

1 exclude the same people from the control regimen. I  
2 don't know who those people are.

3 I would agree, though, that whereas the  
4 primary analysis should be exactly what ALLHAT  
5 presented, which is the ITT, it's certainly important  
6 to give a descriptive analysis of what was overall  
7 level of adherence. What were the frequencies and the  
8 timing of patients receiving ancillary care that, in  
9 particular, could be anticipated to influence the  
10 endpoints?

11 So I would argue descriptive analyses that  
12 provide more globally what adherence was and what  
13 supportive care was are relevant and should be also  
14 considered.

15 ACTING CHAIRMAN BORER: Let me  
16 specifically ask Bob Fenichel, do you have any  
17 additional comments to make about this issue?

18 DR. FENICHEL: No.

19 ACTING CHAIRMAN BORER: Okay. Anything  
20 else that the Committee members want to add beyond  
21 what we've heard from the two statisticians?

22 DR. HIRSCH: Maybe one brief comment, just  
23 that this is not your classical randomized clinical  
24 trial between two treatment groups. You have to  
25 remember what ALLHAT really is, which is again the

1 real-world trial of what happens when doctors  
2 prescribe medications.

3 I look at this 76 percent continued use  
4 rate over many years and say that would be great to  
5 achieve in real life. That's exactly the analysis ITT  
6 that we want to have to understand what we are being  
7 told in ALLHAT.

8 ACTING CHAIRMAN BORER: Okay. Yes, Bob?

9 DR. TEMPLE: You can't tell precisely, but  
10 since much of the difference between the two  
11 treatments was that it was observed early, it seems  
12 likely that the on-therapy rate was much higher when  
13 much of the action was going on. So that might affect  
14 some of the other outcomes, but maybe not that, maybe  
15 not the heart failure outcome so much.

16 ACTING CHAIRMAN BORER: You say much of  
17 the difference was early. You're thinking heart  
18 failure difference was early.

19 DR. TEMPLE: That's all I'm referring to.

20 ACTING CHAIRMAN BORER: Stroke, I might  
21 argue, somewhat surprisingly to me, was more evident  
22 emerging later.

23 DR. TEMPLE: Right. I tend to discount  
24 that, because it's easily explained by the blood  
25 pressure, but leave that aside.

1                   ACTING CHAIRMAN BORER:   Well, blood  
2                   pressure differences were greater early.  The length  
3                   between pathophysiologic changes and ultimate natural  
4                   course of a disease, I think, we don't know so well.  
5                   So maybe that's a side issue we'll get at later.

6                   Okay.  Have you heard enough, Ray, to give  
7                   you advice about what the Committee thinks about how  
8                   to deal with the other patients?

9                   DR. LIPICKY:  Yes.

10                  ACTING CHAIRMAN BORER:  1.4.  Diastolic  
11                  blood pressure control was similar in the doxazosin  
12                  and chlorthalidone treatment groups, but systolic  
13                  control was less similar.  Might any differences in  
14                  outcome be attributable to the degree of systolic  
15                  blood pressure control?

16                  I think we've heard a fair bit about that,  
17                  but just to make sure that there is some sense of  
18                  everybody's idea, Marvin, why don't you start again?

19                  DR. KONSTAM:  Yes.  I certainly think that  
20                  certainly at least some of the results may be  
21                  attributable to blood pressure differences.  I think,  
22                  frankly, in my mind, I think a large percentage of the  
23                  results could be attributed to or at least  
24                  significantly contributed to by the blood pressure  
25                  difference.

1                   You know, as Bob just said, magnitude-wise  
2 it seems very rational to say that with regard to the  
3 stroke. You know, I just want to comment about the  
4 heart failure magnitude. You know, I don't know what  
5 the magnitude effect means anymore when you are  
6 getting to a component of a secondary endpoint, and  
7 how reliable is the magnitude of the effect.

8                   I just want to say that point. But I  
9 think even there, assuming that that magnitude is  
10 correct, I think that the blood pressure differences  
11 could be contributing to that in a couple of different  
12 ways.

13                   One is effect on natural history of events  
14 with regard to the myocardium, but the other is  
15 ongoing afterload effects which, if different, I  
16 think, could have been contributing significantly to  
17 that early difference in heart failure. So I think  
18 the blood pressure has probably a fair amount to do  
19 with it.

20                   ACTING CHAIRMAN BORER: Michael?

21                   DR. ARTMAN: Well, I was impressed with  
22 the difference in the time to achieve target blood  
23 pressure in the doxazosin group versus chlorthalidone.  
24 I think that was an important consideration and may,  
25 in fact, contribute to the differences.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1. I think also that the issues related to  
2 stroke, I think, are more likely related to  
3 differences in blood pressure control. The heart  
4 failure issue, I think, is still pretty murky.

5 ACTING CHAIRMAN BORER: Ileana?

6 DR. KONSTAM: Can I just add one thing?  
7 I think, again, the thing about 3 millimeters -- you  
8 know, I think there could be an awful lot going on  
9 with that 3 millimeters, and it would be lovely to  
10 see, again, the range of blood pressure responses, to  
11 what extent there might be some-- just the proportion  
12 of patients who were way out of control in one group  
13 versus the other group, and then finally, you know,  
14 actually see an analysis, again, linking or relating  
15 the events to blood pressure control in those patients  
16 who have events.

17 So those are all important issues.

18 DR. PINA: I think that 3 millimeters  
19 alone doesn't give me any sense of confidence about  
20 the occurrence of heart failure. However, if patients  
21 were coming off of drug that had them -- that are  
22 controlled and they are going on whatever the study  
23 drug is -- in this case, doxazosin -- and the blood  
24 pressures are higher, that could contribute to the  
25 early separation of the curves.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           Again, I'm very struck by the early  
2 occurrence of those curves splitting apart, and I  
3 don't think the effect early on, necessarily, has  
4 anything to do with the blood pressure. But I think  
5 the blood pressure is contributing to what we are  
6 seeing.

7           The fact that the blood pressure remains  
8 high for a year later, higher than in the  
9 chlorthalidone group, I think that may be contributing  
10 to the stroke level, but not necessarily to the heart  
11 failure, which is seen very early.

12           ACTING CHAIRMAN BORER: Alan.

13           DR. HIRSCH: Well, on a blood pressure  
14 interventional trial comparability of blood pressures  
15 is important, and 2-3 millimeters is important for  
16 stroke. Like Ileana, I'm not sure it explains the  
17 heart failure outcome, but the analyses, as Marv said,  
18 are certainly very important. I'd love to see them as  
19 well.

20           ACTING CHAIRMAN BORER: Tom?

21           DR. GRABOYS: Yes.

22           ACTING CHAIRMAN BORER: Tom?

23           DR. FLEMING: This is again a tough issue.  
24 Diastolic pressure was the same. Systolic was less  
25 similar, 3 millimeters, then 2 millimeters after a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 year. My sense is that it is very unlikely that this  
2 explains the full having of the heart failure that  
3 diuretics provide.

4 Marv, you referred to the difficulty  
5 interpreting that estimate because it came from an  
6 interim analysis, and you are certainly right about  
7 the fact that there is a bias that arises in estimates  
8 of effects when you have interim monitoring, and that  
9 interim monitoring --

10 DR. KONSTAM: Well, not only interim but  
11 also a component of a subset -- a component of a  
12 secondary endpoint.

13 DR. FLEMING: Yes. When you have --  
14 That's more regression to the mean kind of phenomenon  
15 where you are looking at multiple endpoints, but it's  
16 really the same phenomenon. It's just multiple  
17 testing. You are noting it as multiple testing, as  
18 one element of many in and outcome. I'm noting it as  
19 over periods of time.

20 There is, in fact, some bias that arises,  
21 although not anything close to what would account for  
22 this having. There are other phenomena, though,  
23 that could. Is it maybe just a masking, so the having  
24 isn't really real, and those are completely different  
25 issues. But from a statistical perspective the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 multiple testing has more of an impact on significance  
2 levels and your interpretation of those rather than  
3 bias in the point estimate, even though - you're right  
4 -- there is some bias, but not at a level that I would  
5 think could explain this.

6 So my sense is its very unlikely that the  
7 difference of 3 millimeters that becomes 2 millimeters  
8 in systolic when diastolic is the same could, in its  
9 own right, account for the difference in heart failure  
10 or a large part of it.

11 It could account for the differences in  
12 stroke, although again it's speculation as to whether  
13 it would. I'm interpreting too much into the data,  
14 but where the biggest difference is in blood pressure  
15 is not over the time frame where I see the largest  
16 excess in stroke, and I don't know if it's a delayed  
17 effect or what. I don't know.

18 It's difficult to also understand whether  
19 this is important, and let me clarify. If we used the  
20 wrong regimen, and if we had used the right dose  
21 schedule, we would have achieved the right blood  
22 pressure control, then this is a relevant question.

23 On the other hand, if there is something  
24 intrinsic about delivering an alpha blocker as opposed  
25 to a diuretic that makes it harder to achieve full

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 blood pressure control, then it's a moot point,  
2 because this is an intrinsic characteristic of the  
3 regimen.

4 If I achieve lesser efficacy mediated  
5 through lesser biologic effect on blood pressure and  
6 that's intrinsic to the regimen, then it doesn't  
7 matter. So I'm left also with trying to -- coming  
8 back to the first question again. Can I say with any  
9 kind of reliability that I would have achieved the  
10 right blood pressure control, had I had the right  
11 schedule and dose?

12 DR. KONSTAM: I'm sorry. Tom, you've  
13 confused me about something you said. I mean, I hear  
14 you say -- Getting back to the multiplicity issue,  
15 whether it be multiple looks or whether it be multiple  
16 endpoints, I heard you say, well, that influences the  
17 statistical validity of the finding but not  
18 necessarily the magnitude of the finding?

19 DR. FLEMING: Well, there are two ways of  
20 doing -- I mean, there are two important aspects to  
21 statistical analysis. One is estimation. The other  
22 is inferential or testing. Multiple testing  
23 influences both, i.e., when you do multiple testing  
24 over time or you have multiple different outcomes and  
25 you happen to choose the one that really looked the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 most impressive, there's a regression to the mean  
2 phenomenon. It looked that impressive, partly because  
3 there was a real effect, but you happen to have seen  
4 an overestimate of that real effect, and that's why it  
5 stood out.

6 So in that sense, you're right about the  
7 fact that there's some overestimate. I'm saying that  
8 that statistical phenomenon, though, doesn't explain  
9 the magnitude of what we are seeing when you put into  
10 context the number of analyses that were done and the  
11 fact that stroke wasn't one of 100 different endpoints  
12 or heart failure wasn't one of 100 --

13 DR. KONSTAM: I'm just saying that the  
14 magnitude of the heart failure effect seems pretty  
15 large. I'm just saying that --

16 DR. FLEMING: It's the same size as in  
17 SHEP.

18 DR. KONSTAM: No, no. Okay, but I'm just  
19 saying the degree to which we are confident about that  
20 magnitude diminishes substantially as we get to the  
21 fact that it comes from an interim look, and the fact  
22 that it's a component of a secondary endpoint, as  
23 opposed to being a primary endpoint at the end of the  
24 study.

25 ACTING CHAIRMAN BORER: Joann?

1 DR. LIPICKY: Tom, there weren't 100 other  
2 endpoints, but there were 21 all told.

3 DR. FLEMING: But as you would say when you  
4 looked at, let's say, carbatylol and death was a  
5 secondary measure, you might argue death isn't like  
6 every other secondary issue.

7 DR. LIPICKY: Well, but that was not a  
8 good decision. So I wouldn't use that as an example.

9 DR. FLEMING: Not all secondary endpoints  
10 are the same, and one has to ask whether specifically  
11 death, MI, stroke and heart failure stand out as  
12 particularly clinically relevant.

13 DR. KONSTAM: You know, the carbatyl  
14 example, I think, is a great example, because there  
15 the magnitude effect seemed enormous, and at least for  
16 what it's worth, we know it's very disproportionate to  
17 every other beta blocker study that's ever been done  
18 since then. I think that may be an example.

19 DR. LIPICKY: -- an endpoint contrived  
20 after the first nonapproval letter.

21 DR. KONSTAM: Right.

22 ACTING CHAIRMAN BORER: Joann?

23 DR. LINDENFELD: I just want to take a  
24 little bit more clinical view of this question. I  
25 think that you could make a case for the blood

1 pressure being important here.

2 We know that the differences in heart  
3 failure were early on. The biggest differences in  
4 blood pressure were early on, but later on with  
5 stroke. There's a lot of information we don't have  
6 here.

7 One is what was the incidence of atrial  
8 fibrillation? We know that one of the predisposing  
9 factors to atrial fibrillation is hypertension. It's  
10 quite conceivable in my mind that there could have  
11 been more atrial fibrillation in the group with the  
12 slightly higher blood pressure, which predisposes to  
13 stroke, and that could explain this late sort of slow  
14 progression in the increased incidence of stroke.

15 So while I'm not sure about any of this,  
16 I think one could make a plausible explanation here,  
17 and we just -- Without knowing if there were  
18 differences in atrial fibrillation, I think that's  
19 just where, again, we could use more data.

20 ACTING CHAIRMAN BORER: Steve?

21 DR. NISSEN: I think we shouldn't have any  
22 illusions here. Three millimeters systolic blood  
23 pressure difference is a lot. I would point out to  
24 everyone that that's the difference that was seen in  
25 the HOPE trial between placebo and ramapril. It was

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 associated with very strong differences in a whole  
2 variety of endpoints, and many of us believe that that  
3 was the exclusive explanation for the results of the  
4 HOPE trial.

5 So I think that from that perspective, 3  
6 millimeters is large. But I also have some concerns  
7 here about how blood pressure was measured. You know,  
8 this was not chronic ambulatory blood pressure. We  
9 don't know whether this was peak or trough.

10 These drugs work by different mechanisms,  
11 and they may have different peak and trough effects.  
12 They may have different effects on ambulatory blood  
13 pressure versus an office blood pressure. So there's  
14 a lot of fuzziness here that I can't get my arms  
15 around, because I don't have the data. So I don't  
16 know what it means in this context.

17 ACTING CHAIRMAN BORER: Bob?

18 DR. FENICHEL: It's hard to answer no to  
19 a question that begins with "might." But I guess I'll  
20 give sort of the same answer other people have given.  
21 It's pretty plausible for the stroke, notwithstanding  
22 the delay. But I find the delay plausible. It's  
23 certainly clear enough that one shouldn't expect  
24 people to have a stroke tomorrow if you take them off  
25 their medication today, and so on. Things take time.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Congestive failure, to the extent you  
2 believe it really happened and was not simply an  
3 unmasking, as Ray has hypothesized -- that's a little  
4 bit harder to pin on 3 millimeters, but I go along  
5 with what Steve said. It's really hard to know on the  
6 basis of the data we had what the real blood pressure  
7 differences were, integrated over time view.

8 ACTING CHAIRMAN BORER: Ralph?

9 DR. D'AGOSTINO: In the Framingham study  
10 where I spend most of my life, we always think that  
11 systolic is a better measure than diastolic, and  
12 especially as you get older. So I'm not upset that  
13 the diastolic was similar and the systolic at a  
14 difference.

15 I think that, in fact, the difference  
16 observed is pretty important, and with the possibility  
17 of racial effects here -- there's a lot of non-whites  
18 in the study -- it may have more of an effect than  
19 some of the meta-analysis would indicate.

20 I do think that it's probably -- and here  
21 I'm sort of stepping out of analysis, because we don't  
22 have it. It's probably more with the stroke and the  
23 congestive heart failure, but I think that with the  
24 stroke you could probably say that not all of it but  
25 a good portion is explained by the blood pressure,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 reasonably explained by it.

2 ACTING CHAIRMAN BORER: Okay. So, Ray,  
3 the answer to this is resoundingly yes. Any  
4 differences in outcome might be attributable to the  
5 degree of systolic blood pressure control.

6 DR. TEMPLE: Jeff?

7 ACTING CHAIRMAN BORER: Yes?

8 DR. TEMPLE: I guess I wanted to explore  
9 that one little bit further. Again, it's hard to know  
10 how to cross studies, but the entire effect of the  
11 treatment difference in SHEP, which is, as I recall  
12 it, about 6 or 7 millimeters of mercury, produced a 50  
13 percent reduction in this endpoint.

14 Here you have to believe that a difference  
15 -- Now I mean granting what Marv says about the  
16 instability of the estimate, you sort of have to  
17 believe that 2 to 3 millimeters of mercury had an  
18 effect similar to the entire effect of the treatment  
19 in SHEP, not for stroke where I find it plausible, but  
20 in the heart failure.

21 ACTING CHAIRMAN BORER: No, I don't think  
22 that's what people have answered. The issue is, is  
23 there any impact of the blood pressure, not could all  
24 the heart failure difference be explained by blood  
25 pressure. It could be or couldn't be. But I think

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the question here is could the data have been  
2 confounded by this factor, among others?

3 I think everybody is saying yes, without  
4 knowing the extent to which it could be confounded.

5 DR. TEMPLE: Okay. I'm just reading the  
6 question, Jeffrey. It says "might any differences in  
7 outcome" -- any --

8 ACTING CHAIRMAN BORER: Yes, any.

9 DR. TEMPLE: -- "be attributable," which  
10 I would read as entirely, "to the degree of systolic  
11 blood pressure control." So you're saying, no, not  
12 all of it but some of it?

13 ACTING CHAIRMAN BORER: No, no, I'm not  
14 saying that. I'm saying I interpret the question  
15 differently, a little bit, and that what I'm  
16 understanding people to say is, number one, it's hard  
17 to know what the absolute magnitude of the difference  
18 really is, although we have point estimates, and  
19 number two, it's hard to know how to relate blood  
20 pressure changes to those differences, but that,  
21 number three, it seems plausible and reasonable from  
22 all the data we've ever seen that differences of this  
23 magnitude in blood pressure could affect the outcomes  
24 that we saw, maybe not totally. Maybe it doesn't  
25 account for all of it, but could have an important

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 impact.

2 That may be one of a number of  
3 confounders. I don't want to jump ahead in the  
4 questioning, but there may be other confounders as  
5 well that might make us less than fully comfortable in  
6 drawing very firm conclusions from the data we've seen  
7 so far.

8 DR. LIPICKY: Jeff, you are interpreting  
9 "any" as if it had been "some."

10 ACTING CHAIRMAN BORER: That's right.  
11 More than none.

12 DR. TEMPLE: Okay. That's fine. I just  
13 want to be sure what you were telling us.

14 ACTING CHAIRMAN BORER: Number 1.4: The  
15 primary endpoint in ALLHAT was the combined incidence  
16 of fatal coronary heart disease plus non-fatal  
17 myocardial infarction. The primary hypotheses were  
18 that the three comparator arms would be superior to  
19 chlorthalidone; this was not an equivalence study.

20 1.4.1: Did ALLHAT demonstrate a  
21 difference between doxazosin and chlorthalidone for  
22 the primary endpoint? I don't think we need a  
23 discussion of that. I think that the general  
24 consensus has been that it did not, although, as Tom  
25 pointed out, there was a small difference, the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 importance of which can't be evaluated from the data  
2 we have.

3 1.4.2: If not, how should one interpret  
4 any secondary endpoint when the primary endpoint  
5 showed no significant difference?

6 We've heard some discussion of that, but  
7 I think we need to hear just a bit more. Tom, why  
8 don't you begin, and then we'll go to Ralph, and we'll  
9 see if anybody has anything to add?

10 DR. FLEMING: Yes. Just to clarify. You  
11 had referred to my answer to 1.4.1. Unequivocally,  
12 the data do not establish superiority of doxazosin in  
13 the primary endpoint.

14 Usually, when we ask how to interpret a  
15 secondary endpoint then, it's in the context of saying  
16 you have not shown superiority in the primary, but at  
17 least do you get superiority out of a secondary? So  
18 I'm not exactly sure I understand the question,  
19 because if we've said that the primary endpoint  
20 clearly didn't establish superiority, the secondary  
21 endpoint goes in the wrong direction.

22 In what way did you wish us to comment  
23 about this?

24 ACTING CHAIRMAN BORER: I think, if I'm  
25 not mistaken -- and, Ray, you can clarify this

1 further. I think what we've often heard in  
2 discussions from statisticians at these meetings is  
3 that, if the primary endpoint isn't achieved -- that  
4 is, you don't show a consistent difference between  
5 treatment A and treatment B -- that it's very  
6 difficult to interpret a secondary endpoint result.

7 If you don't make it on the primary, you  
8 can't look to the secondary. Is that what you are  
9 asking, Ray?

10 DR. LIPICKY: That's at one extreme, and  
11 the other extreme, I guess, is if it's important,  
12 you're supposed to look at it. So where does this sit  
13 in that spectrum, in your estimation?

14 Then the next question sort of gets at  
15 what does that -- How should you interpret p-values?  
16 Where do you get your strength of evidence? So I  
17 guess 1.4.2 and 1.5 are sort of tied together, with  
18 1.4.2 being initial thoughts before getting into the  
19 particulars of 1.5.

20 Does it make sense or do you think it's a  
21 ridiculous question to provide? It could be a  
22 ridiculous question. It's all right.

23 DR. FLEMING: Well, if one needs to  
24 determine or one needs to interpret the significance  
25 level of .001 or less than .001 and determine whether

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 this is, in fact, validly interpreted as conclusive  
2 statistical evidence of better results on heart  
3 failure with the dialysis regimen or worse results on  
4 heart failure with the alpha blocker regimen, I think  
5 we could get into a major controversial issue here as  
6 to whether this -- on a secondary measure, whether  
7 this statistical significance level is interpreted as  
8 being conclusive.

9 My read of all of this is it's very  
10 relevant to -- It's always relevant to consider  
11 secondary measures. One of the reasons we go through  
12 an effort of identifying, hopefully, a small number  
13 of secondary measures is to be able to -- whereas, we  
14 don't give it the same attention as the primary  
15 endpoint, to be able to make clear that these aren't  
16 just data exploration endpoints that showed up in a  
17 large myriad of different analyses that were done.

18 So there's kind of a middle ground.  
19 Clearly, the major focus is on the primary endpoint.  
20 We would always say in a DSMB, though, any decision  
21 about early termination must take into account global  
22 consideration of all relevant information on efficacy  
23 and safety where you look often first and foremost to  
24 secondary efficacy measures and to safety measures as  
25 well as to relevant external data.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 That's exactly what this committee did.

2 DR. LIPICKY: Well, that's okay. It's not  
3 with respect to what the committee did. It's with  
4 respect to how we should be taking inference from  
5 this. How firmly do we know that this observation,  
6 whatever the observation is, and in 1.5 is the  
7 congestive heart failure, that that observation is  
8 pretty sound; because we have this one thing of, you  
9 know, we hear this business of, if you don't make the  
10 primary endpoint, don't bother me with the secondary.

11 DR. FLEMING: All right. Well, in that  
12 context, my answer to 1.4 is -- and it's ordered in  
13 the correct way. 1.4.1 is the most important  
14 question. Clearly, these data do not establish  
15 superiority for the alpha blocker. In fact, if  
16 anything, they suggest that the results are the same  
17 or a minuscule worse. Clearly, they don't establish  
18 superiority.

19 The secondary endpoint, the most important  
20 one, as I see it, would be the heart failure and  
21 stroke measures. Those also trend in the wrong  
22 direction. My interpretation is I view the strength  
23 of evidence from heart failure to be fairly strong,  
24 but because it's in the wrong direction, I don't know  
25 whether it's even necessary to get into the rigors of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 saying is it conclusively negative. I don't see why  
2 that's a necessary issue.

3 DR. LIPICKY: Well, we may get to that,  
4 but okay. So then what you're saying is you don't  
5 even need a nominal p-value. That is, the p-values  
6 for the secondary endpoints here have no particular  
7 relevance to you. It's that indeed the point estimate  
8 and confidence limits are really very different, and  
9 whether you calculated a p-value or not is irrelevant.

10 DR. FLEMING: Absolutely, if in fact you  
11 hold to the 1.4.1 assumption that what one needs to do  
12 first and foremost is establish superiority on the  
13 primary endpoint.

14 If we open a whole different issue here  
15 and say, well, that's not true, the quality on the  
16 primary endpoint is enough because SHEP has shown  
17 diuretics are effective. So if alpha blockers are the  
18 same, that's -- Now it does matter more whether we  
19 think that the heart failure evidence is conclusive.  
20 But 1.4.1 is putting us in the context of saying you  
21 have to show superiority on the primary endpoint.

22 Clearly, they didn't. And having trends  
23 in the wrong direction or significant effects in the  
24 wrong direction on secondary measures isn't going to  
25 change my impression.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. LIPICKY: But don't we have to  
2 interpret the data the way the protocol was written?  
3 Can't we take the liberty here now of saying, well,  
4 we're going to treat this like a nonsuperiority?

5 DR. FLEMING: And that's the way your  
6 questions are phrased, and that's the way I'm  
7 interpreting them.

8 DR. LIPICKY: Okay, but that's legitimate,  
9 you think?

10 DR. FLEMING: Yes.

11 DR. LIPICKY: Not illegitimate.

12 DR. FLEMING; If we follow the protocol,  
13 this study -- and this is my belief for why the Data  
14 Safety Monitoring Board and the Steering Committee  
15 made their judgment. Based on the intention to show  
16 superiority, clearly that evidence made it clear that  
17 the probability that you could achieve superiority was  
18 minimal. And added to that, as they said, they were  
19 also persuaded by the strong evidence for an  
20 unfavorable trend in heart failure.

21 One doesn't have to put a p-value on it to  
22 justify that conclusion.

23 DR. LIPICKY: Okay, fine. So that it  
24 isn't the p-value. It is the directionality and other  
25 kinds of --

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 fashion. So why are you splitting things out with the  
2 secondary endpoints?

3 I've mentioned a number of times, and I  
4 could be all wet on it, but I think that, no matter  
5 what vocabulary we want to use, the DSMB was driven by  
6 safety concerns, and I'm not sure that they were  
7 sitting around saying, hey, we have a primary  
8 endpoint, we have an analysis, now can we look at the  
9 secondary endpoints.

10 I think they rushed to all the safety  
11 concerns, and in this case safety is the -- One of the  
12 safety components is the heart failure.

13 To respond formally, 1.4.1 is no. After  
14 1.4.2, how do you interpret the secondary endpoints?  
15 You can't interpret them. You shouldn't do it. But  
16 I think that, in fact, as I say, that they were driven  
17 by different concerns, and I switch more to saying  
18 that, well, I don't have a problem with understanding  
19 how stroke turned out to be p of .04 with all the  
20 multiple testing, with the blood pressure.

21 I look at congestive heart failure, and  
22 I'm not sure I know what they are talking about in  
23 terms of heart failure in this case here. So my  
24 response, and maybe it's something that Tom was saying  
25 also, that you start mixing the clinical

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 interpretation with the statistical interpretation.

2 I think that the statistical  
3 interpretation of the p-values has run out of steam,  
4 and that they are really being motivated by  
5 considerations like the safety data and the importance  
6 of stopping a drug if they think that there is a real  
7 problem with it.

8 There they can pull p-values, and they can  
9 be overwhelmed by them, but the straight  
10 interpretation, which I'm -- I'm taking this in a  
11 formal sense as opposed to how do you then put all the  
12 clinical -- that there's no p-value really that makes  
13 sense in the 1.4.2.

14 Even if it were mortality, you could say  
15 that, well, what if it were mortality? You should be  
16 overwhelmed by mortality. It's not the way the study  
17 was designed, and you have a hard time attaching a p-  
18 value post hoc to it.

19 So I think that the p-values really are  
20 almost uninterpretable. It's really a different  
21 consideration, that you saw something very upsetting,  
22 and that you did your confidence interval. You did a  
23 p-value, but it's not in the same fashion as the  
24 formal noninferiority or superiority primary, then  
25 versus secondary.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   ACTING CHAIRMAN BORER: Ileana and then  
2 Bob.

3                   DR. PINA: Yes. I want to bring this back  
4 to the clinical reasons why this trial was ever done,  
5 at least how I interpret it, to look at the use of  
6 drugs that are commonly used now as first-line therapy  
7 for hypertension and compare it to chlorthalidone,  
8 which has been so nicely proven in the SHEP trial.

9                   If I'm a clinician and I'm looking at the  
10 two curves sitting on top of each other for the  
11 primary endpoint, that may give me some sense of  
12 comfort. When I see the heart failure, it gives me a  
13 big sense of discomfort, and would not use the drug,  
14 because I don't want to deal with the heart failure,  
15 even though the heart failure occurrence did not alter  
16 ultimately the mortality.

17                   I don't think that the clinicians will sit  
18 down and say, well, this is a superiority or  
19 inferiority, we're going to look at the p-value. I  
20 think we have to take it back to what the original  
21 reason for the design of this trial was, which was  
22 really to look at true clinical practice.

23                   I think that people don't up-titrate to  
24 the 16 milligrams and they don't up-titrate every two  
25 weeks. They probably up-titrate once a month when

1 they see the patient. So I think it was set up to be  
2 reality.

3 DR. D'AGOSTINO: The difficulty with  
4 pushing that, though, is when you have a big enough  
5 study and you have a large number of outcomes, you are  
6 bound to see something that's going to upset you very  
7 much.

8 DR. PINA: I'm not one to approve of  
9 subgroup analysis or any of these, but this was one of  
10 the grouping of secondary endpoints in a group of  
11 cardiovascular events or cardiovascular effects. So  
12 I think it's very critical. It's there. It's there  
13 as a secondary endpoint. It just happens to be  
14 grouped together among others.

15 DR. D'AGOSTINO: But it wasn't even a  
16 separate endpoint, though, was it?

17 DR. PINA: No. It was grouped together  
18 among others.

19 ACTING CHAIRMAN BORER: Bob Temple and  
20 then Bob Fenichel.

21 DR. TEMPLE: Yes. I'm sort of having a  
22 slightly "through the looking glass" feeling here. I  
23 want to remind everybody that the published report of  
24 the CAST study declared that the CAST trial was  
25 stopped for futility.

1                   They had a one-sided hypothesis, not two-  
2 sided. So they could not find an adverse effect. Now  
3 fortunately, nobody paid any attention to that, and  
4 everybody knows that CAST showed that those drugs were  
5 harmful.

6                   Now why were they able to do that, even  
7 though the study as designed didn't permit that  
8 conclusion? It's because these rules are not  
9 absolute, and you got to use your head.

10                   So having said that, and maybe this just  
11 proves I'm a closet Bayesian, it doesn't shock me that  
12 on heart failure the alpha blockers don't do very  
13 well. There are published reports. There's V-HEFT-1.

14                   It tells you it's not going to do very  
15 well on that; whereas, in contrast, the other drug  
16 that it was compared to is well known to have a very  
17 favorable effect on heart failure, both from  
18 controlled trials and from the simple logic of the  
19 fact that it's a diuretic.

20                   Having said all that, it's hard for me to  
21 imagine that one doesn't take the finding at least  
22 pretty seriously. What the exact p-value is, I don't  
23 know how to put that on it, but that it's strong. I  
24 mean, if you assume there's 21 endpoints and multiply  
25 the p by 21, it still comes out .002 or less than.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 And p-values may not be precise figures, but they give  
2 you some idea of how removed from chance this is  
3 likely to be. So they are not irrelevant.

4 The actuality of the finding, I must say,  
5 seems fairly strong. What it means, what the  
6 implications of it are, that's a different question.  
7 But the finding itself, even though it wasn't the  
8 primary endpoint? Not so strong.

9 DR. FENICHEL: Bob, you mentioned two  
10 points, and I have to jump in on the first. You had  
11 mentioned about CAST. I argue most trials are one-  
12 sided intrinsically, and what one is looking at is  
13 strength of evidence to determine either that there is  
14 benefit ruling out no benefit or that there is lack of  
15 benefit ruling out benefit.

16 Just as you could in a noninferiority  
17 trial have enough evidence to say you can rule out  
18 noninferiority, if it is so positive, you can rule  
19 equality and be superiority. Similarly, in a trial --  
20 In any one-sided trial where the opposite of proving  
21 benefit is to rule out benefit, if it is so bad you  
22 actually rule out equality, which is proving harm.

23 I argue that is always the goal, is to be  
24 able to do one or the other. And if it's so bad it  
25 rules out harm, of course, that's permissible within

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1. the statistical procedures.

2           Let me, though, emphasize -- In your  
3 second point, I am bothered by a comment that would  
4 say heart failure is one of a large array of  
5 endpoints, and we have to interpret its strength of  
6 evidence as though it was pulled out from one of a  
7 myriad of endpoints.

8           I would rather look at the aggregate  
9 picture here, and the aggregate picture here is pretty  
10 consistent. The aggregate picture here is showing for  
11 all of these prespecified endpoints that are secondary  
12 measures similar kinds of patterns, 19 percent higher  
13 stroke, doubling in CHF, 16 percent higher angina,  
14 coronary revascularization 15 percent higher. Then  
15 not surprisingly, the combined CHD and combined  
16 cardiovascular disease endpoints that are driven by  
17 these others are showing the same thing.

18           I see a consistent pattern here, and  
19 there's only a few elements that are driving all of  
20 this that happen to be the most clinically relevant  
21 elements, I would say. In addition to cardiovascular  
22 related deaths and MIs, you look at -- even before you  
23 look at angina. If you go to angina, that's also in  
24 the wrong direction.

25           You look at other measures such as stroke

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 and heart failure. These are one of 23 different  
2 measures. If you choose to look at it that way, doing  
3 a Bonferrani, dividing by 23 isn't the right thing to  
4 do. You look at the aggregation. If they are all  
5 pointing in the same direction, that ought to give you  
6 a composite sense here.

7 DR. D'AGOSTINO: I guess, Tom, the  
8 question, though, is -- Maybe that's what I was trying  
9 to say, but that's not what the question is that, I  
10 think, we are sitting here with, is that it's not sort  
11 of inspiration but what do the p-values mean. There  
12 was nothing that was driving the study.

13 I mean, I think we're all saying the same  
14 thing, that how do you put the ensemble of information  
15 together? If you ask what do the p-values mean, I  
16 don't think they mean at this point anything, but how  
17 do you put this -- Interpretation, I think, is really  
18 the next question.

19 ACTING CHAIRMAN BORER: I think, Bob  
20 Fenichel, did you have a comment? No? Steve.

21 DR. NISSEN: Of course, we're always  
22 making the assumption for statistical purposes that  
23 this was heart failure. I just want to point out to  
24 you that every antihypertensive drug, most of the  
25 direct acting drugs cause fluid retention and some

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 peripheral edema. True for amlodipine, true for  
2 doxazosin, true for a lot of drugs, but not true for  
3 diuretics.

4 It's almost like it's a circular  
5 definition here, because if you look at the criteria  
6 for what was heart failure, edema was one of those  
7 major categories. So, you know, we made all these  
8 assumptions based upon the statistical analysis.

9 This was not a centrally adjudicated  
10 endpoint. We know that heart failure reporting by  
11 investigators tends to be pretty unreliable, and I'm  
12 very concerned that we are doing all these gymnastics  
13 with the statistics when we really don't have a well  
14 adjudicated endpoint, in the first place.

15 ACTING CHAIRMAN BORER: That's a very  
16 cogent point, because it brings us right to 1.6.1, and  
17 I just want to, for the record, point out that we are  
18 always -- we always welcome the comments of a closet  
19 Bayesian.

20 1.6.1 follows 1.6, which is: The  
21 publications attribute the excess cardiovascular  
22 events in the doxazosin arm largely to excess CHF.  
23 This analysis was retrospective.

24 1.6.1 then is: How was CHF diagnosed,  
25 which is exactly what Steve is questioning here, and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 has made a cogent comment about.

2 Ileana, do you have anything else to add?

3 DR. PINA: I think that, you know, taking,  
4 as was shown, two columns and taking a point from one  
5 column and a point from the second column and making  
6 the diagnosis can lead you to error if one of the  
7 columns that you are choosing is simply peripheral  
8 edema and that's what you are calling heart failure.  
9 However, we do have some data that a good number of  
10 the patients had ejection fractions, in fact, below 35  
11 percent.

12 We also know well that this class of drugs  
13 does retain fluid. This has been well described in  
14 the prazosin data. It's been well described with  
15 elevated renin levels.

16 So I am not surprised. I am not surprised  
17 at all, s but I do have some problems with how the  
18 definition was reached, even though it's the same  
19 definition as reached in SHEP.

20 ACTING CHAIRMAN BORER: Why don't you take  
21 one step further, since actually you and Steve have  
22 both answered the other elements of this question. Do  
23 you think that there is -- I'm going to modify this --  
24 important bias in the study outcome as a result of the  
25 issues about diagnosis of CHF?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 DR. PINA: I would have to say possibly,  
2 with the choice of agent, very possibly and very  
3 possibly with the other groups not seeing it, because  
4 you have an ACE inhibitor in the group.

5 ACTING CHAIRMAN BORER: Marvin, what's  
6 your thought about this?

7 DR. KONSTAM: I'm not super-worried about  
8 the bias. You know, I think it depends on what you  
9 mean by bias, of course. So it's up against the  
10 diuretics. So there's no doubt that chlorthalidone is  
11 a diuretic and, therefore, there will be more edema in  
12 the doxazosin group.

13 The question is, you know -- But that will  
14 be a manifestation of heart failure.

15 DR. LIPICKY: That's what bias meant here.

16 DR. KONSTAM: Well, it's bias only in the  
17 sense that the patient actually doesn't have heart  
18 failure but is being diagnosed as having heart  
19 failure, because they have edema.

20 DR. LIPICKY: Or has heart failure and  
21 isn't diagnosed, because they don't have edema.

22 DR. HIRSCH: It's a physiologic bias.

23 DR. KONSTAM: No, I don't think that --  
24 Yes, I don't think I would call that bias. I think,  
25 you know, something happened to these patients. They

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1. presented with an event that was called heart failure,  
2 and the question -- and so there are two different  
3 parts of that.

4 One is what's going on physiologically.  
5 I think that's what you are talking about. But I'm  
6 not super-concerned that these patients actually did  
7 not have heart failure, although I don't know why. I  
8 mean, I might be concerned, but I'm not real concerned  
9 about that.

10 I think the bigger question is, you know,  
11 how important was that to their natural history, given  
12 the fact that if somebody had preexisting ventricular  
13 dysfunction, not being on a diuretic might have caused  
14 that to manifest frank clinical heart failure.

15 So I don't know if I've answered it.

16 ACTING CHAIRMAN BORER: Alan?

17 DR. HIRSCH: Just to reemphasize the same  
18 point, I mean, assuming this is a physiologic bias  
19 based on known mechanisms of the drugs, one might have  
20 pre hoc proposed what Ray is saying would have  
21 happened.

22 On the other hand, I interpreted the  
23 question differently. You have a blinded study with  
24 two customers, in a sense, the doctors and the  
25 patients. The patients suffered some kind of fluid

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 retention, raw S3 edema which I doubt they wanted to  
2 have, and the physician made a diagnosis based on  
3 those findings that I doubt the physician wanted to  
4 see.

5 So whereas it is perhaps a predictable  
6 effect of the study design and may be unfortunate --

7 DR. KONSTAM: I think we're really being  
8 semantic.

9 DR. HIRSCH: It is semantical.

10 DR. KONSTAM: I think when somebody with  
11 ventricular dysfunction retains fluid, gee, I think we  
12 might as well call that heart failure. I mean, why  
13 not?

14 DR. HIRSCH: That's my point.

15 DR. KONSTAM: The issue really then will  
16 become, okay, how important is that? Is that  
17 irreparable harm? Those are the important next  
18 questions.

19 DR. LIPICKY: So it may be better to not  
20 discuss this too much unless you have --

21 ACTING CHAIRMAN BORER: Just one last  
22 point from Steve.

23 DR. NISSEN: Yes. We don't know what the  
24 breakdown was, how many has S<sub>3</sub> gallops, how many had  
25 peripheral edema. We don't know any of that. So, you

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 know, maybe all of this was driven by the edema issue.

2 Now I every now and then practice medicine  
3 for a living, and I can tell you that patients on  
4 direct acting vasodilators come in my clinic every  
5 week complaining of peripheral edema. Is that heart  
6 failure? Do I diagnose that as heart failure?

7 Well, I think that I would have been much  
8 more comfortable here to have had some central  
9 adjudication process and to have in front of us the  
10 data on how many episodes were there of acute  
11 pulmonary edema. I mean hard heart failure endpoints.  
12 These are soft endpoints, and peripheral edema is a  
13 known endpoint of vasodilator drugs that we all see  
14 every day.

15 ACTING CHAIRMAN BORER: Steve, do you draw  
16 any inferences from the fact that the quality control  
17 effort showed that a central adjudication found that  
18 33 percent of the diagnoses were not what the  
19 committee would have accepted?

20 DR. NISSEN: Well, again, I didn't -- I  
21 don't know if that data has been published.

22 ACTING CHAIRMAN BORER: No, but we were  
23 told about it.

24 DR. NISSEN: So it's a little hard to  
25 interpret it, you know, when it's not really in front

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 of us. But again, you know, there are real problems  
2 with heart failure as an endpoint in clinical trials.  
3 That's why it tends to be centrally adjudicated,  
4 because particularly when a known side effect of the  
5 comparator drugs here includes what is probably benign  
6 peripheral edema.

7 I'm concerned that a lot of this could  
8 have been driven by the simple peripheral edema caused  
9 by direct acting vasodilators. I just don't know the  
10 answer to that.

11 ACTING CHAIRMAN BORER: I guess, just  
12 before you speak, Michael, I guess one of the  
13 questions that I want to ask you, Ray, if this is one  
14 of the implications of your question. If you see that  
15 somebody has peripheral edema, whatever the cause, are  
16 you more likely to go look for and even find, whether  
17 it's there or not, other physical signs or symptoms  
18 that would be consistent with the diagnosis of  
19 congestive heart failure that you infer is probably  
20 there because you see the peripheral edema? And that  
21 may actually feed into the bias issue that you're  
22 asking about. Mike?

23 DR. ARTMAN: Along those lines, you got to  
24 check for having heart failure if you were an  
25 outpatient with some edema or if you got hospitalized.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Do you have any information on that breakdown? How  
2 many patients actually were hospitalized with heart  
3 failure or worsening heart failure?

4 DR. CUTLER: Yes. Those outcomes are in  
5 the paper.

6 DR. ARTMAN: I didn't see the numbers.

7 DR. CUTLER: The numbers -- I don't know  
8 if I have the numbers.

9 DR. ARTMAN: Because it would seem to me,  
10 if the majority of those heart failure events were  
11 outpatients complaining of some ankle edema --

12 DR. CUTLER: No. I think it was the other  
13 way around. I think it was the majority were  
14 hospitalized. I don't have the exact breakdown.

15 DR. KONSTAM: But you could fall into the  
16 endpoint of heart failure without being hospitalized?

17 DR. CUTLER: As defined, yes. Then it's  
18 subset to hospitalized or fatal with the same results  
19 in that subset, and the ejection fraction data you saw  
20 was on the hospitalized subset.

21 ACTING CHAIRMAN BORER: Okay. I think  
22 that what we've heard here is that there's some  
23 concern about the lack of precision perhaps in the  
24 diagnosis of CHF, not that the data are wrong but that  
25 we are a little concerned about interpreting those

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 data, and that it may be that the choice of drug  
2 influenced -- without knowledge of the choice of drug,  
3 but the specific drugs used may have influenced the  
4 diagnosis of CHF because of the presence of a symptom  
5 that may not have been due to CHF. But we don't know  
6 that. It's just sort of an amorphous concern, because  
7 we don't have the data.

8 So let's move on to 1.7: ALLHAT is still  
9 in progress. The data from ALLHAT are not available  
10 for FDA review. Are there questions of interpretation  
11 that can be addressed only by review of the complete  
12 data?

13 I think we've heard yes, but Tom?

14 DR. FLEMING: Could I just go back, Jeff,  
15 before we go to that question? This may be what you  
16 were looking for in the manuscript, the result for  
17 fatal and non-fatal heart failure with  
18 hospitalization. Relative risk was 1.83, was similar  
19 to that for all heart failure. Is that what you were  
20 looking for?

21 DR. CUTLER: Yes, but the question was  
22 what proportion of all cases fell into that subset.  
23 The paper doesn't have it.

24 DR. FLEMING: And I don't have that right  
25 here, although it says basically, if you restrict

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 yourself to heart failure with hospitalization, you  
2 see the same rough relative risk.

3 DR. HIRSCH: Just to amplify that, as we  
4 look at other clinical trials there's avoidance of  
5 hospitalization. That's not moot.

6 ACTING CHAIRMAN BORER: Okay. So a cause  
7 of concern but perhaps not overwhelming concern by  
8 itself.

9 We've heard that there are questions of  
10 interpretation that can be addressed only by review of  
11 the complete data from all four arms of the completed  
12 trial. Do you want more of a statement than that,  
13 Ray?

14 DR. LIPICKY: No. I think that's --

15 ACTING CHAIRMAN BORER: Bob.

16 DR. FENICHEL: I think this is really the  
17 central question. I mean, it seems to me, we've had  
18 other meetings of this Committee that center upon very  
19 impressive published papers in major journals. We had  
20 a viserinone meeting several years ago which  
21 essentially followed by a few months a lead article in  
22 the New England Journal in which very small p-values  
23 were described showing how viserinone was the best  
24 thing for heart failure that had ever come along.

25 There were nine voting members on the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Committee, each of whom made a little statement after  
2 having seen the data, which we've not seen today.  
3 After having seen the data, the nine members each came  
4 up with a different and sufficient reason to turn it  
5 down.

6 The sponsor came into the meeting saying  
7 that it would be unethical to do another trial of the  
8 drug, because it was so good. They did another trial,  
9 and it failed.

10 I think that this is the central question.  
11 Do we have the data? Are we the only regulatory  
12 agency in the world that looks at original data or do  
13 we just read the journals?

14 ACTING CHAIRMAN BORER: I think that  
15 everybody would agree with Bob, but the answer is  
16 still yes.

17 Which of the following can be taken today  
18 as adequately -- Oh, I'm sorry. Tom?

19 DR. FLEMING: Sorry to interrupt you  
20 again. Bob has raised an important question, and I  
21 would be interested in knowing from Ray and Bob, who  
22 brought this before us knowing specifically that we  
23 would be in essence relying on the published  
24 manuscripts, whether what Bob's argument -- do you  
25 view Bob's argument to be compelling? Are you asking

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 us to come to judgment here in the absence of having  
2 the formal full dataset?

3 DR. TEMPLE: We, obviously, are. Now  
4 whether you are going to want to do that --

5 DR. LIPICKY: No, we're not

6 DR. TEMPLE: Well, we're asking you for an  
7 opinion about a bunch of things.

8 DR. LIPICKY: No, no. But go ahead with  
9 what you were saying.

10 DR. TEMPLE: Well, we have a petition  
11 before us that asks us to do various things. We're  
12 coming to you for advice on how to resolve and respond  
13 to that petition.

14 So part of the conclusion you are going to  
15 advise us on is whether we can reach any conclusions  
16 with the absence of the complete data.

17 I do want to make an observation.  
18 Viserinone is certainly a good example where, with the  
19 help of a committee, with a lot of help of the  
20 committee, I have to emphasize, we concluded that the  
21 study should not be taken as showing something. But  
22 it wasn't because with full review we blew any holes  
23 in that study.

24 We looked at other data, other studies,  
25 and the Committee and a lot of people found

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 information that was not compatible with that, the  
2 absence of a pharmacologic effect and things like  
3 that. But I have to tell you, I can't think of a case  
4 yet where a very, very low p-value has been reversed  
5 by our review of the data.

6 That's not to say it couldn't happen, and  
7 the concerns about what heart failure actually means  
8 in a particular case is certainly a fruitful area to  
9 look. So I'm not dismissing the idea that it might be  
10 very important, but it's not an everyday occurrence  
11 for very extreme results to be shown incorrect.

12 Marginal results where a couple of people  
13 go the wrong way and it makes a difference? Yes, that  
14 happens all the time. But part of what we are asking  
15 you, I think, is whether we should reach a conclusion  
16 in the absence of the detailed data.

17 ACTING CHAIRMAN BORER: Or at least in the  
18 absence of more data than we have.

19 DR. LIPICKY: But I think the basic issue  
20 is: Is there enough here, with all of the questions  
21 that are unresolved and the importance of the decision  
22 that has to be made, to allow you to come to what you  
23 think are definitive conclusions. That's the question  
24 you are being asked.

25 DR. TEMPLE: Yes, but a component of that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 is whether you could ever do that if you didn't have  
2 the data in your hands. That's one part of the  
3 question.

4 DR. LIPICKY: Well, and I guess a subtitle  
5 to that is that it's the first time you as a committee  
6 have come to grips with not seeing an FDA review of  
7 the data. I guess part of the question is should we  
8 ever do that, and what do we do that for? We make  
9 everyone else send in the data.

10 ACTING CHAIRMAN BORER: Although it wasn't  
11 to the extent that we are doing it today, there was  
12 some sense of the same thing in the review a few years  
13 ago of calcium channel blockers, although some of the  
14 data had been reviewed by the FDA; some were not.

15 DR. LIPICKY: Yes, but that was really  
16 overview kind of stuff. It's just -- You know, SHEP,  
17 for example, as a trial has never been reviewed by us.  
18 Chlorthalidone is not approved for that indication.

19 We have the data sitting on a shelf in one  
20 of the project manager's office. We've never been  
21 asked by anyone to approve the indication, and it  
22 still sits on the shelf -- SHEP.

23 So SHEP, which is isolated systolic  
24 hypertension, not the kind of hypertension here, a  
25 very different population, is a trial that we've never

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 analyzed, and we couldn't tell you any details with  
2 regard to SHEP and have a publication to look at.

3 You know, the question is how can you be  
4 satisfied? I can tell you, I feel very uncomfortable,  
5 because I know that when you go into a dataset, you  
6 don't start to figure out what the problems are until  
7 you start analyzing it and look at it in different  
8 ways, and the kinds of questions that you've been  
9 asking sometimes lead somewhere and sometimes they  
10 don't.

11 I can't tell you the number of times that  
12 a trial that was part of an NDA which looked very good  
13 from the vantage point of the way in which it was  
14 analyzed, in fact, kind of fell apart when you started  
15 looking at it in detail. You know, that's numbers of  
16 times that that has happened.

17 It has been very rare indeed -- this is,  
18 I think, only the second time in 20 years in my  
19 experience that a publication is given, and we're  
20 being asked to say make an important decision on the  
21 basis of that publication.

22 I feel uncomfortable with that, but I  
23 don't know whether I should, and that's one of the  
24 things that you are supposed to answer.

25 DR. TEMPLE: Jeff, it's worth pointing out

1 also that in hypertension, unlike a lot of other  
2 cardiovascular diseases, we've never been asked, and  
3 never have, addressed the outcome components in  
4 labeling. This has been to the Committee. We've  
5 discussed it a little bit. It turns out to be very  
6 hard to do, because every study is different and so  
7 on. But whatever the excuses, we never have.

8 So we've reviewed very few hypertension  
9 outcome studies, hardly any, maybe none.

10 DR. NISSEN: It's not just that we don't  
11 have all the results of the trial. It's that we have  
12 missing data from the interim analysis that resulted  
13 in this ending of the trial. I mean, things that I  
14 would consider to be very basic like what the mean  
15 doses were and that sort of thing. What were the  
16 kinds of events of heart failure events? What was the  
17 distribution of kinds of heart failure events? How  
18 many peripheral edemas? How many S<sub>3</sub>, etcetera?

19 So it's really hard, because not only we  
20 don't know about the other arms of the trial, we don't  
21 know very much about this arm of the trial at this  
22 point. We have one relatively express type  
23 publication, and that's really all we have

24 DR. LIPICKY: Well, but for example, it  
25 would be pretty important to know how things looked

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 with amlodipine. If this business of heart failure  
2 goes on and you just mask it with chlorthalidone is a  
3 farce, then amlodipine wouldn't show any heart  
4 failure.

5 So there's all kinds of stuff that would  
6 really lend insight, because indeed if you believe  
7 this secondary endpoint, striking, which looks like  
8 you ought to pay attention to it -- If you believe  
9 that result, if you think it's real and attributable  
10 to doxazosin as having done something, not that it was  
11 insufficiently dosed but that it did something, well,  
12 then chlorthalidone -- amlodipine should have had that  
13 same kind of effect or at least in part, unless this  
14 was all hypertension and it was dose.

15 Without that kind of comparative look at  
16 the results of the entire trial, it's very hard to put  
17 this in a perspective, and I want to just emphasize  
18 that the DSMB said don't stop the trial. An  
19 independent board said that.

20 So, obviously, the people who were looking  
21 at the results systematically, who were concerned, who  
22 knew what was going on, had a difference of opinion  
23 with respect to whether or not the trial should be  
24 continued, and I still don't have a flavor for how  
25 that decision got made or what the considerations

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 were.

2 Ordinarily, we get the minutes of the DSMB  
3 and look at them and find out what it is that they  
4 were talking about and what data did they have and  
5 what direction were the point estimates going in, and  
6 how did they get to or not get to the boundary  
7 conditions that led to whatever claim they were  
8 making.

9 All of that is missing, but it's possible  
10 -- because, Tom, you seem convinced for a moment. So  
11 it's possible that one can be convinced from the  
12 published data and that all of this other stuff is  
13 just stuff, and you're being asked to make that  
14 decision. So that's question 2 or 3 or 4 or whichever  
15 one it was. That's what that was meant to elicit,  
16 whichever question that was.

17 ACTING CHAIRMAN BORER: Tom, you wanted to  
18 respond earlier?

19 DR. FLEMING: I'll try to be brief. In  
20 essence, to paraphrase what I'm hearing from Ray and  
21 Bob, when I look at what the protocol team specified  
22 as their prespecified rationale for early termination,  
23 they said, quote, "Compelling evidence from this or  
24 another study of an AE of a study treatment sufficient  
25 to override any potential benefit on CHD and preclude

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 its further use in the target population."

2 Now they obviously struggled with this  
3 criterion, and they came to a conclusion that this  
4 result should be released as it related to the alpha  
5 blocker and, in particular, though, the other regimens  
6 in the study were to continue, which is what put them  
7 in the difficult position of not releasing all the  
8 information to us.

9 What I hear you saying is, certainly, we  
10 don't have to agree with their judgments. They may  
11 terminate a trial. We may not view that to be  
12 conclusive to act on. But to answer -- To address Bob  
13 Fenichel's point in my words, yes, it is important to  
14 be cautious, not having the totality of information.  
15 Nevertheless, in a setting such as this the results  
16 may be viewed by us to be so compelling on such  
17 clinically important endpoints that it is important to  
18 take action before waiting for the entire completion  
19 of the trial.

20 DR. LIPICKY: And that, in fact, is the  
21 entire issue.

22 ACTING CHAIRMAN BORER: Now that the issue  
23 perfectly well defined, which of the following can be  
24 taken today as adequately established?

25 2.1: Doxazosin is less effective than

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 other treatments for the ALLHAT primary endpoint of  
2 prevention of fatal coronary heart disease and  
3 nonfatal myocardial infarction.

4 I don't think we need to discuss that.  
5 We've already heard that we can't take that as  
6 adequately established.

7 2.2: Doxazosin is less effective than  
8 other treatments for the ALLHAT secondary endpoints of  
9 -- Maybe we ought to modify that just a little bit, if  
10 you will allow me to, to "doxazosin is less effective  
11 under the regimen that was used in the study than  
12 other treatments for the ALLHAT secondary endpoints  
13 of."

14 Is that a fair way for us to look at it  
15 for you?

16 DR. LIPICKY: At the doses studied?

17 ACTING CHAIRMAN BORER: At the doses  
18 studied, the whole regimen used.

19 DR. LIPICKY: Yes, right.

20 DR. PINA: Jeff, wouldn't that be then  
21 chlorthalidone, since that's the only data that we  
22 have? Is it really fair to say "than other  
23 treatments"? We only have one.

24 ACTING CHAIRMAN BORER: Yes.

25 DR. LIPICKY: Well, you asked what other

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 treatment?

2 ACTING CHAIRMAN BORER: Yes. I think that  
3 comes down the list here, and the answer will be  
4 chlorthalidone, if we have a yes.

5 All cause mortality: Does anybody on the  
6 Committee think that we have shown that doxazosin is  
7 less effective than other treatments for all cause  
8 mortality? I see no hands going up.

9 Combined coronary heart disease plus  
10 revascularization procedures plus hospitalized angina?  
11 Any takers on that one?

12 Stroke? Does anybody believe that, as of  
13 today, we have adequately -- or it has been adequately  
14 established that doxazosin is less effective at the  
15 doses studied than other treatments for the ALLHAT  
16 secondary endpoint of stroke?

17 DR. FLEMING: I want to make sure I am  
18 interpreting the question as you intend. Do you mean  
19 by this "less effective," do you mean do we believe  
20 that there is adequate strength of evidence to  
21 conclusively establish this?

22 DR. LIPICKY: Correct.

23 DR. FLEMING: As opposed to there are data  
24 to suggest this?

25 DR. LIPICKY: No. This is as if it were

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 an approval issue.

2 DR. FLEMING: Okay. And we all recognize  
3 that the world shouldn't be black and white, i.e.,  
4 there are middle ground, particularly if you are  
5 looking at secondary supportive data.

6 DR. LIPICKY: I thought you saw everything  
7 as black and white.

8 DR. FLEMING: Certainly not for secondary  
9 supportive measures.

10 DR. LIPICKY: But it is -- For each of  
11 these things, is the strength of evidence the  
12 equivalent of two trails at p 05, to put it in those  
13 terms. And I don't -- I'll leave it there.

14 ACTING CHAIRMAN BORER: We are going to  
15 get beyond this just to general impressions. But I'm  
16 inferring from the silence along the table here that  
17 nobody believes that we have as yet adequately  
18 established that doxazosin is less effective at the  
19 doses studied than other treatments for stroke in the  
20 ALLHAT trial.

21 Left ventricular hypertrophy by ECG? No?

22 Renal disease by slope and reciprocal of  
23 serum creatinine or by need for chronic dialysis or  
24 transplant? No.

25 Health related quality of life? No.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Major costs of medical care? No.  
2 Fatal or nonfatal cancer? No.  
3 Gastrointestinal bleeding? No.  
4 Combined coronary heart disease plus  
5 stroke plus coronary revascularization procedures plus  
6 angina, hospitalized or medically treated, plus CHF,  
7 hospitalized or medically treated -- that's outpatient  
8 treated -- plus peripheral arterial disease,  
9 hospitalized or outpatient revascularization  
10 procedure?

11 There is the key endpoint. Do we believe  
12 -- Does anyone believe that, as of today with the data  
13 that we have, it is adequately established that  
14 doxazosin is less effective at the doses studied than  
15 other treatments for the ALLHAT secondary endpoint of  
16 this, 2.2.1? This is the endpoint that reached a p  
17 less than .001, I believe.

18 DR. LIPICKY: Correct. Does the silence  
19 mean no?

20 ACTING CHAIRMAN BORER: I'm asking.

21 DR. FLEMING: This is an extremely hard  
22 question for me to answer. When you are looking at  
23 this composite endpoint and you look at either heart  
24 failure itself or the combined cardiovascular disease  
25 endpoint that includes heart failure and these other

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 elements, there is in my words considerable evidence.

2 Whether it matches .025 squared on a  
3 primary endpoint, I'd be hard pressed to say yes, but  
4 that's where I really struggle with everything else is  
5 irrelevant then, which I don't know that you are  
6 saying. But a lot of people might conclude that from  
7 this discussion, if nobody says any of these event  
8 prove it, then everything is fine.

9 DR. LIPICKY; Oh, no. No, no, no. That's  
10 not the case. This is how strong is it. You can  
11 still argue they didn't find anything, but you want  
12 something in labeling, if you think that makes a  
13 logical argument. So you how you answer this question  
14 is sort of important.

15 ACTING CHAIRMAN BORER: You could say that  
16 you don't think that the standard of evidence of a p  
17 less than .05 times two is appropriate.

18 DR. LIPICKY: Yes. So maybe the answer to  
19 2.2.10 is "sort of."

20 ACTING CHAIRMAN BORER: Well, maybe, but  
21 I think we need to hear some specific comments here.  
22 Ralph, why don't you start?

23 DR. D'AGOSTINO: The endpoint or this  
24 combined endpoint when analyzed did come out to be  
25 significant, but it is very much driven by the CHF.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I mean, to look at a composite endpoint and sort of  
2 indict all these components is very hard for me to do.  
3 I mean, it's a secondary endpoint, and there isn't  
4 necessarily consistency in terms of if I see one  
5 endpoint being significant, another one should be  
6 significant, another one should be significant.

7 So I don't really have a hard time saying  
8 that I'd put a no to this, and then my difficulties  
9 would come in with something like the stroke, which  
10 we've addressed above, and then the CHF which we will  
11 address below.

12 DR. TEMPLE: Jeff, can we be sure we're  
13 getting the answer we need? There isn't a separate  
14 question on heart failure alone. Right?

15 ACTING CHAIRMAN BORER: There is, 2.3.  
16 Yes, there is.

17 DR. TEMPLE: Okay, fine.

18 ACTING CHAIRMAN BORER: Bob Fenichel? I'm  
19 sorry. Ralph, were you finished?

20 DR. FENICHEL: Yes. Well, I think the  
21 answer is no. I think it is a harder call than any of  
22 the other components of 2.2, but I think that I agree  
23 with Tom that there are conditions under which, even  
24 in the absence of looking at the data, one has to be  
25 carried away with the force of an apparent result and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to wonder, gee, how could it possibly be undermined if  
2 we saw what was really there.

3 Well, if this were an unequivocal measure  
4 of irreversible harm, I think one has to give more  
5 weight to this sort of data-less finding, but as  
6 things are, I would say no.

7 ACTING CHAIRMAN BORER: Steve?

8 DR. NISSEN: You know, it's very  
9 difficult, because this is driven so much by the heart  
10 failure endpoint, and I remain terribly troubled with  
11 the problem of diagnosing heart failure for two  
12 classes of drugs, one of which produces edema and one  
13 of which relieves edema.

14 So it's just such a soft endpoint in this  
15 application that I have to tend to factor a lot of  
16 that out, and I'm just very concerned that  
17 investigators saw some peripheral edema, looked for  
18 other things and found them, and that that's driving  
19 all of this.

20 So I would have to say no.

21 ACTING CHAIRMAN BORER: Joann?

22 DR. LINDENFELD: I would also say no, I  
23 don't think this is conclusively established.

24 ACTING CHAIRMAN BORER: Tom?

25 DR. FLEMING: Is your thought the same,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 even recognizing that when you say heart disease with  
2 hospitalization, you still have basically the same  
3 relative risk? You still think that's soft,  
4 hospitalization with heart failure?

5 DR. NISSEN: Yes, I do think it's soft,  
6 and I'll tell you why it's soft. That is that  
7 somebody comes in the clinic with some symptoms  
8 perhaps and has edema. They may be hospitalized for  
9 that. I mean, this is enough -- There is enough that  
10 might suggest a bias in choosing who you are going to  
11 put in the hospital that would make me concerned.

12 Is it a better endpoint? Yes. But I just  
13 would have been much -- I would have felt much better  
14 about this if the whole adjudication procedure and all  
15 of that had been somehow cleaner, because of all of  
16 the endpoints that we look at in medicine, those like  
17 heart failure where it's a multifactorial combination  
18 of symptom and physical finding, it's a very subtle  
19 clinical diagnosis. That subtlety can get played out  
20 in lots of ways.

21 I think, you know, edema can drive a lot  
22 of things, and I've actually -- I will tell you that  
23 there's data from several generations of cardiologists  
24 to suggest that an awful lot of people get put on  
25 digitalis for benign postural edema. We've known that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 for years.

2 So I think we just have to be terribly  
3 careful here.

4 ACTING CHAIRMAN BORER: Tom? Tom Graboys?

5 DR. GRABOYS: Well, I feel in a query  
6 about this. I'm not sure how to answer it.

7 ACTING CHAIRMAN BORER: Alan?

8 DR. HIRSCH: I've expressed my concern  
9 about the diagnosis of heart failure from the  
10 beginning. So I think that it's hard to be  
11 definitive, and I guess I'd say no, but I'm worried.  
12 But no.

13 ACTING CHAIRMAN BORER: Ileana?

14 DR. PINA: That combined endpoint comes  
15 out to be statistically significant, but again it's  
16 driven by heart failure. But it's also driven by  
17 angina, and so I can't say that the entire combined  
18 endpoint is, but it causes me great concern.

19 ACTING CHAIRMAN BORER: So do you think  
20 that this is adequately established or no?

21 DR. PINA: I think there's some heart  
22 failure there. I don't know that every single -- and  
23 I'd love to see how the adjudication was made. I  
24 don't know that every single diagnosis of heart  
25 failure was truly heart failure.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I'd love to see the amlodipine data  
2 because amlodipine causes a lot of peripheral edema,  
3 which is not heart failure, and it would be very  
4 interesting to see how many clinicians identified that  
5 as heart failure. Of course, we're not going to have  
6 access to that data.

7 DR. LIPICKY: So are you refusing to  
8 answer the question?

9 DR. PINA: No.

10 DR. LIPICKY; Is that the answer to the  
11 question?

12 DR. PINA: Yes.

13 DR. ARTMAN: Now I'm really confused. A  
14 simple no.

15 ACTING CHAIRMAN BORER: Marvin?

16 DR. KONSTAM: Well, I'm going to answer  
17 the question by suggesting that, if the results were  
18 the opposite and Pfizer was in here asking for an  
19 extension of the indication, you would throw them out  
20 of the room. So I guess the answer would have to be  
21 no.

22 ACTING CHAIRMAN BORER: Okay. And I also  
23 believe that it hasn't been established.

24 2.3: Doxazosin is less effective -- I'm  
25 going to add again here "at the dose employed" or

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 "with the regimen employed" -- than other treatments  
2 for the ALLHAT other protocol specified outcome  
3 measurements or endpoints of: Mortality from coronary  
4 heart disease?

5 DR. FENICHEL; Wait a second, Jeff. Is  
6 this question different from -- Why is this not just  
7 more of 2.2? What's different here?

8 DR. LIPICKY: The difference is that in  
9 the protocol there were primary and secondary  
10 endpoints clearly indicated, but we are also  
11 interested in the following. So that these are the  
12 following.

13 ACTING CHAIRMAN BORER: Mortality from  
14 coronary heart disease? Does anybody believe that a  
15 difference has been established here? No.

16 Mortality from other cardiovascular  
17 disease? No.

18 Mortality from neoplastic diseases? No.

19 Mortality from other medical causes? No.

20 Mortality from non-medical causes? No.

21 Myocardial infarction? No.

22 Angina? Tom?

23 DR. FLEMING: Well, I'll just jump ahead  
24 and say angina and CHF are the two elements that I  
25 can't give a no answer to. I cannot say it's a .025

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 squared primary endpoint conclusive level of evidence,  
2 but there are, in my view, strong data here indicating  
3 that -- in fact, I would argue, stroke, heart failure  
4 and angina are more frequently occurring in the alpha  
5 blocker regimen.

6 ACTING CHAIRMAN BORER: Okay. Does  
7 anybody else on the committee have a sense that  
8 there's adequate information to establish doxazosin as  
9 less effective for angina or for preventing angina  
10 from developing? Steve?

11 DR. NISSEN: Can I make just a comment?  
12 There's something that I'm troubled by here, and that  
13 is that 3 millimeter difference in systolic blood  
14 pressure.

15 I would have felt much better about that  
16 conclusion if the drugs were given to equal blood  
17 pressure effect, and we then saw a difference in the  
18 event rates. So I can't attribute it to the choice of  
19 drug as opposed to the way the drug was used.

20 I think it's terribly important as the  
21 committee that we have to understand what we've  
22 learned and what we haven't learned here, and what we  
23 know is that there was a blood pressure difference.  
24 I can't tease that out of the data.

25 DR. FLEMING: But, Jeff, I thought you

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 clarified very carefully at the beginning that this  
2 question is relating to the regimens as they were  
3 delivered.

4 ACTING CHAIRMAN BORER: Right.

5 DR. FLEMING: So for the regimen as it was  
6 delivered, and your point is well taken. But that  
7 changes the question.

8 DR. LIPICKY: It's strength of evidence.  
9 It's an intent-to-treat, strength of evidence. It's  
10 everything as done.

11 ACTING CHAIRMAN BORER: Integrating  
12 everything that we know.

13 DR. NISSEN: I guess what I'm saying is  
14 I'm concerned that doxazosin was not titrated to its  
15 optimal dose, and so what we're doing is we are  
16 comparing a suboptimal dose of one drug to an optimal  
17 dose of another.

18 That means that weakens the strength of  
19 the evidencetremendously, in my view, and makes that  
20 standard that has to be demonstrated here much, much  
21 more rigorous before I'm going to be convinced.

22 DR. LIPICKY: No. No, it would be okay to  
23 say that dose X of drug A is less effective than dose  
24 Y of drug B. Okay? That's a perfectly acceptable  
25 thing. It doesn't mean that the two drugs are

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 different from one another if they are used at equally  
2 effective doses, but at the doses studied, it's okay  
3 to say that one regimen is less effective than the  
4 other. That implies nothing with respect to the drugs  
5 and their potential to be effective. It just means  
6 those doses are different.

7 ACTING CHAIRMAN BORER: With that -- Yes,  
8 Ralph?

9 DR. D'AGOSTINO: Let me give my two cents  
10 on it. I have a feeling that the CHF, no matter how  
11 you beat the data, you're not going to lose that  
12 significance. So I find it very hard to put a no  
13 there. I don't know what the alternative is, though.  
14 I wouldn't want to put a yes.

15 DR. LIPICKY: Well, that's fine. I wrote  
16 down "sort of."

17 ACTING CHAIRMAN BORER: Okay. Well, there  
18 we are. Okay, I think to move ahead here, my sense is  
19 that, although there are some concerns that Tom has  
20 voiced here about angina, nobody else, including Tom,  
21 really is ready to say that it is adequately  
22 established that doxazosin is less effective at the  
23 dose employed, with the regimen employed, than other  
24 treatments for prevention of angina.

25 Peripheral arterial disease? No.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Nonfatal accidents and attempted suicides?

2 No.

3 CHF? That's where the rubber meets the  
4 road here, and I think Ralph made one very important  
5 statement here. He can't say no, but it's very hard  
6 to know whether you say -- He can't say that it is  
7 less effective, but it's very hard to say no.

8 Why don't we pick up from there? Ralph,  
9 do you want to add to that?

10 DR. D'AGOSTINO: Well, you know, this is  
11 where, if we had the other arms, we could see how  
12 consistent the CHF is. I mean, is it going to turn  
13 out to be the diuretic, so that it beats out everybody  
14 on all the other treatments? And then we don't --  
15 Then we suddenly say maybe there's something strange  
16 about the diuretic arm and so forth.

17 So I don't know what more you want me to  
18 say on this, but I don't know how to really interpret  
19 the results that we have except that from a statistics  
20 point of view -- and we're stopping with two zeroes  
21 and a one. What we were told earlier, the zeroes  
22 extend out even beyond that. So this is a highly  
23 significant result. How you interpret it, I think, is  
24 the real problem for me.

25 ACTING CHAIRMAN BORER: So this is a real

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 cause of concern here, and we haven't come to closure  
2 yet on whether we can definitively say that doxazosin  
3 is less effective at the doses employed and the  
4 regimens used than other treatments so far.

5 Next, Bob Fenichel?

6 DR. FENICHEL: Well, I'm not sure -- I  
7 thought we had already answered this.

8 ACTING CHAIRMAN BORER: Well, we didn't  
9 answer the CHF part, I think, or maybe we did.

10 DR. FENICHEL: Oh. Well, okay. Well, I  
11 would say no on the same grounds as before.

12 ACTING CHAIRMAN BORER: Okay. Steve?

13 DR. NISSEN: No.

14 DR. LINDENFELD; No.

15 ACTING CHAIRMAN BORER: Tom?

16 DR. FLEMING: Yes.

17 ACTING CHAIRMAN BORER: Okay. Tom Graboys?

18 DR. GRABOYS: I continue to be troubled  
19 about the CHF occurrence. I think there is something  
20 there that we are missing. We are bending over to try  
21 to come up with some rationalization which would allow  
22 us to kind of cosmetically accept it, and I can't do  
23 it at this point.

24 ACTING CHAIRMAN BORER: I don't know that  
25 we have to cosmetically accept it. I think this

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 question is have we definitively -- are the data  
2 sufficient at this moment that we have seen -- Are  
3 they sufficient to adequately establish to our  
4 satisfaction, based on whatever strength of evidence  
5 we choose to use as the bar, that doxazosin is less  
6 effective at the doses used in the regimen employed  
7 than other treatments in the ALLHAT study for  
8 prevention of CHF?

9 The answer can be no, it hasn't been  
10 adequate established, but we may still at the end of  
11 the day feel so unsettled by all this that there's a  
12 conclusion or an action item that could follow.

13 DR. GRABOYS: Then, no.

14 ACTING CHAIRMAN BORER: Alan?

15 DR. HIRSCH: Boy, I'm troubled. Very  
16 close to yes, and the rationale, just to say one more  
17 time, is that we have a different kind of study here  
18 than normally we analyze. I can take any study I've  
19 ever looked at that we could design and, based on dose  
20 and administration routes, find a way of criticizing  
21 a single study, and never coming up with a definitive  
22 answer.

23 It's very easy to look backwards and ask  
24 for the second study, the different p-value that are  
25 justification of the point estimate. So you're going

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 to ask me what do I think.

2 ACTING CHAIRMAN BORER: Well, I think you  
3 just said what you think. Ileana?

4 DR. PINA: I mirror exactly what Alan  
5 says. I can't sit here and say definitively no, but  
6 I'm very close to saying yes, because I think that  
7 even if we remove some of the cases, there were enough  
8 hospitalizations, that a hospitalization for heart  
9 failure is one of our key diagnostic points for  
10 defining heart failure.

11 ACTING CHAIRMAN BORER: Mike?

12 DR. ARTMAN: No.

13 ACTING CHAIRMAN BORER: Marvin?

14 DR. KONSTAM: At the risk of being  
15 unhelpful, but maybe this will be helpful, maybe not,  
16 I'm going to -- Can I offer a statement that I would  
17 say yes to?

18 ACTING CHAIRMAN BORER: Please.

19 DR. KONSTAM: And maybe this articulates  
20 some of the discomfort that people have, and this is  
21 as far as I would go with it, that doxazosin in doses  
22 used appears to be less effective than chlorthalidone  
23 for prevention of the clinical manifestations of heart  
24 failure without indication of any implication with  
25 regard to irreparable harm.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 I think that there is something going on  
2 here. So just saying no -- and I think that's where  
3 a lot of the discomfort is. So I don't know whether  
4 it's worthwhile or not, but it might be worthwhile  
5 crafting what it is that we think is going on. And  
6 that's what I think is going on.

7 DR. LIPICKY: It is worthwhile, and it  
8 probably should have been written that way, but  
9 basically I think you're saying the same thing  
10 everyone else said. I still take what everyone else  
11 said as "sort of."

12 You had added the irreversible harm part,  
13 and I think that's very important here, because if one  
14 things that -- and that's a preamble to the next  
15 question. If one thinks that doxazosin caused heart  
16 failure, then this is applicable stuff to BPH also.  
17 It isn't not as effective in hypertension and not  
18 effective in hypertension causes the ventricular  
19 dysfunction.

20 It is doxazosin causes something, and then  
21 it's equally applicable to BPH, and we would have to  
22 incorporate some language to say something about that.  
23 So the irreversible harm is important.

24 ACTING CHAIRMAN BORER: Okay. So to  
25 summarize the statements about 2.3.1.0, I think it

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 would be fair to say the sense of the Committee is  
2 that, no, it is not adequately established that  
3 doxazosin is less effective at the dose used in other  
4 treatments for the prevention of congestive heart  
5 failure, but there's enough information here so that  
6 everyone is concerned, and that may lead to an action  
7 suggestion of some sort -- I'm not sure what sort yet  
8 -- and that we have some other issues to deal with,  
9 and Marvin just began to deal with them.

10 Number three -- Tom?

11 DR. FLEMING: I actually hadn't done this  
12 before. I just did a quick chi square just to see  
13 what the strength of evidence is, and I come up with  
14 a z-value of 10. I ran it quickly twice. I'm not  
15 certain, but I'm pretty certain that's right.

16 So there is an enormous number of zeroes  
17 in front of this one. So if we're talking about  
18 statistical strength of evidence -- I know that there  
19 are other issues.

20 DR. LIPICKY: Well, I thought you said p-  
21 values don't count here.

22 DR. FLEMING: Well, everything is in the  
23 context of -- I think what I said was -- weighing  
24 strength of evidence with clinical judgment. And  
25 strength of evidence is, in fact, a relevant factor.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1. So I'm just throwing out the fact. This  
2 isn't a p-value of .001. You had raised the .025  
3 squared paradigm, and that's not enough here, because  
4 this is a secondary endpoint, generally speaking.

5. So I just wanted to, for the record, point  
6 out that this is -- Unlike the other associations  
7 here, this one has a very strong statistical  
8 association, granted, though, it's a secondary  
9 endpoint.

10 ACTING CHAIRMAN BORER: Okay. Number 3  
11 gets to the issue that Marvin just raised again. If  
12 you answered in the affirmative for any part of  
13 question 2, was doxazosin worse than placebo would  
14 have been?

15 We heard some information from Tom about  
16 that from a quick and dirty calculation, and I think  
17 that, even though formally the answer to 2.3.10 may  
18 have been no, I think we really do have to resolve  
19 this as a committee, and perhaps also with regard to  
20 strokes and maybe we'll ask for an opinion about  
21 angina.

22 Was doxazosin worse than placebo would  
23 have been? In other words, does it cause harm? Can  
24 we infer that it causes harm of any kind, number one?  
25 Number two, does it cause irreversible damage,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 myocardial damage, irreversible harm?

2 Let's try and grapple with 3.1, and we'll  
3 begin with Marvin. Are we giving you information you  
4 don't want?

5 DR. LIPICKY: Pardon me?

6 ACTING CHAIRMAN BORER: I say, are we  
7 giving you advice you don't want?

8 DR. LIPICKY: Yes, you're doing good, but  
9 I want to just sort of preamble, Marvin, just a little  
10 bit from an interpretation point of view.

11 The intent here is not to, from the data  
12 available, I think, calculate what the probabilities  
13 are that it had beat placebo, had the placebo been  
14 present. Although that's part of it, it's just that  
15 you don't have the proper control group or the proper  
16 trial to estimate size of the effect. So it would be  
17 very difficult to go through that calculation with any  
18 precision.

19 I think Tom's sort of thing of, well,  
20 you're not going to be sure is probably right, even if  
21 you did everything and so on and so forth. So I don't  
22 think that's the issue. It isn't this noninferiority  
23 stuff or would you, had placebo been present. It is  
24 the business of from the data can you conclude somehow  
25 or another from something you've seen that this does

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 harm and that there is something intrinsic. Then, in  
2 particular, is the harm irreversible?

3 Those are the things to struggle with, if  
4 you can.

5 ACTING CHAIRMAN BORER: Bob?

6 DR. TEMPLE: Maybe my thought will be  
7 wrong, but I didn't hear anybody suggest that the  
8 answer to that was yes. So maybe you could just find  
9 out if anybody thinks that there is evidence of harm,  
10 as opposed to just not working.

11 ACTING CHAIRMAN BORER: It's a good point.  
12 Does anybody believe that this drug caused bad things  
13 to happen to the heart?

14 DR. GRABOYS: Irreparable?

15 ACTING CHAIRMAN BORER: As opposed to just  
16 not working. Well, let's have any, and irreversible,  
17 or irreversible, both. Answer the one and the other.

18 Tom, do you have something?

19 DR. TEMPLE: But particularly, by doing  
20 something bad as opposed to not being good.

21 ACTING CHAIRMAN BORER: Yes, an active  
22 badness. Well, in other words, did it cause  
23 myocardial damage? Did it cause the heart failure?

24 DR. TEMPLE: Should someone with BPH  
25 worry?

1 DR. GRABOYS: If we think it contributed  
2 or caused the CHF, then the answer to that would be  
3 yes.

4 ACTING CHAIRMAN BORER: Do we think that  
5 it did? The question applies to someone without  
6 hypertension but with BPH. Would your expectation be  
7 that that person would develop heart failure because  
8 of being on the drug? That would be an implication of  
9 it, or is it just that it doesn't do the good thing  
10 that chlorthalidone did, which could have a bad  
11 outcome. We don't really know that.

12 DR. KONSTAM: Can I just make the  
13 statement and see if anybody disagrees with it? You  
14 know, I don't think that you can conclude from the  
15 data, even with regard to the clinical manifestations  
16 of heart failure, that doxazosin causes it as opposed  
17 to some imputed placebo, and I think there's a lot of  
18 reason to believe that, in fact, it wouldn't.

19 ACTING CHAIRMAN BORER: But I want to be  
20 sure that Tom Graboys is satisfied with this.

21 DR. GRABOYS: Yes, I accept Marv's  
22 explanation.

23 ACTING CHAIRMAN BORER: Okay. We're  
24 saying we have no evidence that it causes harm,  
25 irreversible or otherwise. Tom?

1 DR. FLEMING: We might even be able to say  
2 more than we have no evidence that it -- "We have no  
3 evidence" would seem to suggest that we don't know  
4 anything; whereas, we have evidence. I would say  
5 there is evidence that suggests on some of these  
6 measures, most notably heart failure, that the rate is  
7 higher than it is with diuretics.

8 Also on other measures such as stroke and  
9 angina, it appears to be somewhat higher as well.  
10 However -- However, if I can use information on  
11 diuretics, such as SHEP, the evidence there suggests  
12 that the overall level of benefit that diuretics  
13 provides exceeds the amount that alpha blockers are  
14 worse than diuretics.

15 So when I put all this together, my sense  
16 is that the best evidence I have would suggest that  
17 there is maybe no effect of alpha blockers on heart  
18 failure, i.e., if I had an imputed placebo, I would  
19 expect the results are similar, but I'm having to make  
20 a leap of faith about using SHEP and imputing that  
21 into ALLHAT. And if I do the same thing on the  
22 primary endpoint or on stroke, I actually see some  
23 evidence that alpha blockers would be better than  
24 placebo. But again I'm having to stretch, but not  
25 statistically significantly better.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           ACTING CHAIRMAN BORER: Okay. I think  
2 that's the -- Bob?

3           DR. FENICHEL: Well, one more thing in the  
4 same vein: Once again, looking across trials and  
5 slightly looking across drugs, I think it's reassuring  
6 if one looks at the V-HEFT-1 study, where prazosin, a  
7 close cousin, was not any good for people with  
8 congestive failure, but it certainly didn't do any  
9 harm. The results were absolutely superimposable,  
10 placebo versus prazosin.

11           So that also is somewhat reassuring that  
12 harm is not being done.

13           ACTING CHAIRMAN BORER: Okay. I think  
14 we're all in agreement on that one. Ileana?

15           DR. PINA: I disagree with that last  
16 statement. It showed that there was no difference in  
17 mortality, but there was nothing in there about the  
18 occurrence of heart failure with prazosin, and I don't  
19 remember ever seeing that in the trial either.

20           ACTING CHAIRMAN BORER: Okay. But I mean,  
21 I think we've all agreed that we don't see any  
22 evidence that doxazosin caused harm.

23           In comparison with which other treatments  
24 is doxazosin less effective? Again, I would ask for  
25 a response with regard to CHF predominantly, and if

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 anybody has any thoughts about stroke or angina, you  
2 can give them. But, Ileana, you raised this issue  
3 before. Why don't you try to answer that for us?

4 DR. PINA: The only drug that I can say  
5 right now is chlorthalidone, because we don't have any  
6 other data available. Maybe at the end of the trial  
7 we will.

8 ACTING CHAIRMAN BORER: Okay. So is the  
9 evidence sufficiently strong so that you can say that  
10 doxazosin is less good than chlorthalidone for  
11 prevention of CHF development?

12 DR. PINA: I'd have to say yes, with that  
13 p-value.

14 ACTING CHAIRMAN BORER: Okay. Any other -  
15 - Does everybody agree with that? Does anybody have  
16 any other comment? Ralph?

17 DR. D'AGOSTINO: Well, it's back to the  
18 CHF, but we've not really sure that we're that  
19 comfortable with CHF. I would prefer not to leave  
20 this study in terms of making the interpretations. So  
21 I think that the data does indicate that it might be  
22 less effective than other drugs, in particular, the  
23 diuretic here. But again, there's all sorts of  
24 caveats attached to that: What is the CHF that we're  
25 really talking about?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I would not extend it to stroke. I think  
2 the result for stroke was significant at a .04, and  
3 one may argue that there's a right direction and so  
4 forth, but I think that's really overreading -- that  
5 might get us into overreading the data. So I would  
6 stay with the CHF.

7 DR. TEMPLE: Jeff, I read this question as  
8 asking what the comparator, that the thing you thought  
9 in 2.3 was is a guess, and since the only drug it  
10 compares to is chlorthalidone, maybe just see if  
11 anybody thinks there is any other drug this applies  
12 to.

13 ACTING CHAIRMAN BORER: Well, I was trying  
14 to get at something more. It's clear that only  
15 chlorthalidone was involved, but rather do we believe  
16 that there is a clear superiority of chlorthalidone?

17 DR. TEMPLE: Right. But isn't that what  
18 2.3.10 was? I mean, I admit, the results are not  
19 equivocally obvious, but it's the same question.

20 DR. FENICHEL: No, it's not the same  
21 question. One might believe that, inasmuch as the  
22 other arms of the ALLHAT study have not been stopped,  
23 the other comparators to chlorthalidone can't possibly  
24 be as bad, and therefore, from that one might believe  
25 that doxazosin is a little bit worse, at least, than

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 those others.

2 I think that's a terrific stretch, but I  
3 think that may be the intent of the question.

4 DR. TEMPLE: You're right, Bob, but I  
5 think I was wondering whether Jeff could ask whether  
6 anybody believes that, so you don't have to spend a  
7 lot of time on it.

8 ACTING CHAIRMAN BORER: I'm going to ask  
9 if anybody believes that. No. Okay, let's move on  
10 then.

11 Do the findings generalize to other drugs  
12 with predominant alpha-adrenergic antagonist activity?  
13 Does anybody believe that we should draw that  
14 inference, extrapolate that way? I'll take that as a  
15 no.

16 With alpha-adrenergic antagonist activity,  
17 in part?

18 DR. PINA: Jeff, let me ask a question of  
19 Ray. Ray, do you know if in the label of prazosin, is  
20 there any statement about volume retention? I mean,  
21 it's been a long time, but do you recall?

22 DR. LIPICKY: I guess my best answer would  
23 be what's prazosin? Does that answer your question?

24 DR. PINA: I guess that answers it.

25 DR. TEMPLE: Jeff, I know what prazosin

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 is. I think the answer is yes, because there was a  
2 lot of agony we spent about the fall in hematocrit and  
3 certain other blood borne things with prazosin which  
4 was attributed to fluid volume expansion. I'd bet a  
5 lot, without looking, that there's some discussion of  
6 it in there.

7 How much edema and stuff like that, I  
8 don't remember, but I know there was concern with fall  
9 of hematocrit and sodium and stuff like that, and it  
10 was attributed to volume expansion. So I know that  
11 much.

12 DR. LIPICKY: You're right.

13 ACTING CHAIRMAN BORER: Again, do we want  
14 to extrapolate from the results of these data to other  
15 alpha-adrenergic agonists or drugs that have some  
16 alpha-adrenergic agonist activity, if they also have  
17 other properties? I'm not hearing a groundswell.

18 DR. LIPICKY: If you take 3.3.1 as no, the  
19 rest of the questions aren't worth asking.

20 ACTING CHAIRMAN BORER: Okay. We won't  
21 ask them.

22 Number 4 -- since you are the one who is  
23 asking for the advice: Should an antihypertensive  
24 agent be considered as "second line" if it is less  
25 safe than another agent? Less effective at reducing

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 systolic or diastolic pressure? Less effective in  
2 reducing cardiovascular events? If so, which ones?  
3 Less effective in reducing mortality?

4 I think that we would all say that it is  
5 true that, if it was less safe, less effective at  
6 reducing cardiovascular events, and we can name some,  
7 and less effective in reducing mortality, that one  
8 would not want to consider it first line. But then we  
9 come back to 4.2, less effective at reducing systolic  
10 or diastolic pressure?

11 I assume you mean going to maximally  
12 tolerated dose and determining that there is such a  
13 difference. Is that what you are asking us?

14 DR. LIPICKY: Well, yes, I guess. Well,  
15 let me sort of see if I can make an assertion, and  
16 then someone on the committee can disagree.

17 I think what this question was trying to  
18 get at through multiple questions, and we only have an  
19 hour left, was how does one get to be second line?  
20 Right? And is it the way in which Tom was reasoning  
21 earlier today or is it on some specific reason like  
22 you know it's less safe or you know it doesn't reduce  
23 blood pressure as much or you know it has some event  
24 problem -- you know, it doesn't reduce some event  
25 rates enough -- or it doesn't reduce mortality?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1                   So I think what this question was meant to  
2 do was to say, if you really knew that the drug did  
3 something, and we've talked about all of the things  
4 that you know and don't know, which one of those  
5 things would be sufficient in your mind to make it  
6 second line?

7                   ACTING CHAIRMAN BORER: Can I just begin  
8 by asking for clarification. I mean, I spoke very  
9 quickly when I was reading the question. But 4.1,  
10 "less safe than another agent" -- We don't think about  
11 approvability or utility of a drug in terms of safety.  
12 We think of it in terms of safety for the intended  
13 use, and we relate the safety to the efficacy.

14                   So you know, one would have to look at  
15 this question in totality. We would have to know  
16 something about the efficacy for what, not just blood  
17 pressure but for event lowering, if we wanted to make  
18 a statement, and then relate safety to that.

19                   You know, it's hard to answer 4.1 in a  
20 vacuum. Similarly, with regard to all of these  
21 issues.

22                   DR. LIPICKY: Well, I'll tell you what.  
23 Let us retract that question, because it's too  
24 theoretical, and there is no real setting to answer it  
25 by, and you will be answering some of that question in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the next question.

2 ACTING CHAIRMAN BORER: Ah, we've just  
3 saved some time. Steve?

4 DR. LIPICKY: Right. So skip 4.

5 DR. NISSEN: Not to want to waste any  
6 time, I want to make a point here about all of this,  
7 and it relates to this whole discussion today. That  
8 is, what does "first line" mean, and what does "second  
9 line" mean?

10 Well, I think thoughtful practitioners who  
11 treat hypertension choose drugs on the basis of a lot  
12 of factors, including the concomitant conditions. So  
13 if I see somebody that has hypertension and angina, I  
14 may favor a beta blocker. In somebody who has  
15 hypertension and congestive heart failure, I may favor  
16 an ACE inhibitor.

17 So in one setting, a drug could be first  
18 line, and in another it could be second line. So one  
19 of the complicating factors here is that we use these  
20 drugs in a context of multiple other factors. So I  
21 think it would be a disservice to label drugs first  
22 line, second line or anything like that, because we  
23 don't know the context.

24 DR. LIPICKY: You're 100 percent right,  
25 and this is sort of oriented toward stupid FDA, in a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 way, in that when a new antihypertensive is approved,  
2 it's just approved. You get to make whatever choices  
3 you want, but the labeling doesn't say use me first,  
4 use me second, use me third or use me in certain  
5 circumstances. Okay?

6 Sometimes for safety reasons that are even  
7 less than we have seen in ALLHAT, drugs don't get  
8 approved for hypertension, and sometimes they will  
9 definitely be approved as second line because we know  
10 they work, but for safety reasons we say it shouldn't  
11 be used before you know you have to use it.

12 In those circumstances we usually require  
13 that there be evidence that it lowers blood pressure  
14 in circumstances where other drugs are used and they  
15 do not lower blood pressure.

16 ACTING CHAIRMAN BORER: A primary example  
17 is captopril when it was first approved.

18 DR. LIPICKY: Yes.

19 DR. TEMPLE: Jeffrey. Or minoxidil.  
20 Minoxidil, if you were basing it on blood pressure  
21 lowering effect, would be the number one drug for  
22 everybody. But we know it isn't.

23 It's also important to appreciate the  
24 possible nuances of various recommendations. The  
25 insertion of a word like "generally" allows people to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 think about other things, if they want to, doesn't  
2 lock them in, and you can do that. But just as a  
3 proposition, if you really believe -- if -- that if  
4 the first line therapy doesn't have some ability to  
5 treat developing heart failure, some people might  
6 reach the conclusion that the first drug you use in  
7 the treatment of hypertension ought to be a drug that  
8 has that capability.

9 I'm not asserting that as a truth, but one  
10 could give that advice. I mean, advice to doctors is  
11 going to include things like that. Other people feel  
12 free to make those generalizations. The question is  
13 whether labeling might want to do that, too, and it  
14 doesn't have to be absolute, and it doesn't have to  
15 threaten disbarment if you don't do it.

16 It could say as a general idea, it's a  
17 good idea to have a drug that treats heart failure,  
18 because a lot of people with high blood pressure get  
19 that. So there's a lot of possibilities, and you  
20 don't want to think of only one.

21 Okay. I'm sorry, Bob?

22 DR. FENICHEL: I find the whole idea of  
23 second line therapy for a class of drugs which is  
24 approved on the basis of a surrogate to be very  
25 difficult. I think this is a systemic problem.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I mean suppose -- Let's take something  
2 that no one has a commercial interest anymore. Take  
3 reserpine. Let us suppose for the sake of argument  
4 that reserpine is just awful, that it causes lots and  
5 lots of suicidal depression, you know, much more than  
6 with any other antihypertensive.

7 Well, suppose that's all true. It still  
8 might be true if one showed that in fact mortality --  
9 even counting all those suicides, mortality at the end  
10 of the day or the end of the year was less on  
11 reserpine, and all your patients who are now on ACE  
12 inhibitors or doxazosin or whatever, chlorthalidone,  
13 would be better off -- more of them would be alive and  
14 happy -- even counting all the reserpine stuff, and  
15 happy at the end of a year, well, then it doesn't  
16 matter that reserpine is less safe.

17 What does that mean, it's less safe? The  
18 whole business of -- or even suppose you had something  
19 which didn't reduce the blood pressure as much. Well,  
20 if there are more people standing at the end of the  
21 year, that's all that matters.

22 The business of trying to make second  
23 line, first line calls in an area of surrogate  
24 endpoints is, I think, fraught with paradox. I think  
25 it's probably to be avoided.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 ACTING CHAIRMAN BORER: Bob?

2 DR. TEMPLE: There's a partial truth in  
3 that and a partial non-truth. This is the largest and  
4 best attempt to compare outcomes we are ever going to  
5 see, and it found something that has a p-value as long  
6 as your arm, and people are still extremely doubtful  
7 about whether it has shown anything at all.

8 All the rest of the comparisons are going  
9 to be, I presume, less impressive since they haven't  
10 stopped the trial yet. It's very hard to detect a  
11 difference when the bulk of the effect of the  
12 therapies is due to lowering blood pressure, which  
13 based on all the data we have for a wide variety of  
14 drugs simply must be true.

15 The differences are likely to be very  
16 small. I think in an area like this you have to look  
17 at possible other advantages. You may or may not  
18 decide to have one thing be second line or another,  
19 but it isn't ridiculous to do that, based on the  
20 assumption that, other things being equal, blood  
21 pressure tells us what to do and that you can find  
22 differences that you think will be meaningful even  
23 though you have no guaranty. I don't think that's  
24 crazy.

25 DR. FLEMING: Bob, I agree. Bob Fenichel,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 I understand your point in the world of surrogates,  
2 how difficult it is really to order and sort things  
3 through. It's the reason that I find the ALLHAT trial  
4 so remarkably important.

5 Here we have a major study that involved  
6 randomization of 24,000 people followed at this point  
7 in time of our analysis 3.3 years and eventually six  
8 years as it presents its final data where we are  
9 looking at hard clinical endpoints.

10 We are looking at fatal CHD and nonfatal  
11 MIs. We have 1,000 events. We have 600 strokes. We  
12 have nearly 1,000 heart failures. I know that there  
13 is some ambiguity in some of these, but to my way of  
14 thinking, I'm not persuaded that we cannot view  
15 hospitalization with heart failure as a very relevant  
16 point, and I am persuaded by the strength of evidence  
17 here.

18 I believe it's real, and I believe that's  
19 what, in essence, the team was telling us as well, is  
20 they had to make an ethical judgment as to whether it  
21 was acceptable to continue this regimen in this study.

22 We have two facts on important clinical  
23 endpoints. Heart failure is much more frequent on  
24 alpha blockers, point one. Point two, evidence on  
25 1,000 events suggests similar outcomes on fatal CHD

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealgross.com](http://www.nealgross.com)

1 and nonfatal MIs with enough evidence to rule out  
2 that, if this study had gone all the way to its bitter  
3 end, there would have been much chance at all that  
4 that would have been altered meaningfully.

5 To my way of thinking, this is an  
6 incredibly important insight that should guide our  
7 thinking, and I don't see all of these being equal.  
8 Specifically, I don't see the diuretic's profile to be  
9 the same as the alpha blocker's profile.

10 DR. LIPICKY: Well, it's doxazosin  
11 profile, because you already said you can't generalize  
12 to alpha blockers. Okay? But I do think -- I don't  
13 disagree with a word you said, Tom, with the exception  
14 being that I don't know how to incorporate that  
15 information into the context of what we know about  
16 doxazosin and how you are supposed to use it.

17 ACTING CHAIRMAN BORER: We're about to  
18 tell you.

19 DR. LIPICKY: All I know is that you  
20 shouldn't use it as ALLHAT did. That's all I know.

21 ACTING CHAIRMAN BORER: Steve?

22 DR. NISSEN: There's another problem here,  
23 and it's one that really has bothered me all along  
24 with this whole discussion. That is that we're  
25 looking at these agents as if they are used alone, and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 the number of patients that I see that are on  
2 monotherapy or hypertension is pretty small.

3 So now we have the complex issues of what  
4 happens to patients -- I mean, many patients are going  
5 to be on doxazosin, you know, in clinical practice and  
6 a diuretic or on doxazosin and an ACE inhibitor.

7 So there are so many combinations and  
8 permutations, and the fact is we rarely treat patients  
9 with hypertension with monotherapy, and I don't know  
10 how to factor any of that into our thinking about what  
11 to recommend here.

12 DR. HIRSCH: But, Steve, don't you  
13 basically have the data here? This is the practice  
14 group sort of like you're asking for, and we're going  
15 to be more and more looking at data like this. So at  
16 the end of the day you have to look at the global data  
17 to have the answer.

18 ACTING CHAIRMAN BORER: Okay. that's what  
19 we're going to try and do now. I mean, I think the  
20 general consensus here is that, with a greater or  
21 lesser degree of assurance, depending upon where at  
22 the table you sit, everybody believes that, as Tom  
23 said, heart failure is more frequent among the  
24 patients who took doxazosin than the patients who  
25 didn't take doxazosin in this trial.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1           There are a lot of confounds, etcetera,  
2           etcetera, but that seems to be reasonably well  
3           established. Now it's the interpretation of it on  
4           which we differ or on which we can't draw a  
5           conclusion, and we are being asked at the end of the  
6           day to provide a suggestion for action by the FDA,  
7           which is really the ultimate goal of this exercise.

8           So what action is now indicated for  
9           doxazosin? We'll do this, rather than by free  
10          comment, just by a vote and, if you have a cogent  
11          comment to make about why, make it. But let's try and  
12          keep it short, because we are going to have to discuss  
13          --f we find something that needs to be done, we're  
14          going to have to be pretty precise about our  
15          recommendations.

16          Withdraw marketing approval? Yes or no.  
17          Start down with Tom -- I'm sorry, with Marvin.

18                 DR. KONSTAM: No.

19                 ACTING CHAIRMAN BORER: Mike?

20                 DR. ARTMAN: No.

21                 DR. PINA: No.

22                 DR. GRABOYS: No.

23                 DR. FLEMING: No.

24                 DR. LINDENFELD: No.

25                 DR. NISSEN: No.

1 DR. FENICHEL: No.

2 DR. D'AGOSTINO: No.

3 ACTING CHAIRMAN BORER: Okay. Nobody is  
4 suggesting withdrawing marketing approval.

5 Change the label to remove the indication  
6 for essential hypertension? Let's start with Ralph.

7 DR. D'AGOSTINO: No.

8 DR. FENICHEL: No.

9 DR. NISSEN; No.

10 DR. LINDENFELD: No.

11 DR. FLEMING: No.

12 DR. GRABOYS: No.

13 DR. HIRSCH: No.

14 DR. PINA: No.

15 DR. ARTMAN: No.

16 DR. KONSTAM: No.

17 ACTING CHAIRMAN BORER: So it's unanimous  
18 that nobody wants to remove the indication for  
19 essential hypertension.

20 Indicate for second line use in  
21 hypertension? This is the issue we've just been going  
22 over. If you just want to vote, that's fine. If you  
23 have a succinct and cogent comment, make it. Marvin?

24 DR. KONSTAM: Well, I'll just comment. I  
25 would say no at the present time. You know, I do

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 think that more data needs to come in from this trial.  
2 I think, in particular, I think that we need to  
3 understand the relationship between the events and the  
4 blood pressure effect before we could do anything, and  
5 it is possible after that's clarified that there might  
6 be other changes that make sense. But without even  
7 understanding that, anyway I would vote no at this  
8 point.

9 DR. FENICHEL: Jeff.

10 ACTING CHAIRMAN BORER: Yes, Bob Fenichel.

11 DR. FENICHEL: Yes. Actually, one could  
12 believe the worst of doxazosin now. Suppose we had  
13 all the data, and everything was as it appears to be,  
14 and we all agree that it is worse than chlorthalidone.

15 It would not then be appropriate to offer  
16 second line status. Second line status is given to  
17 drugs which are shown to be effective when other  
18 things are not, which might not be true of doxazosin.  
19 It might be that by the time people have flunked other  
20 therapy, they are going to flunk doxazosin, too. I  
21 don't know that, but I think that's a separate  
22 question.

23 DR. TEMPLE: Jeffrey, the term has an odd  
24 use in this case. What Bob says is what second line  
25 usually means, don't use unless you failed on

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 something else.

2 In this case, it's the distinction between  
3 initial therapy and add-on therapy, and what I think  
4 people might be talking about is whether this should  
5 be the first drug you use, which has one implication,  
6 or whether you would reserve it for adding on to gain  
7 control when the other therapies you tried hadn't  
8 worked yet.

9 DR. FENICHEL: But isn't that the same  
10 thing, Bob? Do we know that it works as add-on?

11 DR. TEMPLE: Sure, we do. We have data  
12 that shows these drugs work when you add them to a  
13 diuretic.

14 ACTING CHAIRMAN BORER: Well, that they  
15 lower blood pressure.

16 DR. TEMPLE: And in that case, presumably  
17 the diuretic takes care of the heart failure, since as  
18 based on a previous vote, nobody thinks this causes  
19 heart failure. They think it just fails to treat it.

20 ACTING CHAIRMAN BORER: Okay. Marvin,  
21 would you change your vote at all, given those  
22 comments?

23 DR. KONSTAM: You know, not at this point.

24 ACTING CHAIRMAN BORER: Okay. Mike?

25 DR. ARTMAN: I don't think we have enough

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 information and, if the drug were used as labeled for  
2 hypertension, it may be just fine. So I would say no.

3 ACTING CHAIRMAN BORER: Ileana?

4 DR. PINA: I think that's going to be up  
5 to JNC-7, whenever it happens, to define the first  
6 line and the second line. So I don't think we should  
7 do anything about it.

8 DR. HIRSCH: Agreed. I think that's not  
9 our role. That's the JNC role. No.

10 DR. GRABOYS: No.

11 ACTING CHAIRMAN BORER: Tom?

12 DR. FLEMING: Well, I'm struggling with  
13 this, because in essence the data, as I -- Well, two  
14 points. First, ultimately this issue needs to be  
15 reassessed when we have access to full data from  
16 ALLHAT.

17 I'm uncomfortable with the results at this  
18 point being viewed as doxazosin is an equally  
19 appropriate first line choice with diuretics, and I  
20 don't know how specifically to convey that that isn't  
21 an appropriate perspective. I don't know what our  
22 options are here in order to convey the sense that the  
23 overall evidence that we have here -- I'm in spirit  
24 very much in understanding what the data monitoring  
25 committee and what the Steering Committee judged and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 what they decided when I look at the totality of this  
2 evidence.

3 So how does one convey from these data  
4 that there is evidence to suggest benefit to risk  
5 profiles favor diuretics?

6 DR. KONSTAM: Well, can I just say  
7 something. You know, we're going to get to the last  
8 item here where there is going to be an opportunity to  
9 try to come to some clarity, and that might be a lot  
10 more effective than just saying second line therapy.

11 DR. FLEMING: All right. That being the  
12 case, then I'll abstain.

13 ACTING CHAIRMAN BORER: Joann?

14 DR. LINDENFELD: I would say not. Not  
15 yet, I wouldn't. I think there might be a more  
16 effective way to do this.

17 ACTING CHAIRMAN BORER: Steve?

18 DR. NISSEN: Not yet.

19 ACTING CHAIRMAN BORER: Bob?

20 DR. FENICHEL: No.

21 DR. D'AGOSTINO: No.

22 ACTING CHAIRMAN BORER: And I'll add a no  
23 also.

24 Add a black box warning? I would say that  
25 if you want to answer that one yes, tell what the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 black box warning is. Ralph?

2 DR. FLEMING: I don't know. For me, it  
3 would be helpful. Could we give a good regulatory  
4 review of the factors that really draw the line in  
5 your mind between whether we give a black box warning  
6 or not, and whether we give a bolded warning or not?

7 DR. TEMPLE: Well, there's a lot of  
8 judgment in it, and I think -- I'm sure you should  
9 hear what Ray says, too. There are no fixed rules  
10 yet. We don't even have clear internal guidance yet.  
11 However, the black box usually refers to something  
12 terrible that's going to happen and that you're quite  
13 sure of, and you use dark print if you're a little  
14 less sure and it's a little less terrible.

15 What you're talking about here is a  
16 somewhat unusual case, which is you don't think the  
17 drug actually does anything. You think it fails -- At  
18 most, you think it fails to provide a benefit that  
19 some other class does.

20 Those things have appeared in dark print  
21 sentences added to the indication section or to  
22 warnings in a variety of other places. But I think  
23 the bottom line is you have complete discretion.  
24 Remember that a box is louder. It prevents certain  
25 kind of advertising such as reminder advertising. it

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 has to be featured prominently in all promotion, as do  
2 all of these things, but it makes a bigger splash.

3 I think you have a lot of discretion, as  
4 we think we do.

5 DR. FLEMING: So the description you just  
6 gave, Bob, of the dark print for an intervention that  
7 maybe doesn't do something important that another  
8 intervention does -- that would correspond to the  
9 bolded warning. Is that what that is?

10 DR. TEMPLE: That would be the more usual  
11 thing you would do, if that's what you wanted to do.

12 DR. LIPICKY: And I would add that in  
13 thinking about that it should be done, you need to say  
14 something about what that should say to people with  
15 BPH, because it doesn't seem right to say, geez, you  
16 people with hypertension ought to worry, but you guys  
17 with BPH are perfectly okay, or do we know that?

18 DR. PINA: One more point. Is the bolded  
19 warning -- Does the bolded warning have to appear on  
20 advertisement?

21 DR. TEMPLE: We would generally say that,  
22 if an advertisement didn't have a bolded warning, it  
23 would be misleading. So it does. It's not as  
24 obvious, because the box sort of stands out.

25 DR. PINA: So both of them have to appear

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 in some form?

2 DR. TEMPLE: Yes. We would say that. B

3 FLEMING: And then the last option was describing the  
4 clinical findings, which is a less significant step.  
5 Is that correct?

6 DR. LIPICKY: That's correct. It would  
7 just go into the clinical pharmacology section, but  
8 then if you chose that option, I would ask you to say  
9 -- You know, it's easy enough to write down the  
10 demographics and who was randomized and what the  
11 results are. But you have about two sentences to say  
12 what they mean, and it's going to be hard for me to  
13 see how to write that when we have spent the day  
14 trying to figure it out.

15 DR. FLEMING: One of the issues that was  
16 apparent in the presentation to us in the citizens'  
17 petition was some research that they had done that  
18 suggested that a large number of clinicians were  
19 unaware of ALLHAT, and we were challenged to consider  
20 whether at a minimum we should take steps to ensure  
21 that people are informed.

22 Now that could be accomplished by either  
23 the bolded warning or describing the clinical  
24 findings?

25 DR. LIPICKY: No. No, that could only be

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701