. HARRINGTON: Emil.

DR. PAGANINI: I would go along with I would say the 3rd, Avalide, and I would change that to "Avalide can be considered as initial treatment for Stage 2 hypertension." So, I would use Stage 2 there as opposed to severe hypertension or moderate to severe hypertension.

DR. TEMPLE: What should make you decide to do that, if you can consider it? Do you want to tell them?

DR. PAGANINI: What do you mean?

DR. TEMPLE: Well, can be considered.

DR. PAGANINI: Am I going to tell the doc, you mean use this here because this is what you should do?

DR. TEMPLE: Can be considered if, and might be used because, or anything like that?

DR. PAGANINI: As long as it is not discounted, you can use this as a first-line drug. It is not necessarily only a second-line drug. So, what I am trying to get across to the

caregiver, in his hands or her hands, to use this drug as opposed to putting it on some sort of cycle, is that this drug can, in fact, be considered as first-line use in Stage 2, pure and simple.

Now, if I am the caregiver, it would be up to me to decide whether I want to use that, or I want to use monotherapy, or I want to use some other drug, or whatever, for that particular patient at that particular time.

DR. TEMPLE: The thing we have been thinking about, and it is illustrated by those curves that show what percentage of people reach goal, goal to be determined by the caregiver obviously, depending on their starting pressure.

That implies that you would consider it if you really thought it was more important to get to goal quicker, so that could be considered "if."

DR. TEERLINK: [Inaudible comment.]

DR. HARRINGTON: So, that would be the other alternative, right, on second proposal, I have reworded it to say Avalide is also indicated

as initial treatment when hypertension is sufficiently severe such that control of blood pressure is unlikely to be achieved with a single drug.

DR. TEMPLE: Yes.

DR. HARRINGTON: And then you have the probability curves to guide that.

DR. TEMPLE: That is what I have been sort of noodling with, too. I am not happy with any of those three actually.

DR. HARRINGTON: It is sort of a blend of 2 and 3.

DR. TEMPLE: It gives the reason, and it doesn't say you have to know they are going to blow their head off. It says if you think you are just not going to get there and you are wasting everybody's time, get on with it. That is what your proposal is.

DR. HARRINGTON: Yes, and again I was struck by Dr. Weber, who said if you don't get there early, you are not going to get there, and you are trying to provide some framework for that,

and the graphs help you do that.

DR. TEMPLE: Yes.

DR. HARRINGTON: Michael.

DR. LINCOFF: I can't add much to that. I was favoring 3 for Stage 2, and I understand "indicated" means it can be considered. That is what an indication is.

Just like all the other choices that are indicated as first line, we leave it up to the physician to decide. We don't tell them how to decide between them, but I think it is reasonable, since this is a combination using a pre-existing product, to mention in cases as you have described where it is unlikely to reach goal in single therapy.

So, in short--

DR. HARRINGTON: So, add in the moderate to severe or some statement Stage 2 that says that it is not just the extreme but the broad group who you do not believe you will get there with one drug.

DR. LINCOFF: Right, you believe it is

unlikely.

DR. HARRINGTON: John.

DR. TEERLINK: I agree with what has been said so far, so No. 2 with the modification, and I don't know if I would go to saying moderate to severe or Stage 2 inasmuch as I am aware of the consistent pattern of not referring to specific guidelines, specific definitions of things unless it is really well established, because we do use NYHA class and things like that sometimes.

But that being said, I would emphasize more a functional definition saying when it is in your opinion and based on these curves that we are going to present for you, you think it is unlikely that they will achieve the desired goal with a single agent.

DR. HARRINGTON: So, are you saying then, John, that the phrase "sufficiently severe" works for you?

DR. TEERLINK: No, no, I am saying actually that I would modify that to say--and I have not noodled enough to come up with a good

enough answer here--but it's, you know, for hypertension when it is unlikely that a single agent will be sufficient to achieve desired goals or desired--and that is where it broke down, because I couldn't get a wording on that.

DR. TEMPLE: So, what need to be sufficient is the likelihood of failing?

DR. TEERLINK: Yes.

DR. TEMPLE: You are sufficiently unlikely to achieve your goal, so that you want to get on with it, which obviously is related to the severity, but that is not the crucial element.

DR. HARRINGTON: The crucial element didn't seem to be from the committee, that rapid control. It was more ultimate control.

DR. LINCOFF: But not predicating it on severity would allow for realities of the clinical setting. I mean if you have patients that you are unlikely to see every two weeks, then, that that factors in, as well, to the likelihood of achieving goal.

DR. HARRINGTON: That would get to the

part of not likely to be achieved, right.

DR. TEMPLE: What I was noodling with was something that said you should do this if you are not very likely to get to goal with a single drug, and then illustrating that, for example, in people whose blood pressure is over 180, here is this figure. It shows you, you are very unlikely, but even in people who are lower, depending on what your goal is, you might be moderately unlikely to get there, and you decide.

DR. STOCKBRIDGE: This has been very helpful and I appreciate everybody's input on this. I wanted to ask one additional question since we are on the verge of having an opportunity to invite some changes to monotherapy labels as we get outcome claims put in there.

Do people want to see some terse discussion of this issue in monotherapy labels as part of the general monotherapy label?

DR. TEMPLE: When to start with two drugs?

DR. STOCKBRIDGE: Yes.

DR. HARRINGTON: Ask me one more time,

maybe two more times.

DR. STOCKBRIDGE: We can not mention the first-line use of monotherapy except in the setting of a combination label, first-line use of a combination product except in the specific combination labels, but we could also put some general comments about when you might want to start with two drugs in the monotherapy labels.

DR. TEMPLE: All antihypertensives now say for use alone or in combination with other antihypertensives to lower blood pressure, so I think you can understand Norm's question to mean when do you want to add a little to that, and talk about when you might want to start with its use in combination.

Of course, we usually won't have the factorial studies at that point.

DR. STOCKBRIDGE: I am not even suggesting that it says anything about a combination with that particular agent any more than it says, you know, the outcome claims exactly pertain to this particular drug. General advice about doing

various things including paying attention to other cardiovascular risk factors.

Do you want to say as part of general advice whether there is a combination product or not? Do you want to say, and you maybe ought to think about, you know, if you are far from where you want to be, you probably ought to be thinking about starting, not with this drug, but with a combination product.

DR. HARRINGTON: So, it is following that general theme of when we had the outcomes meeting, that these are going to be general comments that don't necessarily apply to that specific drug, but across the class, or across the category of antihypertensives.

I will have to think about it a bit more, but on the face of it, adding general advice, there is now, I think Mike Lincoff said, we have got pretty compelling data that lowering blood pressure is a good thing in terms of reducing cardiovascular outcomes, and we are going to add that advice in general terms.

We now have pretty good evidence that the majority of patients are going to require two drugs, and it is almost solely based on what their starting blood pressure is.

So, from a general advice perspective, that seems quite reasonable, but I would be interested in what other people have to say.

DR. WARNER STEVENSON: Well, I have to say one of the things I have learned today is that I am not the only one who seems to need two drugs a lot. I thought it was unusual that I was needing two drugs this often, and I am reassured that that is, in fact, what is happening, and there must be many other people in the same situation.

I think it would be useful to have a curve that just shows systolic blood pressure and the percent of control on single agent without necessarily talking about what single agent it is. This percent of people will require more than one drug and have that up front, I think may be useful, so people aren't expecting necessarily to get success.

DR. LINCOFF: Is that going to be drug specific, though?

DR. WARNER STEVENSON: Well, that depends on how much data there is. I would defer to them. I don't know how big the archives are that you could have data like that for every class of drugs or not, but at least if you just even knew generically this group will likely require two drugs.

DR. LINCOFF: Certainly, it would be useful from the standpoint of emphasizing the importance of monitoring the patients and coming back to escalate.

DR. TEMPLE: You have some information in every new antihypertensive. You could draw a curve that said how many people with a diastolic here got to this value here, or got to this goal here. I mean you always have that information from every trial.

DR. WARNER STEVENSON: Well, I guess the problem is if you try to compare it across classes of drugs--I think the Hyzaar data was very

interesting here, because they studied a group who had already been relatively refractory, so they had a lower response rate. I think you would end up with a lot of problems trying to adjudicate what number success you were going to put for each class if you are going to truly compare it head to head.

Maybe there is enough data to do that, I just don't know if there is or not. It certainly would cause a lot of controversy.

DR. TEERLINK: I think Lynn is getting at the point that I was going to try to make, as well. I am very much in favor of putting in a very strong statement saying most patients do not get to go with one agent and will require two, three, four other agents at times, you know, and you can pick out how strong you want to make the wording.

But I would make it fairly strong to raise the consciousness that hypertension nowadays usually requires more than one drug without getting into the nitty-gritty of how many got to the point or not, because then you get into this issue of which patient population, which drugs, and which

class.

DR. TEMPLE: Two things. One place to put that might be this sort of general statement on outcomes, that is, all these outcome studies, people were titrated to some particular goal pressure, often adding other drugs, so that might go in there.

I had another thing I was going to say, and I forgot what it is--oh, yes. This goes to what we were saying before. We generally present only the data that we are the primary endpoint, although there are exceptions to this.

So, for example, for drugs for Alzheimer's disease, the primary endpoint was the numerical change average in the ASCOG standard test for that. But we also showed response data, how many people changed by 2, by 4 or 5 units on everything.

Our principal purpose was to show how modest the effects were and how nobody really had a major effect but it's a cumulative distribution of effect thing. You can either do a bell-shaped curve to show the distribution of responses or do

it in a cumulative way, you can have your choice.

But one of the things that I have certainly been thinking of is that that is almost always interesting. If you do depression, people are always interested in what fraction of people get to any given goal on the HAM-D or something like that.

One of the issues we would always raise is oh, that's another analysis, you didn't preserve your alpha for that, or you didn't plan on doing it sequentially, and we have to talk about this. But, to me, if you pick one value out like how many people got to 20, that's the way to cheat but if you show the whole distribution of the effect, it is really the same finding all over again, so maybe there is not too much of a statistical penalty.

Anyway, we are going to have discussions of all this in the future, but it may be that along with telling people that the average change in blood pressure was 5, you might want to show routinely how many people got to goal.

The flaw with that, of course, is that you

definitely have to show the placebo group in there. Otherwise, you can make them any way you want, and it all depends--how well you do depends on who you put into the trial, which is a funny kind of incentive, too, so there is a lot to think about.

DR. HARRINGTON: Isn't this discussion around superiority, non-inferiority, and equivalence? It is essentially the same test. You are just changing where the boundary is, but there is no penalty for moving from superiority to non-inferiority.

DR. TEMPLE: Yes, there is. There is no penalty for moving from non-inferiority to superiority. If you win in an equivalence trial, that's great. We get very nervous about trying to win and then not losing.

DR. HARRINGTON: But what I am saying is that you are essentially setting a line, and you are just seeing where you are relative to that line is what you are saying.

DR. TEMPLE: No, I am saying that dichotomous and the discontinuous data and

continuous data are really the same data. We shouldn't maybe get so exorcised when you look at it one way or another. However, that said, we know that the results will come out different.

You know, you can fail on your primary endpoint of HAM-D and win on the number of people who got to goal. Well, what do you do when that happens?

So, everything I am saying involves winning on your primary endpoint, and then what are you allowed to do with these other ways of looking at the data? I probably shouldn't have said anything, but that is a future thing we are going to talk about.

MR. FINDLAY: Just to clarify, you were asking about making a statement that is specific to starting with two drugs, correct, not just the benefit, because that is already in some labeling Did you say that that is already in labeling?

DR. TEMPLE: That is what Norman was asking for.

MR. FINDLAY: Yes, that's right.

DR. TEMPLE: He said in the regular drug, not a combination product now--

MR. FINDLAY: Right. So, a specific statement that really isn't out there as a public health message today, that starting with two drugs is not only advisable, but perhaps strongly advisable in a large subset of patients.

DR. TEMPLE: That's right, saying that the people who are very high are unlikely to be controlled on a single drug. You might want to continue to--

MR. FINDLAY: I would say I concur with that, and there is a public-health benefit to making that statement.

DR. TEERLINK: Obviously, your statements about the primary endpoint are tantamount. But can you view these other curves as kind of a sensitivity analysis where it's descriptive data rather than it saying okay, it won on this point, and here is a little more information on over the range, and in that way not be presented as a statistical test.

DR. TEMPLE: That is exactly how I think of it.

DR. HARRINGTON: Bob, any parting business for the group? No. I want to thank everybody, I want to thank the sponsors for the presentations, thank the panel members, and adjourn the meeting.

[Whereupon, at 3:19 p.m, the proceedings were adjourned.]

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