

1 accomplished by doing the talk papers, by doing "Dear
2 Doctor" letters, by getting press releases, and by
3 having a Med Alert kind of thing; because if you just
4 put a black box on the label, it will go into the PDR
5 edition after next, and no one will ever know it.

6 DR. TEMPLE: No. It goes into promotion,
7 too. But the petitioners made a fairly strong case
8 for arguing that, if you don't do something more than
9 change the labeling, oftentimes people don't know
10 about it. That's why they suggested it, and Sid
11 suggested a Med Guide.

12 DR. LIPICKY: Well, but I think there are
13 a couple of distinctions to make here from the vantage
14 point of what we're being asked to do, and I guess we
15 should have paid more attention to it in the
16 questions.

17 There's a certain amount of professional
18 information that is needed, presumably. Presumably,
19 that is up to FDA to supply, because medical schools
20 don't, and the societies don't, and journals don't and
21 stuff like that. So only FDA can educate physicians
22 through labeling. But I'll drop that.

23 So there is the element of educating
24 physicians. That's what Pfizer's poll was about.
25 Okay? The other component of what we have been asked

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1 to do by the citizens' petition is to get to the
2 patients, each individual patient, because this is
3 obviously an emergency to the patient who is receiving
4 doxazosin, and that patient must absolutely know and
5 make a decision as to whether or not their lives are
6 at risk because they are on doxazosin, and they should
7 go see their doctor and get off it.

8 DR. FLEMING; So the suggested FDA
9 approved mandatory Med Guide which we were hearing
10 this morning as a suggestion actually is not on your
11 list here.

12 DR. LIPICKY: That's correct. It's an
13 inadvertent omission.

14 DR. FLEMING: And if you were to insert it
15 based on a level of concern that would generate the
16 need for such information, where does it get inserted
17 in terms of severity relative to these other five?

18 DR. LIPICKY: Well, it would be other
19 actions, I guess, and then what you're asking someone
20 to do is to put into plain English for people who
21 don't know what congestive heart failure is what it is
22 that we haven't been able to figure out here today.

23 DR. TEMPLE: Tom, there are three reasons
24 for having the Med Guide that are listed in our
25 regulation. One is to warn people about something

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1 that they can prevent. That's why you engage the
2 patient in this.

3 The other is to let them know that there's
4 some terrible risk that they want to think about
5 before they go on this. The third -- never used so
6 far -- is that there's important information to them
7 about how to use the drug. This might be conceivably
8 one of those. That is, maybe you should be on
9 something else first. So it --

10 DR. LIPICKY: But I don't think that's the
11 message. I think the message is, if you are not on 16
12 milligrams, go see another doctor.

13 DR. TEMPLE: Well, there are possibly
14 multiple messages, but in any event, they are all in
15 that third category of how do use either this therapy
16 or how to use general therapy. Those are the
17 conditions for a Med Guide, particularly.

18 I just want to say one other thing. Don't
19 think of any of these categories as limiting. For
20 example, you could describe the study, but it sort of
21 screams for you to say something about what it means.
22 So maybe that goes in the indication section.

23 You can think broadly. There's a lot of
24 possibilities, if you think they are worth it and
25 right.

1 ACTING CHAIRMAN BORER: Tom?

2 DR. GRABOYS: You know, at the end of the
3 day and a lot of discussion, you have to take a step
4 back and ask the question, am I going to prescribe
5 this drug for my patients, number one? Number two, if
6 I have patients on the drug, am I going to withdraw
7 the drug?

8 There's enough ambiguity, enough concern
9 for me personally to indicate that I won't prescribe
10 the drug at this point, and I will pull patients off
11 of that drug, because we don't know. There's a lot of
12 "we don't know."

13 ACTING CHAIRMAN BORER: I want to ask you
14 to add a little bit to that comment, Tom. What have
15 we heard that says that, if somebody is on a medical
16 regiment, whatever that medical regiment is -- you
17 know, I won't pick one yet -- and part of it is
18 doxazosin, that that person is going to be harmed by
19 it?

20 We concluded that there was no evidence
21 that the drug caused harm.

22 DR. GRABOYS: We concluded with a lot of
23 angst, with a lot of discussion about the data, is it
24 hard, is it soft.

25 DR. FLEMING: Basically, is the only thing

1 that we have to be sure we inform patients about is if
2 something is harmful? When you have -- Whether this
3 applies or not, let me just state a general
4 circumstance.

5 When you have highly effective standard
6 therapy and now you come along with an experimental
7 therapy that maybe is the same in certain parameters
8 and clearly worse in others but not worse than
9 placebo, does that mean patients aren't needing to be
10 fully informed? Does that mean that it's not
11 perfectly clear that the standard in this case would
12 be preferred?

13 DR. HIRSCH; Just to amplify that, that's
14 exactly right. It's not about harm. I have no worry
15 that this drug is causing harm, but I know where he's
16 coming from. Tom is saying that the patient has a
17 right, as the petitioner said, to additional
18 information.

19 ACTING CHAIRMAN BORER: Okay. I think we
20 have several separate issues here, and I think we are
21 going to have dissect them out and deal with them
22 separately.

23 It may be that it's important to inform
24 patients better than we do, not only with regard to
25 doxazosin but with regard to everything in the

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1 pharmacopeia. That may be a very important note.

2 DR. KONSTAM: I'd just say there is
3 information that will be -- that should be available
4 that will have enormous impact on any way we want to
5 answer this question. You know, that is the blood
6 pressure related effects of the endpoints and the
7 doses that were actually used.

8 How do we know what it is we are talking
9 about and whether this is worthy of some kind of
10 letter without knowing what that letter is going to
11 say, and how do we know what that letter is going to
12 say if we don't even know whether we are talking about
13 the fact that patients' blood pressure should be
14 better treated or this drug isn't as effective even in
15 equivalent blood pressure doses?

16 How do we even approach the answer to this
17 question?

18 DR. PINA: Well, I disagree with you. I
19 think that we do have enough information that you can
20 say something, whether it gets modified later on
21 whenever this particular manuscript that you've said
22 is somewhere in press and has more information. But
23 I think we have enough --

24 DR. LIPICKY: What can you say?

25 DR. PINA: -- to say something.

1 DR. LIPICKY: What?

2 DR. PINA: I wrote something down, but I'm
3 waiting for you to --

4 DR. LIPICKY: Go ahead.

5 ACTING CHAIRMAN BORER: Okay, go ahead,
6 please.

7 DR. PINA: Here's what I wrote: In a
8 blood pressure trial of 24,335 patients with
9 hypertension and at least one other cardiovascular
10 risk factor, doxazosin was associated with a
11 significant increased risk of heart failure compared
12 to chlorthalidone. The doxazosin arm of the trial was
13 terminated early. The dose of doxazosin was --

14 DR. LIPICKY: Yes, and what are patients
15 supposed to do with that? Now this is true confession
16 time, and you feel good. What are patients supposed
17 to do with that? And you said that --

18 ACTING CHAIRMAN BORER: The implication,
19 I think, of Ray's comment, if I can interpret because
20 he's asked you a question, is where is the information
21 there about the dose that was used? Where is the
22 information about the regimen? Where is the
23 information about the specifics?

24 As Marvin says we don't have a lot of
25 that. But that's something to think about. I'm not

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1 saying it's wrong.

2 DR. KONSTAM: You have to resolve -- I
3 don't think you can get away from resolving the basic
4 core issue. That is, if you think there's something
5 wrong here, then is it that their blood pressure was
6 not adequately affected or is it that at equivalent
7 blood pressure effects, there still were adverse
8 effects?

9 Without knowing that answer, what are you
10 going to say? What's the message?

11 ACTING CHAIRMAN BORER: Steve?

12 DR. NISSEN: Okay. Do we really want to
13 put a black box warning, a bolded warning or describe
14 clinical trial findings for a trial that's incomplete
15 where we don't even have the data that's known? We
16 don't even know what the doses were that were used in
17 these two drugs.

18 I mean, to me, it really is a terrible
19 reach. Now I'm prepared to make such a conclusion,
20 but not until we have an adequate amount of data on
21 which to base such a decision.

22 I think that I'm not rejecting the
23 possibility, but I'm saying there's just too much that
24 we don't know here, and I still to this day don't even
25 know what the mean dose of doxazosin that was

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1 administered to these patients were. So how can you
2 write something about the clinical trial when you
3 don't even know what the mean dose was? It makes no
4 sense to me.

5 ACTING CHAIRMAN BORER: Bob Fenichel?

6 DR. FENICHEL: Yes. Can we have a black
7 box that uses some of that neutroceutical language
8 that says these results have not been reviewed by FDA?

9 ACTING CHAIRMAN BORER: Okay. Rather than
10 focusing on what we would say yet, let's first conclude
11 that we want to say something, and perhaps now that
12 there's been a clarification of the options for saying
13 things, which, if any, of them we want to suggest to
14 the FDA that it mandate or use.

15 We were on black box warning. Let me just
16 ask, is there anyone here -- Just raise your hands.
17 Is there anyone who votes for a black box warning?
18 No. A bolded warning? We have one "hard to know" and
19 any yeses?

20 DR. TEMPLE: Can we include the idea of
21 a bolded something? I mean, not everything you say is
22 a warning.

23 ACTING CHAIRMAN BORER: Okay. Bolded
24 anything. Okay, let's go down from the end. Marvin,
25 do you want anything in bold put into the label? Just

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1 yes or no.

2 DR. KONSTAM: Well, I'm not sure yet. I'd
3 rather deal with the last part of this and see if
4 there is consensus reached, and then say, okay, is
5 that worth bolding.

6 ACTING CHAIRMAN BORER: Okay. We can.
7 You mean describe clinical trial findings?

8 DR. KONSTAM: Right.

9 ACTING CHAIRMAN BORER: Okay. Let's hear
10 about that. Why don't you start commenting, Marvin?

11 DR. KONSTAM: Well, you know, I do think
12 that there is something going on here, and I think that
13 we've heard loud and clear that there is an impetus
14 that this ought to be communicated -- that the results
15 of the trial ought to be communicated. I do believe
16 the results of the trial ought to be communicated.

17 I think that, you know, just with regard
18 to the heart failure endpoint, I proposed some
19 language a little bit earlier which I think reflects
20 what the trial showed, which is at the doses used,
21 compared to chlorthalidone, there was -- doxazosin
22 appeared less effective at preventing the clinical
23 manifestations of heart failure, although this did not
24 show evidence of irreparable harm.

25 Something to that effect at this point, I

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1 would be comfortable with and, I think, ought to be
2 communicated.

3 I think that beyond that, again, I think
4 that we really need to know -- and I want to say it in
5 a positive way, not just say, well, we shouldn't do
6 anything until we know more. I think that we should
7 know more with all due haste, and we should find out,
8 and the FDA should find out more about the blood
9 pressure relationship with the events, what doses were
10 patients on, in order to fine tune this message and
11 see if there is something more definitive that can be
12 said.

13 I think those sorts of pieces of
14 information, I think, ought to be in the label.

15 ACTING CHAIRMAN BORER: Marvin, can I just
16 ask you. I mean, I think that's a well crafted
17 statement, but I wonder if it's missing one piece of
18 information that you might want to add, which is that
19 there was a difference in the level of blood pressure
20 lowering with the two regimens.

21 DR. KONSTAM: Right.

22 ACTING CHAIRMAN BORER: Because there's a
23 message to people as patients.

24 DR. KONSTAM: That's right. So then to
25 say that -- Well, what you are saying is then these

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1 differences may have been, at least in part, a
2 reflection of clearcut differences in the degree and
3 rapidity with which blood pressure lowering was
4 achieved -- pressure control was achieved.

5 DR. LIPICKY: For me to get a feel of what
6 you mean, in addition to what you said and what Jeff
7 said, I added a sentence that said "Do not use
8 doxazosin like it was used in ALLHAT. Follow the
9 instructions for use."

10 Would that be objectionable to you, and
11 had that in bold and the rest of it in lower case?
12 What are we trying to communicate is what I'm asking.

13 DR. TEMPLE: Well, it's worth noticing --
14 what to do about is not so clear -- that our
15 impression of the average dose that's used is that
16 it's not 16 milligrams. It's some lower dose. Now to
17 the extent that is true -- and I'm sure that's
18 discoverable -- when it's used as initial therapy,
19 there people are in fact using it just this way, and
20 as Ray suggested, maybe that's not such a good thing.

21 DR. LIPICKY; But I don't see that that's
22 relevant.

23 DR. TEMPLE: You do think or don't think?

24 DR. LIPICKY: I don't. How it is used, I
25 don't know. I don't know how you know.

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1 DR. TEMPLE: No. I'm just saying that's
2 discoverable, because someone has done the --

3 DR. LIPICKY: But we don't know. So we
4 shouldn't be deciding what to write when we don't know
5 what to write.

6 DR. TEMPLE: Well, you can find out
7 certain things. You can find out the dose that was
8 used, for example.

9 DR. LIPICKY: We can find out whether
10 doxazosin is really bad. We can get the whole results
11 of the trial. We can look at all four arms. We can
12 see if amlodipine suffered the same problems. We can
13 get all kinds of -- There's no question that a lot of
14 the indecision that exists here, we can resolve. We
15 just can't resolve it today.

16 DR. TEMPLE: Ray, this is a different
17 question. It is knowable in very short order what the
18 average dose of this drug is, and you can find it out
19 for any of its indications. That is discoverable.

20 DR. LIPICKY; I agree 100 percent, but it
21 depends on whether you think you have an emergency
22 here.

23 DR. TEMPLE: No, that's got nothing to do
24 with further analysis of the trial.

25 DR. LIPICKY: Well, it does to how rapidly

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1 you can come up with the data.

2 DR. TEMPLE: That's not hard data to get,
3 and I'm sure Pfizer knows it already.

4 DR. LIPICKY: Well, but that's not
5 relevant if it doesn't matter.

6 ACTING CHAIRMAN BORER: Is it reasonable
7 for us to suggest that the FDA should consider adding
8 to the label some kind of description? I'm going to
9 suggest one in a minute -- suggest that you consider,
10 and that that decision be modifiable with the
11 acquisition of new data in short order about dose and
12 other things that may come out of the study that we
13 heard is almost ready for submission for publication.

14 Let me just put this forward and see if it
15 flies and, if it doesn't, it doesn't.

16 When used as initial therapy at doses
17 lower than those for which it is labeled -- maximally
18 labeled or something -- in patients with -- describe
19 the descriptors, the population -- for whom blood
20 pressure often was not reduced to the target range,
21 there was more congestive heart failure among patients
22 treated with doxazosin than among patients treated
23 with chlorthalidone.

24 That's not directive, but I think it's an
25 accurate description of what we know.

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1 DR. KONSTAM: I would say the greater
2 clinical manifestations of heart failure.

3 ACTING CHAIRMAN BORER: Okay. More
4 clinical manifestations.

5 DR. NISSEN: Jeffrey, I wrote some
6 alternative language for you to consider.

7 ACTING CHAIRMAN BORER: Okay.

8 DR. NISSEN: In an incomplete clinical
9 trial of antihypertensive therapy, an uncertain dose
10 of doxazosin was associated with a higher incidence of
11 investigator reported congestive heart failure
12 compared to an uncertain dose of chlorthalidone.

13 ACTING CHAIRMAN BORER: Let me ask. I'll
14 champion that.

15 DR. LIPICKY: That is informative, and
16 these findings were not reviewed by FDA, and we do not
17 know what they mean, but we think we must communicate
18 them.

19 DR. KONSTAM: And then put it in bold.

20 DR. TEMPLE: I suggest that this is
21 getting inappropriate and should stop.

22 ACTING CHAIRMAN BORER: Let's just get a
23 sense from the committee, just by a yes or no vote.
24 Do we agree -- Do we believe that some information
25 needs to be communicated by the FDA, either in

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1. labeling or in some medication guide for patients or
2. in both or some combination thereof? Just a yes or
3. no. Ralph?

4. DR. D'AGOSTINO: You said just a yes or
5. no, but you are including other means beyond the
6. label?

7. ACTING CHAIRMAN BORER: Yes. I'm
8. including other means beyond the label, but that the
9. FDA must mandate it.

10. DR. D'AGOSTINO: Yes.

11. ACTING CHAIRMAN BORER: Bob?

12. DR. FENICHEL: No.

13. DR. NISSEN: I want to wait for more data.

14. ACTING CHAIRMAN BORER: Okay. So that's
15. a no.

16. DR. LINDENFELD: Yes. I think something
17. should be communicated.

18. ACTING CHAIRMAN BORER: Tom?

19. DR. FLEMING: Yes, definitely.

20. ACTING CHAIRMAN BORER: Tom Graboys.

21. DR. GRABOYS: Yes.

22. ACTING CHAIRMAN BORER: Alan?

23. DR. HIRSCH: Yes, to be revisited again
24. when we have more data.

25. DR. PINA: Yes, not only to patients but

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1 also to physicians.

2 ACTING CHAIRMAN BORER: I'm sorry.

3 DR. ARTMAN: Yes.

4 ACTING CHAIRMAN BORER: Yes. Mike?

5 DR. KONSTAM: I'm sorry. Are we talking
6 including a change in labeling or are we saying --

7 ACTING CHAIRMAN BORER: Anything. We are
8 saying do we want the FDA to cause communication of
9 something?

10 DR. KONSTAM: Something which could simply
11 include a change in labeling and nothing more?

12 ACTING CHAIRMAN BORER: It could.

13 DR. KONSTAM: Well, I'd say the answer is
14 yes, and I think something should be done, and I think
15 that that message needs to be refined based on
16 additional data that needs to be gathered.

17 ACTING CHAIRMAN BORER: Okay. so the
18 sense of the committee is that something needs to be
19 or should be communicated in some form. That might
20 include some addition to the label, might include
21 something beyond that, might not include something in
22 the label. Bob?

23 DR. TEMPLE: The two pieces of data that
24 have come up a few times -- One is finding out what
25 the actual doses were. I'm sure we can actually get

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1 that from them. But Marv has referred to something
2 else, and I wonder whether we are going to have that,
3 which is some attempt to relate the outcome in terms
4 of frequency of heart failure to the degree of
5 control. That, obviously, is not a randomized
6 observation, but it doesn't mean it's entirely silly
7 either.

8 Is that something that you guys can
9 actually do? And strokes, too, I guess.

10 DR. CUTLER: We have largely done it, not
11 entirely to my satisfaction at this point, but --

12 DR. TEMPLE: Okay. So we will be getting
13 that not too far from now?

14 DR. LIPICKY: You'll be getting it as a
15 publication.

16 ACTING CHAIRMAN BORER: Well, okay, but--

17 DR. LIPICKY: We're back to the same
18 place.

19 ACTING CHAIRMAN BORER: All right. That
20 leads us to two ancillary questions. The sense of the
21 committee is that something needs to be communicated.
22 Let me break it down further.

23 Should the something be communicated at
24 least in part in the label? Marvin?

25 DR. KONSTAM: Yes, in the label.

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1 ACTING CHAIRMAN BORER: Mike?

2 DR. ARTMAN: Yes, I would agree with that.

3 DR. PINA: Yes.

4 ACTING CHAIRMAN BORER: Alan?

5 DR. HIRSCH: Yes.

6 ACTING CHAIRMAN BORER: Tom?

7 DR. GRABOYS: Yes.

8 ACTING CHAIRMAN BORER: Tom?

9 DR. FLEMING: Yes.

10 DR. LINDENFELD: Yes.

11 DR. NISSEN: No.

12 DR. FENICHEL: No.

13 DR. D'AGOSTINO: No.

14 ACTING CHAIRMAN BORER: Okay. So we have
15 a split vote here, but there is a sense of the
16 Committee. The majority think that something should
17 be put in the label.

18 Now should the something be put in now or
19 should we wait until we have some of the additional
20 data that we've been talking about, specifically the
21 average dose or, on top of the average dose, the
22 result of the analysis that Dr. Cutler is now
23 reviewing and may be done sometime in the next few
24 months? Ralph?

25 DR. D'AGOSTINO: I voted that I don't

1 think anything should be put in the label, and you're
2 asking me now -- Should I?

3 ACTING CHAIRMAN BORER: Oh, I'm sorry.
4 That's right. No, you're right. You voted no. Bob
5 voted no. Steve voted no. Joann?

6 DR. LINDENFELD: I think something could
7 be added now. It would just be average doses. I
8 don't know that we need the whole additional analysis.

9 ACTING CHAIRMAN BORER: Okay. So we have
10 to have at least --

11 DR. LINDENFELD: Once we have the average
12 doses --

13 DR. LIPICKY: So just average doses or --

14 DR. LINDENFELD: I think so. I don't
15 think we need --

16 DR. LIPICKY: -- range of doses or what
17 more information do we need before --

18 DR. LINDENFELD: Well, we know the range.
19 Right? Because we know -- So we know the range.

20 DR. LIPICKY: No, we don't. The
21 distribution of doses actually used.

22 DR. LINDENFELD: We know the range,
23 because it was fixed.

24 DR. LIPICKY: From zero to eight. Yes,
25 right.

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1. DR. LINDENFELD: Right.

2 DR. LIPICKY; But we don't know the
3 distribution.

4 DR. CUTLER: The distribution is in the
5 paper.

6 ACTING CHAIRMAN BORER: So that vote is
7 that nothing should be put in the label until we have
8 some additional information, but then something should
9 be put in.

10 DR. LIPICKY: But I want to be sure. Now
11 means now. If you mean get more data, then what --

12 ACTING CHAIRMAN BORER: That's what I
13 understand this vote to be that Joann --

14 DR. LIPICKY: She said now means after we
15 get something, and mentioned one.

16 DR. LINDENFELD: Once we know the mean
17 doses of the --

18 DR. LIPICKY: Well, we can calculate that,
19 if the distributions are in the paper.

20 DR. LINDENFELD: Okay. I think that's
21 enough.

22 DR. FLEMING: We interrupted Marv. He was
23 in the process of constructing a recommended
24 statement, and in general I would like to pursue more
25 what he -- where he was leading us with his suggested

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1 statement. My sense of the matter is, when I have a
2 clearer sense of what that is, it will be easier to
3 answer whether or not there are elements that we need
4 to know more information about.

5 I am assuming that, if there are more
6 specific elements that this Committee would like to
7 have before this study reaches its planned termination
8 point in March of 2002 -- and I assume there will be
9 some lag after that before everything is released,
10 which by the way, isn't that far away. But if there
11 was more immediate need, I would assume we could
12 request specific information from the protocol team
13 that would not put in jeopardy the continued blinding
14 of the comparative arms that continue in the trial.

15 So my sense is I would prefer to see
16 something in as soon as possible. I would like to go
17 further and hear more exactly where Marv was headed
18 with that statement and, if there are elements that we
19 would need that aren't already apparent to us, I would
20 suggest we might be able to communicate with the
21 ALLHAT team, and the FDA may be able to get that
22 information.

23 DR. D'AGOSTINO: Can I make a comment? I
24 guess I thought one of the outcomes of this meeting
25 would be to go back to the ALLHAT team and say, you

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1 know, you don't seem to have great reliability on the
2 CHF, why don't you do something to see how you can
3 improve on that retrospectively, realizing it's
4 retrospectively. But there are lots of questions
5 raised by our deliberations, can you do something with
6 them?

7 I feel very uncomfortable suggesting a
8 label change when we have so many uncertainties that
9 have been raised today. Maybe I'm missing something.

10 ACTING CHAIRMAN BORER: Steve?

11 DR. NISSEN: Yes. I guess I need to
12 understand from Ray how much precedent there is for
13 altering a label based upon data that the FDA has not
14 reviewed. Do we commonly do this, and how important -
15 - I mean, I just need to get a sense for this from a
16 historical point of view. Is this unprecedented or
17 has it been done before?

18 DR. LIPICKY: I think Bob Temple will have
19 a better recollection than I. There is once, and that
20 was with CAST. There, I think it was a very different
21 circumstance. I wasn't a single trial and one adverse
22 effect and that sort of stuff. It was that a whole
23 belief structure got damaged.

24 It's not clear to me that a whole belief
25 structure got damaged by ALLHAT, primarily because one

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1 doesn't know why it was less effective. I don't think
2 anyone would conclude that it was not less effective
3 or didn't have data that would make it look like it
4 was not less effective, but basically there are a lot
5 of questions that remain unanswered, and certainly one
6 doesn't have the answer even for doxazosin, let alone
7 the class of alpha blockers.

8 So it isn't the same, but there is once in
9 50 years, if that answers your question.

10 ACTING CHAIRMAN BORER: Tom, you suggested
11 that we should hear a statement and then see if
12 elements are missing. But I would ask you to
13 prospectively to determine whether from what you've
14 heard you have enough information to write anything
15 that would be useful for people to know, that would be
16 directive, that would actually inform them in a useful
17 way.

18 If the answer is yes, fine. But if it's
19 no, then we don't really need to hear that draft at
20 this point to make a decision.

21 DR. FLEMING: Well, I had thought we had
22 already come to the conclusion, not by unanimous vote
23 but by, I think, with two dissenting votes, that
24 information needed to be communicated.

25 Then when we asked if it was in the label,

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1 I think we had a majority but with three dissenting
2 votes. So my impression is, whereas it's not
3 unanimity, there was strong sense in the Committee
4 that we needed to communicate.

5 Now what we're really getting at is what
6 is the right way to do it, and what is the substance
7 of what we communicate? In general terms, what we're
8 confronting here we may actually confront in the
9 future more often than we've confronted in the past.

10 Specifically, what's given rise to this
11 circumstance is that we have a major trial that's
12 dealing with a number of important scientific
13 questions, one of which, the team viewed, was
14 conclusively established, that required release of
15 information so that the public could be aware of what
16 was evidence that no longer was within what they
17 thought was equipoise.

18 They released that information, and yet to
19 preserve the integrity of the remaining objectives of
20 the trial, the rest of the information was kept
21 confidential. This circumstance isn't unique.

22 I'm chairing a data monitoring committee
23 for a breast cancer trial that, in fact, was in a
24 similar circumstance last December, and the FDA was
25 asked to approve the agent based on progression with

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1 our proposal that we be allowed to keep survival data
2 confidential, not entirely unlike this type of
3 circumstance; and it may happen again in the future.

4 I respect the FDA and the scientific
5 community for allowing this randomized trial to
6 continue in a blinded fashion, even though we have
7 need for having a better understanding of certain
8 elements of the data.

9 To say, however, that because we're not
10 fully informed, we as an FDA aren't going to take any
11 action or ensure that people are aware of what the
12 results are seems to be inconsistent.

13 DR. LIPICKY: Well, but, Tom, I don't know
14 who people are.

15 ACTING CHAIRMAN BORER: One second, Ray.
16 Tom has gone through the process that we have, just
17 resummarized it. But what I was actually asking was,
18 okay, we all decided -- or not we all, but the
19 majority believed that something should be
20 communicated.

21 My next question was when, and the answer
22 to that is based on do we have all the elements of
23 information that we want to put into that warning to
24 make it useful. If we are leaving out elements and
25 we're just giving a sort of a general warning to

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1 people, then they are going to be generally afraid,
2 but I don't know what they are going to be afraid of,
3 and they may take inappropriate action.

4 If we are comfortable that we have all the
5 elements that we can put in to give a reasonable
6 person a reasonable warning, well, fine. If we don't,
7 then we ought to wait until we have them. Some of
8 those elements may be available right away. Some may
9 be available in a few months. Some may be available
10 later than that. I don't know.

11 So that was really the thrust of my
12 question. Ileana?

13 DR. PINA: Yes. I want to go back to that
14 same point that you just made. I think that we do
15 have enough information now to say something, based on
16 the facts. There is a published article. It's a peer
17 reviewed journal article, and we're here being asked
18 by consumers to allow physicians and patients to know,
19 because of the lack of knowledge out there of the
20 preliminary findings of this trial and of the stopping
21 of the arm.

22 I mean, that's why we're here. We're
23 being asked -- This is a consumer group asking us to
24 allow physicians to know and telling us how few
25 physicians really do know what's going on, what has

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1 gone on with the trial, and that the arm has been
2 stopped, even though I know it was in the news, and
3 how few patients know about this, and then how many
4 patients were actually on the drug.

5 I mean, this is a drug that's being used
6 extensively for BPH. I have a problem with Marvin's
7 initial writing, not that I like mine any better. But
8 you implied that chlorthalidone prevented the heart
9 failure risk rather than doxazosin caused it, and I
10 don't think we know that.

11 DR. KONSTAM: Well, we voted on that. We
12 voted on that. We asked do we think there's any
13 evidence that doxazosin caused harm, and the answer
14 was no.

15 DR. PINA: I agree.

16 DR. KONSTAM: And I thought the sentiment
17 of the panel was it probably didn't.

18 DR. PINA: I agree, but did we vote that
19 chlorthalidone prevented it, which is different?

20 DR. LIPICKY: Well, look. To put this in
21 some perspective -- and I know this is not the
22 sequence of the questions, but the next question asks:
23 If you think it's important to tell physicians and
24 patients that there's something they need to know
25 about doxazosin, don't you think on the same basis,

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1 the same data, we must put this in chlorthalidone?

2 Obviously, people should know that
3 chlorthalidone is the thing to take, and we ought to
4 issue press releases that say that. Why should we
5 wait for JNC? I mean, where are we here? What are we
6 communicating? What are we saying? What do we want
7 people to know?

8 ACTING CHAIRMAN BORER: Steve?

9 DR. NISSEN: I want to get to a core
10 point. First of all, I understand and I'm very
11 sympathetic to those on the Committee that want to do
12 something, but I think it's very important that we
13 dissociate regulatory action from the setting of
14 standards for medical practice.

15 You know, we have large organizations like
16 the American College of Cardiology and the American
17 Heart Association and all of their subcommittees that
18 establish standards, and in those standards we make
19 many statements about how we think patients ought to
20 be treated.

21 It seems to me -- and the reason I feel
22 like with incomplete data it would not make good sense
23 to act is that I believe that this area is much better
24 addressed by our colleagues who will come together and
25 make these kinds of recommendations about what the

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1 optimal treatment of hypertension is, and all these
2 issues of first line versus second line.

3 It's just too fuzzy to create regulatory
4 language. I also wanted to address the issue that Tom
5 raised, which is I agree with Tom completely that it's
6 noble to continue the trial. But it is also important
7 for us to keep in mind that, without undermining the
8 trial and its blinding, there is a lot more data we
9 could be provided with.

10 I don't like us to make a decision on the
11 basis of data that is really quite obviously
12 incomplete and that may lead us to make a mistake. I
13 think what we are talking about here fundamentally is
14 a medical standards decision, not a regulatory
15 decision, and I think we are off base to try to make
16 it a regulatory decision.

17 DR. KONSTAM: Can I respond to that?

18 ACTING CHAIRMAN BORER: Marv?

19 DR. KONSTAM: Steve, I agree with what you
20 said up to a point. Where I really disagree with you
21 is I do believe that the FDA has every right and
22 obligation to influence treatment in every way to the
23 extent that it can.

24 I think where the difference is -- and I
25 think you are hitting on it -- is that they have a

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1 different standard of evidence that they draw upon in
2 order to make those judgments than we do when we
3 generate clinical practice guidelines or JNC
4 guidelines.

5 So the FDA leaves big holes in practice
6 recommendations, because it doesn't have data that it
7 considers a high enough standard to act on, and that's
8 where guideline people take over. That's my way of
9 looking at it.

10 You know, I think that there is a study
11 that was done here. It was probably the best study of
12 its kind that's ever going to be done. There are
13 things that came out. There's a lot of difference of
14 opinion, but there's a lot of sentiment that something
15 ought to be communicated.

16 Where I agree with you is that I think
17 that the level of evidence is problematic, and that's
18 what we have all struggled with all day long. How
19 certain are we about what conclusion? That's where I
20 really hold back on saying we ought to go out and
21 communicate something for the public and send letters
22 and say this ought to be second line therapy.

23 I definitely would not do that, because I
24 don't think the level of evidence reaches that point.

25 ACTING CHAIRMAN BORER: Yes, Ralph?

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1 DR. D'AGOSTINO: But doesn't putting
2 something in the label have that spirit to it, that
3 we're saying something profound, that we have
4 established something? Label change isn't a trivial
5 matter, to me, that you go back next week and say,
6 well, we've got a little more data now, we're going to
7 straighten it out.

8 DR. LINDENFELD: It's not a trivial
9 matter, but again I just have to emphasize, this is a
10 very large, well conducted trial with lots and lots
11 and lots of endpoints, and it does appear --

12 DR. D'AGOSTINO: But there are all these
13 questions. I mean, we spent the whole day raising
14 questions, and we don't even have the data. Nobody in
15 the FDA, and myself as a statistician, consultant to
16 the panel, has sort of sat down and actually marched
17 through the data.

18 All I'm doing is reading an article, and
19 I've been on this committee in terms of consulting and
20 on other committees where I have New England Journal
21 Medical articles, JAMA articles and so forth, and we
22 end up saying quite completely different things.

23 I don't think that's going to happen here,
24 but we haven't even gone through that type of
25 activity.

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1 ACTING CHAIRMAN BORER: Ray?

2 DR. LIPICKY: Well, I guess I am less in
3 favor of communicating. I'm an isolationist. But I
4 understand the need to communicate, and certainly FDA
5 wants to communicate more, and it has these Med Alerts
6 and Med Watches and watches for this and that and the
7 other, and everything else, and it's important, and
8 there are media and electronics and communication is
9 the name of the game.

10 How can I say that one should not
11 communicate? The average patient who is receiving a
12 medicine for their blood pressure has absolutely no
13 idea what the basis of their receiving it is. So that
14 now we go and contact all of the patients that are
15 taking doxazosin and say something like the results of
16 ALLHAT?

17 I mean, I think that's misrepresentation.
18 I think it's totally garbage. I think it will be
19 totally misinterpreted, and so --

20 DR. TEMPLE: That's a straw man, Ray.
21 Nobody insisted on a Med Guide and --

22 DR. LIPICKY: That's fine. No, no, no.
23 Hold it. It may be a straw man, but now who are we
24 talking about communicating with?

25 DR. TEMPLE: Well, most people are talking

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1 about the physicians, I think.

2 DR. LIPICKY: So that's clear. That is,
3 nobody is talking about talking to patients.

4 DR. TEMPLE: No. Like everything else
5 today, it's not entirely clear.

6 DR. LIPICKY: Okay. Well, that isn't
7 clear.

8 ACTING CHAIRMAN BORER: That's a good
9 point.

10 DR. LIPICKY: Wasn't clear to me. Fine.

11 ACTING CHAIRMAN BORER: One second. Can
12 we have a statement from the Committee about that. Is
13 there anyone on the panel here who is in favor of
14 mandating the FDA to cause a communication to be sent
15 to all patients who are taking this drug? Any yeses?
16 No. So we've now eliminated that as an alternative,
17 and we are talking only about communicating something
18 to physicians --

19 DR. LIPICKY: Through labeling.

20 ACTING CHAIRMAN BORER: -- and there
21 hasn't been a consensus on what would be communicated,
22 although the majority thinks that there ought to be a
23 communication.

24 DR. LIPICKY: Right, and I would be
25 embarrassed if I had to try to write something that

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1 didn't say something, and I still don't know what to
2 say. The only thing I know to say is, if you use
3 doxazosin, use it according to directions, and I don't
4 know -- Otherwise, you're liable to encounter this.
5 I don't know what else to say.

6 DR. TEMPLE: Actually, Ray, you already
7 have said more, if you believe it, if you describe the
8 consequence of using it the wrong way.

9 DR. LIPICKY: Yes. But that's an
10 encouragement to use doxazosin and at higher doses.

11 DR. TEMPLE: No, it says --

12 DR. LIPICKY: Is that what we should do?

13 DR. TEMPLE: It says, if you are going to
14 use it, you need to use it right. Even that might be
15 an important message, not that you know --

16 DR. LIPICKY: Well, but we don't --

17 DR. TEMPLE: Wait a minute. Not that you
18 know what the results of using it right are either.

19 DR. LIPICKY: But we don't know that
20 that's right.

21 DR. TEMPLE: But what you do know is that
22 using it wrong, which is probably the way most people
23 use it, doesn't work very well.

24 DR. LIPICKY: Well, I'll grant you that.

25 DR. TEMPLE: That's not irrelevant.

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1 DR. LIPICKY: Okay, but that's a very
2 different message from this is a warning about this
3 chemical compound and its effects in man.

4 DR. TEMPLE: Ray, I don't think that
5 anybody has gotten far enough to say how loud, how
6 shrill, how scary this should be. People are
7 grappling --

8 DR. LIPICKY: Well, bold is pretty loud.

9 DR. TEMPLE: What?

10 DR. LIPICKY: Bold is pretty loud.

11 ACTING CHAIRMAN BORER: But we haven't
12 gotten to bold yet, and we haven't said what we are
13 going to say.

14 DR. TEMPLE: Right. It depends what you
15 bold. Can I just make an observation, Jeffrey, about
16 before?

17 It's relatively unusual for us to rely on
18 controlled data that we don't see. And as Ray said,
19 in the case of CAST we did it. But one shouldn't
20 exaggerate that as a precedent. That was a body
21 count.

22 Whatever you believe about the NIH and
23 their competence, I believe they can count death.
24 Okay? That's not a long stretch. Here -- and you
25 know, as you can probably figure out, I'm somewhat on

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1 the side of saying something.

2 The concern is that the observation of
3 heart failure may be not valid. That's the very sort
4 of case where you do probe and you do look. So this
5 is a somewhat longer stretch than CAST. That's in no
6 way saying it shouldn't be the stretch you make, since
7 the local diagnosis may be the best you are going to
8 do anyway. But I just want to make sure that that
9 precedent isn't overstated. A body count is easy,
10 easier than something more subtle.

11 ACTING CHAIRMAN BORER: Mike, you had a
12 comment?

13 DR. ARTMAN: Well, I think we all agreed
14 that there was some red flags raised by this study,
15 and now we're just trying to decide how high to raise
16 the flag and how to wave it around.

17 I'm not sure I have the answer either, but
18 Ray keeps asking what are we trying to say. I think
19 we're trying to say something like: In doses of 8
20 milligrams per day or less, which may be insufficient
21 for optimal control of blood pressure, doxazosin may
22 unmask or promote symptoms of heart failure in
23 patients with mild hypertension and cardiovascular
24 risk factors.

25 I mean, that's basically what came out of

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1 this, I think.

2 ACTING CHAIRMAN BORER: We didn't say
3 promote.

4 DR. ARTMAN: Well, scratch the "promote."
5 May unmask or allow symptoms of -- something like
6 that, less effective than a diuretic.

7 ACTING CHAIRMAN BORER: Alan, why don't
8 you make your comment, and then I want to make a
9 point.

10 DR. HIRSCH: I think I'm hearing sort of
11 consensus toward a two-track approach, which I'm
12 proposing to the rest of the panel members. One is
13 that we can fine tune language, because there's a
14 clear consensus that something be communicated
15 regarding relative protective benefit.

16 The second thing I'm hearing from Ray and
17 from Bob is that we would be wise to take a clear,
18 deeper look at the data, if it could be provided to
19 us, and revisit this again, and make sure that we are
20 accurate, appropriate, and don't set wrong precedents.

21 ACTING CHAIRMAN BORER: Okay. I'd like to
22 suggest a modification to what Alan says, because I
23 think there is sort of a general sense that something
24 needs to happen as a result of all this. But I'm
25 concerned, and I'm concerned that we don't know, as

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1 Ray has really said in several different ways -- we
2 don't know exactly what to say.

3 I don't think that promoting concern is
4 appropriate unless you have a specific basis for the
5 concern reasonably well defined, and then we have to
6 determine what reasonably is. I think reasonably will
7 be when we have information (a) about the dose that
8 was used and (b) about the relation of the results to
9 blood pressure achieved.

10 That make take several months to get those
11 data, and at the end of that time the resulting
12 analysis may show that it's not appropriate to
13 communicate something. But the reason I think that
14 it's appropriate to wait at this point and not send
15 out something right now is that I don't think we have
16 an emergency situation here.

17 I haven't seen any evidence that the drug
18 causes harm. I think that a lot of people will be
19 affected by premature dissemination of information
20 that's incomplete and that there is no great public
21 health problem that is going to be caused by not
22 disseminating that information until it's somewhat
23 more complete.

24 I'm not suggesting waiting until the end
25 of the ALLHAT trial. I'm suggesting that we wait

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1 until we have just those two elements of data that
2 Marvin suggested. If at that time the data, when they
3 are reviewed, are sufficiently clear so that they
4 warrant a well defined statement about what happened
5 with these doses in these patients defined in this
6 way, then that statement ought to be made, and it
7 ought to be added to the label somehow.

8 Marvin?

9 DR. KONSTAM; Jeff, I agree with
10 everything you said. With regard to Michael's
11 language, you know, I really -- and I guess this is
12 why I'm more comfortable advocating saying something
13 when there is more information, is because I would
14 fall away from drawing a conclusion.

15 Your statement is drawing a conclusion.
16 My thought is to be much more descriptive. Describe
17 the results in a way, and then based on the data as it
18 comes in, sort of build as close a circle around what
19 it means as we can based on what we know, but mostly
20 just describe the results.

21 ACTING CHAIRMAN BORER: Okay. So I think
22 that the issue that remains here is how do we properly
23 describe the results. We have some information, but
24 the information is not as complete as we like, and do
25 we have enough information to describe the results in

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1 a reasonable way without misstatements that will be
2 more harmful than helpful.

3 DR. ARTMAN: I just want to clarify one
4 thing. I was in no way, shape or form trying to draw
5 any conclusion, because I don't think we can draw
6 conclusions. I was merely trying to describe the
7 data.

8 ACTING CHAIRMAN BORER: You know, I don't
9 think we are -- Ray, if you will allow me -- Ray, are
10 you here? Ray, you asked for the advice. I want to
11 suggest something to you.

12 You've heard the discussion of the
13 Committee. You've heard that several people are not
14 in favor of making any labeling change at this time.
15 The majority, by a little bit, are in favor of doing
16 something, but among those there's some disagreement
17 about when and what, with some believing we could put
18 out some sort of general statement, or suggest to you
19 that you put out some general statement to doctors,
20 presumably in the label -- I don't know how else we do
21 it -- at this time, and some suggesting you need more
22 information before you can do that, and at that time
23 you can say something, although, of course, the new
24 information may suggest that you don't have to.

25 I don't know how much further --

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1 DR. LIPICKY: So you're asking me do we
2 have enough information from you?

3 ACTING CHAIRMAN BORER: Yes.

4 DR. LIPICKY: Yes, I think so. But the
5 question is does Dr. Temple; because I know what to
6 do. The question is does Dr. Temple know what to do
7 or will we argue with one another?

8 DR. TEMPLE: Well, we'll surely argue, but
9 that's okay. I think we've heard enough. I actually
10 don't think you can actually get closer, and having a
11 vote with another six to seven or something isn't
12 going to help much more. But let's be sure I
13 understand the areas of uncertainty.

14 I'm positive we can find out what the
15 approximate dose was, either in the form of a
16 distribution or the average, and I actually don't see
17 how that makes too much difference, because we know it
18 was well below the 16 that you can go to.

19 I gather there is an analysis closer to
20 being born -- whether we can get more details of it
21 remains to be seen -- that we'll look at whether, just
22 to put it in a simple minded way, the people who did
23 have adequate control also showed a increased rate of
24 heart failure in which case you would not really
25 attribute it to not using the drug properly, I think.

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1 In other words, you would match up groups
2 for the degree of control and see if there was still
3 a difference. That's not a hard thing to do, and if
4 I understand Jeff's facial expressions, that's what
5 they have sort of done.

6 That seems to me to be the area that
7 people are most nervous about, because it makes you
8 ask whether the entire thing is due to the blood
9 pressure. If you saw it in all levels of blood
10 pressure control, you would no longer believe that.

11 So I think there's a fair sentiment that
12 people would like us to get that information before we
13 did much.

14 ACTING CHAIRMAN BORER: I think that's
15 right, and I would add only that I heard several
16 people suggest that it would be nice if there were
17 some effort to firm up the diagnosis of CHF so we
18 could know the magnitude of the problem that exists.

19 DR. TEMPLE: Jeff, the only thing about
20 that is that is the work of a very long time.

21 DR. LIPICKY: Right. We will --

22 DR. TEMPLE: The other two things are much
23 easier.

24 DR. LIPICKY: We will argue some, because
25 what I heard some people saying in the reservations

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1 were, you know, they wanted to get a lot more
2 information than just the average dose. Give me three
3 minutes in the publication, and I'll give it to you.
4 No, Tom will give it to you, because I don't know how
5 to take distributions and get a mean.

6 There are serious things that would
7 require getting some data, and I'm a firm believer in
8 the fact that you don't know what's there until you
9 look, and that when people have taken a lot of time
10 looking, they point you in the directions that are
11 generally important, but that, as we have learned time
12 and time again, sometimes they overlook things, not
13 purposefully, that in fact give you better insights.

14 I must admit that I don't have a better of
15 way of putting it, because I can't demonstrate that we
16 have ever contributed anything by analyzing data. But
17 I would feel violated by having to make an important
18 decision in the absence of having the data and looking
19 at it and doing some kind of an analysis.

20 I just absolutely think -- I as an
21 individual think that dealing from the literature is
22 almost absurd, and I feel sorry for people who have to
23 do that.

24 DR. TEMPLE: For what it's worth, I
25 believe my credentials as someone who believes in

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1 looking at the data are adequate, and I believe I own
2 one of the two or three publications at FDA that
3 actually ever showed how the analysis makes a
4 difference with the Anturin reinfarction trials.

5 So I'm a believer in that. Those cases,
6 it should be noted, were cases in which the
7 statistical values were marginal, entirely based on a
8 subset or something like that. They are not cases
9 that are like this.

10 That said, I don't disagree. We prefer to
11 have all the data, and there's usually a good reason.

12 DR. LIPICKY: No, but, you see, I wouldn't
13 ever dream of calculating a p-value. The question is
14 what's related to what, and how are things related,
15 and how are correlations, and what goes where and, in
16 particular, how do the other arms -- how does
17 amlodipine look compared to chlorthalidone?

18 If I didn't see a trend toward more heart
19 failure reports with amlodipine, I would buy in in a
20 moment. Okay, I'd say, geez, this is real. But
21 without seeing that, I'm saying to myself maybe that's
22 not true.

23 DR. TEMPLE: No, you don't have enough
24 information about amlodipine to tell.

25 DR. LIPICKY: Well, that's what I'm

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1 telling you.

2 DR. TEMPLE: No, but you won't with this
3 trial either.

4 DR. LIPICKY: No. We will when the trial
5 is -- when we look at all of the results, but if we
6 just look at chlorthalidone and doxazosin, we will not
7 be able to -- you will not be able to give me the
8 reassurance I need to buy, like Tom does, the strength
9 of evidence here.

10 I will be always short on that strength of
11 evidence. But if the amlodipine arm really sort of
12 look like the same thing but not quite as bad, I'd buy
13 Tom's argument in an instant.

14 So I'm really -- I guess all I'm saying is
15 I don't think it's the mean dose. That isn't the
16 thing that is of importance. We will argue about that
17 some.

18 ACTING CHAIRMAN BORER: Well, okay. The
19 sense of the Committee is that you need some
20 additional data before it's appropriate to provide
21 information to doctors. That information should be
22 available within the foreseeable future, not years but
23 months. I don't know.

24 At that time, it's necessary to review
25 what the data show and determine whether they still

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1. show the strong suggestion of something that's not
2. being done by one drug that is being done by the other
3. that doctors probably ought to know about.

4. At that time, if the FDA would like
5. additional comments from this Committee, this
6. Committee will be happy to provide them.

7. DR. LIPICKY: Well, when you put it in the
8. context of months, you are clearly saying we do not
9. have to analyze the data.

10. ACTING CHAIRMAN BORER: That's right. You
11. may not need to analyze the data.

12. DR. LIPICKY: No, no, no. You are saying
13. you do not have to.

14. ACTING CHAIRMAN BORER: No, no, I'm not
15. saying that.

16. DR. LIPICKY: Because we can't even get it
17. in a couple of months.

18. ACTING CHAIRMAN BORER: Right, but let me
19. tell you what I'm actually saying. I'm actually
20. saying that you may see information that is so
21. compelling that you will choose to say something
22. without demanding to analyze the primary data. You
23. may, however, find that the data are less compelling,
24. and then we would be happy to provide an additional
25. opinion, or you may choose to say I can't possibly do

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1 this without the primary data, now that I've seen
2 this.

3 DR. GRABOYS: Jeff, so at the end of the
4 day we are all leaving here saying that we feel
5 comfortable continuing our patients on the drug and
6 prescribing it?

7 ACTING CHAIRMAN BORER: I feel comfortable
8 continuing my patients, of whom there are very few
9 taking doxazosin, as it happens, but I feel
10 comfortable continuing my patients on doxazosin.

11 I can tell you that not one of them -- Not
12 one of them is being treated with that drug as
13 monotherapy -- not one -- and that there may be
14 patients who I am seeing who are taking that drug for
15 benign prostatic hypertrophy. If they are and I am
16 seeing them -- and I'm a cardiologist, and I only see
17 patients who have cardiac problems.

18 Those people probably are taking some
19 other cardio-active drug for some purpose, and I don't
20 feel uncomfortable in leaving them on their doxazosin
21 for benign prostatic hypertrophy, because I don't see
22 any evidence that this drug is causing harm.

23 It may not be providing the benefit. It
24 may or may not be. It may not be. I think the data
25 show that it doesn't seem to be providing some benefit

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1 that another drug may be providing in the doses used
2 according to the regimen that was given. But causing
3 harm? No.

4 So, therefore, the answer to your
5 question, Tom, is yes, I do feel comfortable.

6 DR. TEMPLE: Jeff, I think you've done
7 what you can do, and we need to go back, think about
8 it a little more. We may write to you for further
9 suggestions.

10 If anybody overnight thinks of an
11 important new way of writing this that's absolutely
12 definitive and perfect and no one would object to,
13 send it to us.

14 DR. LIPICKY: Send it to Dr. Temple.

15 DR. TEMPLE: We both need to get it.
16 Right.

17 ACTING CHAIRMAN BORER: Okay. Are there
18 any other issues that we need to deal with, any final
19 comments? Does anyone feel terribly upset or
20 unfulfilled? I don't see any yeses here.

21 Meeting adjourned.

22 (Whereupon, the foregoing matter went off
23 the record at 5:07 p.m.)

24

25

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CERTIFICATE

This is to certify that the foregoing transcript
in the matter of: CARDIOVASCULAR AND RENAL DRUGS
 ADVISORY COMMITTEE MEETING

Before: FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND
 RESEARCH

Date: THURSDAY, MAY 24, 2001

Place: NATIONAL INSTITUTES OF HEALTH
 ROCKVILLE, MARYLAND

represents the full and complete proceedings of the
aforementioned matter, as reported and reduced to
typewriting.

Rebecca Davis