

1 information is, and if we look at this as essentially  
2 what we know the most about, basically, Steve, it's  
3 the global analysis. It's a very slight harmful  
4 effect in ACE inhibitors.

5 If we went to E-5, it would be a very  
6 slight positive effect on morbidity as you see right  
7 there.

8 When we subdivide into these subgroups,  
9 there is a fair amount of data in these subgroups. It  
10 leads me to state or leads me to conclude that adding  
11 it to an ACE inhibitor is a very, very negligible  
12 situation. Adding it to a beta blocker, if I believe  
13 the qualitative interaction, is a bad thing to do.

14 And I keep putting forward to my  
15 colleagues here if we look at this and go to E-4 as  
16 well, go to E-4 as well, we see this exact same  
17 qualitative interaction.

18 And if we're going to believe that we  
19 should market it in these people who are on ACE  
20 inhibitors without beta blockers, I want to understand  
21 why we think that when you're adding it to the ACE  
22 inhibitor and the beta blocker it's bad. I need to  
23 understand the biology for why you've got an ACE  
24 inhibitor on board.

25 If you're going to add valsartan without

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1 a beta blocker, that's a good thing. With a beta  
2 blocker, it's a bad thing. And if I can't believe  
3 that, then I really want to go back to Steve's wisdom  
4 and say really the only thing I can take home from  
5 this is the overall ACE inhibitor result, and I will  
6 say I want two studies then. If you really want to  
7 understand the answer to the question do you provide  
8 it when you're not giving an ACE inhibitor, we need a  
9 trial, and those aren't ACE inhibitors.

10 We only have 300 patients of that type,  
11 and if you really want to know if it's an agent that  
12 could be given as Jay Cohn suggested, I believe, in  
13 his presentation, for people who are not able to take  
14 a beta blocker, I don't know that that's this group.  
15 I just know that this is a group that wasn't on beta  
16 blockers. I don't know that this was a group that  
17 couldn't take beta blockers.

18 DR. HIRSCH: So to accentuate that  
19 further, the beta blocker treatment almost looks like  
20 a light switch in terms of benefit on and off.

21 DR. FLEMING: Yes.

22 DR. HIRSCH: And it is hypothesis  
23 generating. So I hate to do this. We usually just  
24 talk amongst ourselves, but I have to ask that  
25 question, which is: did we see or did I miss in the

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1 application something that I'm suspicious as a  
2 clinician, which is as I add agents, I often face the  
3 wall of hypotension. Did we see blood pressure trends  
4 across these beta blocker, ACE inhibitor plus/minus  
5 treatment groups to say whether we had finally  
6 unloaded the patient so much?

7 Did we see it or did we ask for it?

8 DR. COHN: We can show you that.

9 DR. HIRSCH: Please. Well, then if it  
10 doesn't, it will get them to stop worrying, and we can  
11 move on to the next subject.

12 DR. COHN: WE have the blood pressure.

13 DR. HIRSCH: You must have looked at it.

14 DR. COHN: Oh, yeah.

15 DR. HIRSCH: Or some other hormonal  
16 paradox.

17 DR. COHN: All the explanations.  
18 Obviously Tom is raising the biological issue, and I  
19 think it's wonderful to have a biostatistician want to  
20 raise a biological issue.

21 These are the blood pressure changes in  
22 the four main subgroups and then the four combined  
23 subgroups, and you'll notice that there's no trend for  
24 more blood pressure reduction.

25 DR. HIRSCH: Thank you.

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1 DR. COHN: Now, these are the last blood  
2 pressures recorded in those patients before they died  
3 or the trial ended. They aren't measured contiguous  
4 with their death, of course, but there didn't seem to  
5 be any striking trend that there was a greater blood  
6 pressure reduction in the combined therapy.

7 ACTING CHAIRMAN BORER: There is something  
8 there though, Jay. I mean, it's flashing at me too  
9 quickly to do a calculation, but the bottom group  
10 actually has the lowest blood pressure to start with,  
11 and then you're lowering it about the same as  
12 everybody else is being lowered.

13 So, in fact, it may be that the final  
14 absolute blood pressure you reach is a little bit  
15 lower with yes/yes than with the other groups.

16 DR. COHN: It could be. It's a pretty  
17 small difference I would agree with you in the  
18 valsartan group. In the placebo group, the baseline  
19 was not lower. In the valsartan group it was on the  
20 combined drug.

21 So, you know, you get into small numbers  
22 here. If I could just make a couple of comments on  
23 what's going on, and I don't really want to intervene  
24 myself, I share with all of you the concern about what  
25 to do. The reason we've brought this forward is

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1 because of the safety issue on the mortality in the  
2 combined treatment group. ACE is yet, beta yeses.

3 I don't quite share Tom's view that  
4 there's a mortality adverse effect. The confidence  
5 intervals overlap one, and it could just as well be  
6 that there's a mortality benefit.

7 I also think despite the small numbers  
8 that there is some virtue in looking at the combined  
9 drugs, not just the first stage because it clearly,  
10 both by secondary analyses that Al showed you and by  
11 everything else that we have, the quality of life and  
12 the ejection fraction, et cetera, there seems to be a  
13 difference whether you're on a beta blocker alone or  
14 on a beta blocker with an ACE inhibitor.

15 And I think that that makes a big  
16 difference, and from a mechanistic standpoint, I do  
17 believe it is multiple drugs, and we now have evidence  
18 from other trials that have recently been completed.  
19 We've demonstrated that if you lower plasma  
20 norepinephrine, pharmacologically with a central  
21 inhibitor of the sympathetic nervous system, you get  
22 an adverse effect on mortality.

23 We've demonstrated that when you block  
24 endothelia these days in a most recent study or you  
25 block cytokines in patients treated with all of these

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1 other drugs, you seem to see no benefit and, in fact,  
2 a trend for an adverse effect.

3 So we may be getting to the point where  
4 there's too many systems being blocked. So  
5 biologically I don't have a lot of trouble with this,  
6 Tom, although I can't cite you a mechanism, but it  
7 just is intuitive, and I think Alan has sort of said  
8 the same thing, and so has Steve.

9 You know, it's just a little too much  
10 blockade, and I don't know whether it's working  
11 through blood pressure or through conduction or  
12 through something else, but it puts the patient at  
13 some risk potentially.

14 Now, we're going to have more data from  
15 the CHARM trial. We're also going to have a lot of  
16 data from the VALIANT study post MI on the combination  
17 of all three drugs: beta blockers, ACE inhibitors,  
18 and ARB.

19 Those trials are ongoing. The data safety  
20 and monitoring boards for those trials are very aware  
21 of our data. We keep shipping them updated data. So  
22 they're watching it, and they have chosen not to stop  
23 the arm with ARBs added to ACEs and beta blockers.

24 So we're going to have a lot more data,  
25 and I think we're at the cutting edge of this now.

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1 How do we respond to this subgroup in terms of  
2 labeling of the drug?

3 Now, let me just say one more thing about  
4 the p value for the whole study, and this is to help  
5 Ray a little bit. One of the reasons -- I always like  
6 to help Ray.

7 DR. LIPICKY: Thank you.

8 DR. COHN: One of the reasons that the  
9 company did the exercise study was that they were told  
10 that would be a second trial, and if that had been  
11 positive, .05, that would have been the second trial,  
12 and all this trial had to do was achieve .025 or .020,  
13 whatever it was.

14 That trial was not positive, as you've  
15 seen. It was a wash. Now, I appreciate the committee  
16 telling Ray whether a positive exercise test on a 12  
17 week study of .05 would have been more valuable to you  
18 than all of the secondary endpoint significance that  
19 we've shown on ECHO and LV dimension and quality of  
20 life and signs and symptoms and neural hormones. Is  
21 that more valuable or less valuable than a 12 week  
22 exercise test would have done for the statistics?

23 Because from the regulatory standpoint,  
24 that study, .05 on exercise, would have meant it  
25 brought us home free.

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1           ACTING CHAIRMAN BORER: Before we try to  
2 answer that question, let's try to answer the  
3 questions we have. I'd like to give my opinion before  
4 we move on to number eight here about number seven.

5           It's just a little bit different from what  
6 you've heard, and I throw it out to everybody for  
7 whatever it's worth. As I suggested earlier, I think  
8 safety issues have to be dealt with a little bit  
9 differently than efficacy issues. We may demand a  
10 great deal of strength of evidence, a great strength  
11 of evidence to conclude that efficacy exists, but I  
12 don't think we need quite so much evidence to suggest  
13 or to conclude that there's real potential for a  
14 safety problem if you see some data that suggests  
15 that.

16           And I think we see it, but I don't see it,  
17 though the statistical gods may kill me. I don't see  
18 it as a beta blocker issue. Virtually everybody who  
19 is on beta blocker was on ACE inhibitor. That's more  
20 than 1,600 people, and it's the combination of the  
21 beta blocker and the ACE inhibitor that was associated  
22 with the bad outcomes on all the things we looked at,  
23 and that was consistent across the board, even with  
24 the secondary endpoints and the tertiary endpoints,  
25 you know, everything that was looked at here.

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1           So my concern, and I don't have any  
2           problem. You know, I would echo what Jay says. I  
3           don't know what the mechanism is, but I could argue in  
4           favor of one.

5           I think that we have to make a comment  
6           about the inappropriateness at this moment of adding  
7           valsartan to a combination of beta blocker and ACE  
8           inhibitor. When I look at the very small subgroups  
9           that you couldn't draw any conclusions from on their  
10          own and see that the people who were on beta blocker  
11          alone, small subgroup though it may be, look  
12          different, and that is intuitively not unreasonable to  
13          me.

14          Then I'm less concerned about adding an  
15          ARB, valsartan specifically, to people who are on beta  
16          blocker alone. When I look at the ACE inhibitor data,  
17          however, I fall right on the line with Tom. It looks  
18          to me no matter how you slice it that there's a little  
19          bit of a benefit when you're on ACE inhibitors alone,  
20          but I don't know what dose, and I don't know what  
21          drug.

22          In terms of morbidity and equally a little  
23          bit of a detriment in terms of mortality, and I would  
24          caution people about the addition of valsartan to an  
25          ACE inhibitor. I can't say it's bad. Overall it

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1 looks like it's a little bit good, maybe, but I don't  
2 know the dose. I don't know the drug. I don't know  
3 the combination that's appropriate.

4 Since I don't know, I'd like to say I  
5 don't know, but I wouldn't want to proscribe doing it  
6 because I just don't know enough, and when you look at  
7 the totality of the data, in fact, it looks like  
8 there's a benefit.

9 And I want to make another editorial  
10 comment here. I've been looking at NDAs now off and  
11 on for 24 years, and I made this comment at a  
12 conference once when I was sitting in the audience,  
13 and the response I got I'll tell you in a moment.

14 But I don't know how any drug works. I  
15 know the pharmacological effects that are associated  
16 with a lot of drugs. I have no idea what the  
17 mechanism of action is, that is, how the drug produces  
18 its clinical benefit.

19 And I can cite chapter and verse of  
20 disapprovals based on the lack of a putative mechanism  
21 of action for drugs that we now know have exactly the  
22 same effects as other drugs that subsequently have  
23 been approved and now we think we know the mechanism  
24 of action.

25 So I look at the data first. When I said

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1 that at a meeting in which I was sitting at the back  
2 of the room, I said that to somebody else sitting back  
3 there, and he said, "Well, gee, you'd better start  
4 reading the journals and reading the textbooks."

5 And I said, "You'd better hope that's not  
6 true because," I said, "I'm the committee that  
7 approved these."

8 But I think we have to look at the data  
9 first, and to me the data show for the population that  
10 was studied a clinical benefit, not all of the  
11 clinical benefits that we would have liked to have  
12 seen. When I look at the subgroups, I see what  
13 intuitively I would have expected, that in the  
14 subgroups that didn't get the other drugs, the  
15 benefits that I would have expected with at least one  
16 of the other drugs is there.

17 So I don't have a problem with concluding  
18 that this drug does something good, but I'd sure as  
19 heck not want to give it to people for whom I have a  
20 strong signal that I'm going to hurt them when I do  
21 it, and that to me is the group that's taking this  
22 combination of beta blockers and ACE inhibitors.

23 So that's my opinion. Put it in the  
24 hopper, and we'll move on to Question No. 8.

25 Evaluate the following findings with

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1 respect to whether they are considerations related to  
2 approval or to labeling, the lack of apparent  
3 treatment effect in blacks, the very small apparent  
4 treatment effect in patients taking ACE inhibitors,  
5 which we just now talked about, lack of apparent  
6 treatment effect in patients taking beta blockers we  
7 talked about.

8 I think the one issue to deal with here is  
9 the lack of apparent treatment effect in blacks.  
10 We've mentioned it. Is there anything more that we  
11 want to say about it? Is it something that should be  
12 highlighted in some way if we were to give labeling  
13 advice to the FDA?

14 Paul.

15 DR. ARMSTRONG: Jeff, having picked up on  
16 that this morning, I would just say that looking at  
17 the data that has been presented that wasn't in our  
18 briefing book, there are really four factors, I think.  
19 One is the mortality. The other is the morbidity,  
20 both of which go the wrong way.

21 Then there's the BNP, which goes the wrong  
22 way, and then we've learned that there's also the  
23 safety that goes the wrong way.

24 So there's a quartet of factors that for  
25 me are concerning, notwithstanding the fact that we're

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1 talking about seven percent of the population or about  
2 360 patients.

3 ACTING CHAIRMAN BORER: Do we know at all  
4 -- and, again, I don't want to get into sub-sub-sub-  
5 sub-analyses, but do we have a gestalt of how what  
6 other drugs the black people were taking? I mean,  
7 were a lot of them taking the combination of beta  
8 blocker and ACE inhibitor, for example? Do we know at  
9 all?

10 MR. MacNAB: No, they were very similar.  
11 There were, I think, to some degree fewer beta  
12 blockers. The black patients were a little younger,  
13 but, again, in a small group with a wide confidence  
14 interval it's hard to make definitive conclusions.

15 ACTING CHAIRMAN BORER: Okay. So Paul has  
16 verbalized a concern, a real concern, that maybe has  
17 to be highlighted as we move forward. Would anybody  
18 disagree with that?

19 No. Okay. Let's go on to number nine  
20 then. Has adequately information --

21 DR. LIPICKY: Hold it --

22 ACTING CHAIRMAN BORER: -- to describe  
23 instructions --

24 DR. LIPICKY: Wait, Jeff. You're skipping  
25 a couple of things. That said is that -- is you

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1 statement that conclusion with respect to provability  
2 or labeling? Because --

3 ACTING CHAIRMAN BORER: Oh.

4 DR. LIPICKY: -- you made it sound like,  
5 of course, it's just a labeling issue, and it doesn't  
6 influence my approvability conclusion

7 ACTING CHAIRMAN BORER: Well, we haven't  
8 talked about approval yet.

9 DR. LIPICKY: Well, it says how do you  
10 evaluate this.

11 ACTING CHAIRMAN BORER: Oh, I'm sorry.

12 DR. LIPICKY: Approvability or labeling?

13 ACTING CHAIRMAN BORER: No, you're quite  
14 right. You're quite right. Okay.

15 DR. LIPICKY: Because up until now it's  
16 been approvability, and this starts to get mixed now.

17 ACTING CHAIRMAN BORER: To me it's a  
18 labeling issue. I'd like to hear what everybody on  
19 the committee has to say.

20 Go ahead.

21 DR. HIRSCH: Labeling.

22 ACTING CHAIRMAN BORER: Paul?

23 DR. ARMSTRONG: I'm okay with that.

24 DR. LINDENFELD: I think it's an isolated  
25 thing. It's a labeling issue, but with a number of

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1 other subgroups we have questions about, it might be  
2 an approval issue.

3 DR. NISSEN: Label.

4 DR. ARTMAN: It's a labeling issue.

5 ACTING CHAIRMAN BORER: Glorea?

6 DR. ANDERSON: I think it's a labeling  
7 issue, but I also have some concerns because, one, the  
8 population was small and, two, I couldn't find enough  
9 information to answer some questions that I had.

10 And incidentally, I had the same question  
11 about the size of the population of women who were  
12 included in the study, 20 percent, I think it is,  
13 about 20 percent.

14 ACTING CHAIRMAN BORER: Tom?

15 DR. FLEMING: I have nothing to add.

16 ACTING CHAIRMAN BORER: Okay. Now, let's  
17 go on to number nine. Has adequate information been  
18 obtained to describe instructions for the use of  
19 valsartan in heart failure?

20 Would anybody like to give an answer and  
21 then we'll see if there's a lot of dissent?

22 DR. FLEMING: Can I have a clarification?  
23 Does this include if in Question 10 it's the  
24 perspective of some committee members that one needs  
25 to take into consideration whether one is on ACE

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1 inhibitors or beta blockers or whether they're  
2 contraindicated, is that part of -- for example, what  
3 we don't know, I would argue, is what's the level of  
4 effect of valsartan in someone on ACE inhibitors where  
5 beta blockers are medically contraindicated.

6 ACTING CHAIRMAN BORER: Yeah. You know,  
7 I don't want to answer for the FDA, and I think we'll  
8 have an answer from the FDA in a second if I say  
9 something incorrect, but at the end of a development  
10 program, there are many questions that are left  
11 unanswered, and if we have enough information to  
12 provide instructions for use, which also can provide  
13 instructions about what we don't know so that you  
14 ought to be very cautious and maybe not even do it  
15 until more information is available. We can do that.

16 We can provide a very directive or the FDA  
17 can provide a very directive label. It can say you  
18 should only do this in this situation.

19 We don't know anything about this. This  
20 is a potential show stopper. Don't do it till we have  
21 more information.

22 So I think that the question has adequate  
23 information been obtained is a question about how well  
24 we believe we could describe to a physician how the  
25 drug could be used effectively and acceptably safely

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1 today.

2 That may exclude a lot of groups. It may  
3 exclude a lot of drugs. It may do this. It may not.

4 DR. FLEMING: Then my sense --

5 DR. LIPICKY: And it includes those.

6 DR. FLEMING: -- is there are some  
7 additional sources of information, but I'd like to  
8 clarify my answer to that after I answer Question 10.

9 ACTING CHAIRMAN BORER: Ray, do you want  
10 to add to what I or to --

11 DR. LIPICKY: No.

12 ACTING CHAIRMAN BORER: -- refute what I  
13 said?

14 DR. LIPICKY: No, but it includes dose.  
15 And I'll take just a minute, and I know you're in a  
16 hurry and want to get done in ten minutes.

17 ACTING CHAIRMAN BORER: No, no. We'll  
18 give you a few more minutes.

19 DR. LIPICKY: But, you know, the sense of  
20 these questions as they have evolved up until now was  
21 we want to know whether you think a single trial gets  
22 approval and whether it gets approval on the basis of  
23 its primary endpoints or its secondary endpoints or a  
24 combination of the two, and whether you think the  
25 subgroups that are here are adequately enough

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1           portrayed that they cause concern.

2                       So it's possible that the overall trial  
3           result might be weakly positive. Let me put it that  
4           way. Okay? And that the subgroup business makes you  
5           worried about not knowing who to give it to, in which  
6           case you wouldn't care about Question 8 because you  
7           don't have enough -- you know, the dose and stuff like  
8           that doesn't matter or, conversely, that the principal  
9           -- the primary endpoint is so convincing on its own  
10          that it absolutely has to be approved for that, and  
11          that the rest of this is all just window dressing  
12          then.

13                      Okay? So we're -- it's sort of been  
14          graded through this whole business of what is most  
15          important and what is next most important and trying  
16          to get a sense of what you think. I'm not sure I did,  
17          but I don't know why I said this.

18                      Forgive me.

19                      ACTING CHAIRMAN BORER: Okay. Let's move  
20          on then to Question 10, which we'll have to take in  
21          parts. And for this we'll need a vote from everybody,  
22          I think.

23                      Should valsartan be approved for use in  
24          treatment of patients with chronic congestive heart  
25          failure, and if so, what should labeling say about

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1 these various things?

2 Let's start with the global issue because  
3 if the answer were no, then we have nothing else to  
4 add to talk about.

5 Should valsartan be ap-proved for use in  
6 the treatment of patients with chronic congestive  
7 heart failure? Let's start at the far end of the  
8 table. Glorea, why don't you go ahead?

9 DR. ANDERSON: I would disagree at this  
10 point based on the fact that I don't think we have  
11 enough information. At least I don't.

12 ACTING CHAIRMAN BORER: That's a no.

13 DR. ANDERSON: No.

14 ACTING CHAIRMAN BORER: Mike.

15 DR. ARTMAN: I would say yes.

16 ACTING CHAIRMAN BORER: Steve.

17 DR. NISSEN: Yes.

18 ACTING CHAIRMAN BORER: JoAnn?

19 DR. LINDENFELD: I would say no. I think  
20 that the endpoint here doesn't meet the level of  
21 statistical significance that we want, and it's a  
22 modest improvement, and then we have major questions  
23 about subgroups and who to treat.

24 ACTING CHAIRMAN BORER: Paul?

25 DR. ARMSTRONG: Overall, no, but I think

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1 there's a niche.

2 ACTING CHAIRMAN BORER: I'm sorry?

3 DR. ARMSTRONG: Overall the answer is no,  
4 but I want to come back to potential subgroup.

5 ACTING CHAIRMAN BORER: Well, okay, but we  
6 can't. If the vote is no, then it's --

7 DR. ARMSTRONG: All right.

8 ACTING CHAIRMAN BORER: Okay. Alan?

9 DR. HIRSCH: I was going to say yes.

10 ACTING CHAIRMAN BORER: tom?

11 DR. FLEMING: I actually had a similar  
12 response to Paul. It's a no, but it's a qualified,  
13 and I will make very clear what that qualification is  
14 before we finish answering these questions.

15 ACTING CHAIRMAN BORER: Okay. I'd vote  
16 yes.

17 How does that come out?

18 Okay. Now we have to get some  
19 qualifications because it's four to four. Tom, why  
20 don't you start with your qualifications?

21 DR. FLEMING: Well, let me --

22 DR. LIPICKY: You've helped us a lot.

23 DR. FLEMING: -- comment on a couple of  
24 things that --

25 (Laughter.)

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1                   ACTING CHAIRMAN BORER:    Be could stay  
2                   until tomorrow.

3                   DR. FLEMING:    Let me comment on a couple  
4                   of things, and actually the qualifications relate to  
5                   the specifics in 10-1 and 10-2, but there's one or two  
6                   comments I haven't given yet, and one of them relates  
7                   to just interpreting these data first on the primary  
8                   endpoints.    The first is mortality.

9                   I believe the study is, in fact, more  
10                  reliable on its primary endpoint than might have been  
11                  apparent in the sponsor's presentation of the study.  
12                  Looking at mortality first, it was pointed out that  
13                  the anticipated death rate was 12 percent.    It was  
14                  only observed to be nine percent, and that may have  
15                  left the study under powered for mortality.

16                  And in the presentation it was mentioned  
17                  there was no demonstrable effect on mortality, which  
18                  suggests that maybe there is an effect, but we just  
19                  didn't demonstrate it.

20                  The study was targeted for a 20 percent  
21                  reduction in mortality.    It seems to me in the context  
22                  of other agents that are out there, such as beta  
23                  blockers and ACE inhibitors that provide more than  
24                  that level of effect, I think it was reasonable to  
25                  have targeted that level as what was clinically

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1 relevant.

2 The study did achieve essentially 1,000  
3 deaths, which by my calculation is a high power for  
4 detecting that 20 percent reduction, even with the  
5 adjustment for the two primary endpoints. The  
6 estimate is a two percent increase in mortality where  
7 the lower limit of the confidence limit is .9, meaning  
8 it rules out half the level. These data are  
9 inconsistent with even as much as half the level of  
10 mortality effect that the study was powered to detect,  
11 half the level, less than half the level of effect  
12 that we would know we can achieve with other agents.

13 So my sense is this was an excellent study  
14 in many ways, and certainly one of those ways was in  
15 providing us a very good sense about the effect of  
16 mortality. I believe these data are not only not  
17 significant. I believe these data are suggestive of  
18 no effect and ruling out anything more than a modest  
19 effect on mortality.

20 We've already discussed at greater length  
21 the morbidity endpoint. As I see it for 100 percent,  
22 what we're doing is we're presenting ten  
23 hospitalizations over a two year period per 100  
24 people.

25 We're also, as was corrected, we're

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1 preventing one day or reducing one day hospitalization  
2 per year. That is a modest -- that is a moderate,  
3 modest, whatever adjective, benefit you want to put  
4 on, you want to acknowledge, and the effects on  
5 symptoms and the Minnesota living with heart failure  
6 are reinforcing, although I'm still struggling with  
7 how strongly because I'm still struggling with getting  
8 a sense of how strong those data are.

9 Having said all of that then, if we look  
10 at the data where we have information, where do we  
11 have information? We have a lot of data in the global  
12 analysis, and like Steve says, I look at that first  
13 and foremost, and when I look at that, I see one study  
14 that does meet standards for strength of evidence for  
15 a positive trial. I'm really reluctant to call it  
16 though the level of evidence that would be similar to  
17 what we would have from two independent studies, each  
18 of which would meet that standard for positivity.

19 It was possible that we could have met  
20 that standard if we had had, rather than modest, if we  
21 had had moderate effects on morbidity. This was a  
22 very large trial that would have been powered to  
23 achieve that level of effect.

24 Now, what adds a lot of complication here  
25 is the sponsor's acknowledgement that there is

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1 evidence here about potential effect modification. As  
2 I look at it, the data on effect modification are  
3 specific to refining the question about what it means  
4 to add valsartan to ACE inhibitors because we don't  
5 have data of any substance in people that aren't on  
6 ACE inhibitors.

7           So in that context, when you're adding to  
8 an ACE inhibitor, what we have is, as has been  
9 mentioned many times, a modest positive effect on  
10 morbidity, but a comparable modest negative effect on  
11 mortality. The mortality confidence interval, as Jay  
12 points out, includes equality, but so does the  
13 morbidity confidence interval include equality.

14           What we're left with then is this complex  
15 issue about whether there is an effect modifier such  
16 that it's a good thing to be on an ACE inhibitor; it's  
17 a good thing to be on an ACE inhibitor and beta  
18 blocker, but in the former case, it's good to add  
19 valsartan to the ACE inhibitor. In the latter case  
20 it's bad to add valsartan to the ACE inhibitor and  
21 beta blocker.

22           I don't understand that. I don't  
23 understand that. If the FDA understands that, then I  
24 would argue approval in the context of patients who  
25 are on ACE inhibitors and not beta blockers, if the

1 FDA understands the mechanism for that interaction.

2 I would argue that, in essence, coming  
3 back to where I left unanswered in Question 8 and  
4 Question 9, what would I like to know that I don't  
5 know. What I really would like to know is what is the  
6 role of this agent in the setting in which ACE  
7 inhibitors are contraindicated. There's too little  
8 data to answer that here. It's a subset analysis,  
9 much worse.

10 Secondly, what I don't really know -- I've  
11 got clues, but I don't really know -- is what is the  
12 effect of adding valsartan to an ACE inhibitor when a  
13 beta blocker is medically contraindicated. I don't  
14 know. That is also unknown, and that could be  
15 addressed in a second supportive trial if, in fact,  
16 the FDA remains as uncertain as I am as to what's  
17 causing this critical effect modification.

18 So in summary, my sense is clearly in the  
19 answers, in my view, the answer is this an alternative  
20 to an ACE inhibitor, is this an alternative to a beta  
21 blocker, I think the sponsor answered that question.  
22 It's not an alternative we would wish to give beta  
23 blockers and we would wish to give ACE inhibitors in  
24 settings in which they're not medically contradicted.  
25 So the question is: are these agents that would be

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1 given in second line?

2 And my belief is there is additional data  
3 that's necessary, but bottom line is if there is a  
4 clear understanding or a reasonable understanding of  
5 this critical effect modification issue, then I would  
6 be more positively persuaded toward an approval for  
7 the setting in which somebody is on an ACE inhibitor,  
8 but beta blockers are medically contraindicated.

9 ACTING CHAIRMAN BORER: Okay. Does  
10 anybody have any others? Paul.

11 DR. ARMSTRONG: Well, I guess I should  
12 justify my vote, and it's the concern about safety and  
13 the uncertainty about questions, questions in 15  
14 percent of the population over 75 in which we have no  
15 information, concerns about the spironolactone story,  
16 uncertainty about the effect in patients on digoxin,  
17 clear concerns about the beta blocker issue.

18 And so notwithstanding the fact that I  
19 believe this drug has an effect, as a clinician trying  
20 to inform others as to how to use it with the evidence  
21 available, I wouldn't know what to say, Mr. Chairman.

22 ACTING CHAIRMAN BORER: Steve?

23 DR. NISSEN: Yeah. I hear everything  
24 that, you know, the folks saying no are saying, and I  
25 understand your convictions, and I appreciate them

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1 very much. Let me just think out loud with you a  
2 little bit about this because we're obviously on the  
3 fence here.

4 We all look at a trial, I think. The most  
5 compelling data is obviously the data that relates to  
6 the primary prespecified endpoint of the trial, and I  
7 want to point out to the committee that this sponsor  
8 and these trial investigators set an extremely high  
9 bar for themselves. They took a bunch of patients  
10 that were very well treated with dig., diuretics, 90-  
11 plus percent getting ACE inhibitors, a lot getting  
12 beta blockers.

13 These are much better treated patients  
14 than the average heart failure patient in America or  
15 anywhere else is treated, and they said, "Would adding  
16 valsartan to a group of very well treated patients do  
17 anything?"

18 What did it do? Well, for one of the two  
19 primary prespecified endpoints at a p value of .009,  
20 not .00125 --

21 DR. LIPICKY: Oh, oh, two.

22 DR. NISSEN: Yeah, okay. Okay, all right.  
23 Again, we can --

24 DR. LIPICKY: -- oh, two.

25 DR. NISSEN: Okay, but at a level of

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1       significance we can argue about and supported by a  
2       whole constellation of symptomatic, functional,  
3       structural, and biochemical endpoints.

4               And so, you know, looking at this on  
5       balance and trying to decide, you know, whether  
6       there's more harm or good here, you know, I think you  
7       have this trial as to live or die by that primary  
8       endpoint, and I am influenced by the fact that this  
9       endpoint was obtained in a setting of extremely well  
10      treated patients.

11              Now, the big problem is we've got this  
12      subgroup. I don't even know if it was a prespecified  
13      subgroup. Maybe it was; maybe it wasn't, where  
14      something fell out that we didn't like, and I do think  
15      we have an ethical duty to make sure people are  
16      informed about that.

17              And I, therefore, think that there is a  
18      compromise position here, which is to come up with  
19      some labeling that suggests that this agent may be  
20      useful because I happen to think it's a good thing to  
21      prevent PND, dyspnea on exertion, and hospitalization.

22              But to provide very clear warnings that  
23      triple drug therapy was associated with increased  
24      mortality and morbidity, and let the prescribing  
25      physician then make a judgment about that. I

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1 personally don't want to give this drug in triple drug  
2 therapy, but I think I might well add it to patients,  
3 particularly those who are still quite symptomatic,  
4 who have heart failure and are on ACE inhibitors.

5 And one more point I want to make is that  
6 if you look carefully, the worst the heart failure  
7 was, the more the efficacy signal was in this trial,  
8 and that to me suggests to me that if I have a patient  
9 that has fairly severe heart failure symptoms and is  
10 not adequately managed, you know, with current  
11 therapy, that I could add valsartan and get additional  
12 benefits, and I think that's the take-home message of  
13 the trial.

14 We need the warning in there, but I think  
15 the efficacy convinced me.

16 ACTING CHAIRMAN BORER: Tom and Alan, both  
17 have comments.

18 DR. FLEMING: I just wanted to query Steve  
19 about his thoughts. You had mentioned at the  
20 beginning of your comments, Steve, that the sponsor  
21 basically sat a very high bar, a high standard, and  
22 you explained that in the context of having tried to  
23 show that there was additional benefit to adding  
24 valsartan in the context of patients who are already  
25 well treated with ACE inhibitors, beta blockers, et

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1 cetera.

2 I would argue the challenge for any of us  
3 as sponsors and investigators is to address the  
4 efficacy and safety of our intervention in the real  
5 world context of how they would be delivered.

6 Are you arguing that there was a lot more  
7 ACE inhibitor and beta blocker use in this trial than  
8 there should be in the real world, and as a result we  
9 were assessing this in a setting in which there was  
10 too high a goal to hit?

11 DR. NISSEN: No, I guess, Tom, what I'm  
12 suggesting is that it's very challenging to show  
13 efficacy on top of good therapy, and therefore, I give  
14 some significant sort of weight to the significance of  
15 those p values when I understand the context in which  
16 the therapy --

17 DR. FLEMING: But I would agree with you  
18 that in many instances in clinical practice it is  
19 harder to incrementally improve upon clinical practice  
20 when that clinical practice has already reached an  
21 effective level of benefit.

22 But nevertheless, the reality is  
23 fortunately we are in a setting now where we have  
24 these effective agents, and so the real question is:  
25 can we improve on what we already are able to

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1 accomplish with those agents?

2 I thought this was a very good study that  
3 was actually answering the question that was in need  
4 of being answered.

5 ACTING CHAIRMAN BORER: Before we go on to  
6 Alan and to Ray, let me -- you wanted a biological  
7 discussion, Tom, and let me suggest my thinking about  
8 this trial, this development program, and this drug.

9 I must tell you I think it took  
10 extraordinary courage for a drug manufacturer to take  
11 an angiotensin receptor blocker and study it for this  
12 indication with these kinds of a priori projections of  
13 effect in people who are being treated with a drug  
14 that affects exactly the same neural hormonal system.  
15 I never would have expected that an angiotensin  
16 receptor blocker would have any particular effect on  
17 top of an ACE inhibitor.

18 It might. You know, you saw Jay's slide  
19 with the putative mechanism by which maybe you could  
20 get some effect, but I wouldn't have expected much.

21 You know, I think because of analogy with  
22 results with angiotensin receptor blockers and ACE  
23 inhibitors in other settings that one might be a  
24 replacement for the other. I don't know that for sure  
25 in this setting because, of course, that's not the way

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1 the trial was set up, although if you look at the  
2 subanalyses, they're consistent with the hypothesis  
3 I'm suggesting now, that one can be a substitute for  
4 the other.

5 It would have been extraordinary to me  
6 that adding a drug of this particular class on top of  
7 the drugs that were being used that you would see a  
8 tremendous additional beneficial effect.

9 Nonetheless, I'm impressed that we saw  
10 something. We actually saw a reduction in morbidity,  
11 and again, I don't want to make too much of small  
12 group analyses and all of this kind of stuff, but  
13 starting with the hypothesis with which I began, that  
14 is, how this drug works pharmacologically, what system  
15 it's affecting, I would have expected there wouldn't  
16 have been much of an effect in the group as a whole,  
17 but if you looked at the subgroup that wasn't getting  
18 the other drugs, you would have seen an effect, and,  
19 lo and behold, we did.

20 So let me just finish. You know, what I  
21 saw is what I would have expected to see. It  
22 obviously isn't what the sponsor expected to see, but  
23 it's what I would have expected.

24 I think that when you ask how could it be  
25 that it's beneficial when added to an ACE inhibitor

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1 and not to an ACE inhibitor with a beta blocker or  
2 whatever, I would suggest that a lot of people who are  
3 on ACE inhibitors were on relatively low doses of ACE  
4 inhibitors where addition of the ACE inhibitor could  
5 have given you additional benefit just as addition of  
6 the ARB might have given you additional benefit.

7 So I have no trouble with seeing how there  
8 could have been some people in the group that drove  
9 the group as a whole to show an additional benefit  
10 when valsartan was added to ACE inhibitor.

11 I still don't think, given to maximally  
12 tolerable doses, whatever those may be, that you would  
13 see such an effect. That's my bias. I don't know if  
14 it's true or not. Maybe the data could be plumbed to  
15 see if there's a cut point in the doses of drugs that  
16 were used to see whether the addition of the ARB was  
17 better with the higher dose or the lower dose or if  
18 there was any difference at all.

19 But that would be my bias. When you add  
20 the two drugs together, the ACE inhibitor and the beta  
21 blocker and, thus, block a great deal of the neural  
22 humoral activity, I could then see how adding another  
23 drug could cause a problem.

24 So this doesn't seem intuitively  
25 unreasonable to me.

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1           To talk about giving the drug to people  
2 who medically can't take a beta blocker for whatever  
3 reason, the largest subgroups of those patients are  
4 people with pulmonary disease and a smaller subgroup  
5 with diabetes who can't be easily controlled on a beta  
6 blocker. It's not for cardiac problems.

7           So you know, that issue of people who  
8 medically cannot -- for whom beta blockers are  
9 medically contraindicated seems to me to be a side  
10 issue. If it were people for whom ACE inhibitors were  
11 medically contraindicated, that might be another  
12 issue, but even there Steve said it before. The  
13 primary reason why people don't get ACE inhibitors  
14 when we think that, in general, with their disease  
15 pattern they should is that they cough, and it's  
16 annoying to them. So they don't get it, and then  
17 they're left with nothing except a beta blocker alone  
18 if we use the current algorithm for treatment.

19           I'm looking at these data and saying that  
20 valsartan represents a reasonable drug to give to  
21 those people. Now, was a study done to test that  
22 hypothesis? No, but the data from the study that was  
23 done are completely consistent with what I'm  
24 suggesting.

25           Now, that may not be a sufficient basis

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1 for approving a drug, but that's the way I would look  
2 at these data.

3 DR. FLEMING: Jeff, I think there's a  
4 critical distinction to be made in what you're saying.  
5 I'm quite sure I heard you say that you interpreted  
6 these data to be suggestive that you could give this  
7 agent instead of another neural hormonal inhibitor.

8 ACTING CHAIRMAN BORER: Well --

9 DR. FLEMING: And the data are suggestive  
10 that you would achieve a comparable effect. I think  
11 these data tell us essentially nothing about that  
12 question.

13 What these data are telling us is in the  
14 absence of these other neural hormonal inhibitors,  
15 there's evidence of some benefit, but there's nothing  
16 to say that that level of benefit matches what you  
17 would have gotten if you had randomized those patients  
18 against the beta blocker or the ACE inhibitor.

19 In fact, I think there's strong evidence  
20 to suggest that if you did randomize these patients to  
21 an ACE inhibitor or beta blocker, the ACE inhibitor  
22 and beta blockers would substantially improve  
23 survival, and valsartan wouldn't affect survival  
24 because that's what these data are showing.

25 These data are though showing that you're

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1 affecting --

2 ACTING CHAIRMAN BORER: I don't think so.

3 DR. FLEMING: Let me finish. Let me  
4 finish. These --

5 DR. COHN: These drugs were given on top  
6 of those drugs. The only group where they weren't on  
7 the top showed a benefit on mortality. So you can't  
8 say that.

9 DR. FLEMING: Well, that's correct. These  
10 data were given for the most part on top of ACE  
11 inhibitors, but specifically what we're seeing here is  
12 evidence that is suggesting that the use of this agent  
13 on top of an ACE inhibitor is essentially not  
14 impacting overall survival.

15 Now, there's nothing in these data that  
16 would argue that if you added the beta blocker on top  
17 of this ACE inhibitor that it also wouldn't impact  
18 overall survival, and the bottom line point that I'm  
19 making is that the evidence that's more favorable here  
20 for the effects of valsartan are in individuals who  
21 aren't as heavily exposed to the beta blocker or the  
22 ACE inhibitor.

23 But that doesn't tell us anything about  
24 whether if we did a randomized head-to-head trial of  
25 valsartan against those other agents that we would

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1 expect comparable results.

2 ACTING CHAIRMAN BORER: Well, okay. Ray?

3 DR. LIPICKY: Were you going to? Go  
4 ahead. Finish your thought.

5 ACTING CHAIRMAN BORER: No, I was going to  
6 suggest I know that Ray and Alan both have comments  
7 here, but I think we've just discussed a number of  
8 these secondary points that you've made. I was going  
9 to begin to ask if there were any other -- any change  
10 in position or change in vote because if there isn't,  
11 I think we've answered the questions, but there are  
12 other comments here.

13 I mean, Alan, did you have something you  
14 wanted to --

15 DR. HIRSCH: I had a long comment, but I  
16 think ultimately it comes down to one sentence. There  
17 was biologic efficacy that can benefit patients, but  
18 labeling is critical.

19 ACTING CHAIRMAN BORER: Okay. Ray.

20 DR. LIPICKY: But, see, we're fine. I  
21 think you have answered all of the questions in that  
22 we know where things are, and we're about as equally  
23 divided in the division as you guys were in your  
24 conclusions. So that's fine. We understand that.

25 But there are two things I wanted to say

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1 before we quit. One is that if the task is hard, that  
2 doesn't mean the standards for whether or not you  
3 found something have to be relaxed. I think those two  
4 things have to be disconnected and also part and  
5 parcel of the same thing, and it's not clear they  
6 were; and also part and parcel of the same thing is  
7 that a study may, indeed, find a treatment effect.  
8 That doesn't mean it has to be approved. Okay?

9 The level of evidence, how well you  
10 believe that the trial results as a whole are  
11 applicable to a general population are, indeed,  
12 something that is critical, and so something may well  
13 say it very well looks like you have a treatment  
14 effect, and as a single trial, I'll buy you do.

15 That's just not good enough, and I don't  
16 think you thought that through well enough, but that's  
17 okay. All right?

18 ACTING CHAIRMAN BORER: Can I --

19 DR. LIPICKY: And then the last thing  
20 along those same lines was Jay's comment, and you  
21 know, I can't remember the valsartan congestive heart  
22 failure discussions, and I never bothered looking up  
23 the minutes, but you're probably right that the  
24 mistake that was made that you cited was made was  
25 stupid, wasn't it?

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1           You know, I think that that was a bad  
2 bargain. I think if that's the advice you got, we  
3 gave bad advice because to equate the business of  
4 exercise tolerance and morbid mortal, and to consider  
5 them to be equal with respect to coming up with two  
6 positive trials is a stupid bargain retrospectively  
7 and over the course of years.

8           But I know we have done that. Okay? I'm  
9 not denying that. I just say that's very bad advice.  
10 It got you into the pickle you're in, and I'm sorry.

11           Pardon? Well, I understand, but we -- you  
12 know, I'll just acknowledge if that advice was what we  
13 gave and the program was developed on that basis,  
14 that's partly our fault.

15           DR. FLEMING: But, Ray, it's not entirely  
16 clear to me why you're as apologetic as you are. Let  
17 me see if I understand.

18           Basically what you're acknowledging is  
19 that you have a study here with a very large sample  
20 size and duration of follow-up to tell us something  
21 extremely important about morbidity and mortality  
22 primary endpoints and about secondary measures.

23           DR. LIPICKY: Right.

24           DR. FLEMING: And you were looking for, in  
25 a sense, some independent, confirmatory evidence, and

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1 you chose exercise tolerance.

2 DR. LIPICKY: Well, that --

3 DR. FLEMING: Let me go on.

4 And you're apologizing for having  
5 identified exercise tolerance as in any way a relevant  
6 supportive measure that should be weighed in this  
7 decision.

8 And yet the question that I would be  
9 uncertain about is at the same time what we're saying  
10 today is but some secondary measure, such as the  
11 Minnesota living with heart failure measure, dyspnea,  
12 and fatigue were, in essence, being asked do those  
13 things, in fact, elevate this to the same strength of  
14 evidence as two positive trials, and I just wonder a  
15 little bit in retrospect.

16 Those were positive and exercise tolerance  
17 was negative. Would we be having this discussion  
18 if --

19 DR. LIPICKY: Well --

20 DR. FLEMING: -- exercise tolerance was  
21 positive and those were negative.

22 DR. LIPICKY: I hear you, except, you  
23 know, if it had been a positive trial, there would  
24 probably have been -- if it had an effect on exercise  
25 tolerance, it would probably have been a somewhat

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1 difference discussion, but I guess what I was really  
2 saying in shorthand was if a morbid mortal trial were  
3 being done, we should have argued as opposed to doing  
4 hemodynamics and neural humors and all that and an  
5 exercise tolerance trial, which delays things before  
6 you get the other trial started because those precede,  
7 cost money to do them; we should have argued do a real  
8 morbid-mortal trial. It will have another dose in  
9 there at least or double the power, and don't give me  
10 this p of .05 for a morbid-mortal trial because you  
11 get into trouble every time.

12 MR. MacNAB: I think the discussion we  
13 had --

14 ACTING CHAIRMAN BORER: Well, wait, wait.  
15 Let us finish here first.

16 MR. MacNAB: I'm sorry. I just want to --

17 ACTING CHAIRMAN BORER: No, it's --

18 DR. LIPICKY: It's all right. He can  
19 argue.

20 ACTING CHAIRMAN BORER: Well, let's --

21 MR. MacNAB: I don't want to argue.

22 ACTING CHAIRMAN BORER: No, he wants to  
23 support you.

24 Can I ask, Ray? I mean, we've come down  
25 four to four, and we've answered all of the subissues

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1 as best we can, and there's obviously some --

2 DR. LIPICKY: You're fine.

3 ACTING CHAIRMAN BORER: -- concern because  
4 we lack knowledge here and we lack information, but it  
5 seems to me we have some responsibility to provide a  
6 statement about what additional information we would  
7 expect.

8 DR. LIPICKY: No.

9 ACTING CHAIRMAN BORER: Do you want us to  
10 say anything about that?

11 DR. LIPICKY: No, I don't think you have  
12 that responsibility.

13 ACTING CHAIRMAN BORER: Okay.

14 DR. LIPICKY: I think the way I take what  
15 the discussion has said is that as a whole there's a  
16 divided bottom line, that on a whole there is a  
17 divided way of how you look at this and what you  
18 regard as being good stuff and what you regard as  
19 being bad stuff, and that that basically will give us  
20 in the division a reasonable amount of latitude with  
21 respect to what people will be able to say and what  
22 they send to Dr. Temple, and will give Dr. Temple all  
23 of the ability to exercise his judgment.

24 ACTING CHAIRMAN BORER: Okay. Okay.

25 DR. LIPICKY: So it's just fine. I mean,

1 I think you did the right thing, and it's how it came  
2 out. It's a tough problem.

3 ACTING CHAIRMAN BORER: Any other  
4 comments?

5 MR. MacNAB: Really, just to this whole  
6 issue about what was agreed to because I want the  
7 record to be straight, if you really go back to some  
8 time in 1996 the discussion about what had to be done  
9 was about as complex as the discussion that we've had  
10 today because it talked about many things, not just  
11 two trials. Totality of data, mortality, other  
12 endpoints; so I think in fairness to everyone we  
13 shouldn't have an impression that there was some  
14 disagreement or a mistake or you gave us the wrong  
15 advice.

16 DR. LIPICKY: Somebody screwed up.

17 MR. MacNAB: I think if you go back and  
18 look at that, we talked a great deal about totality of  
19 data.

20 DR. NISSEN: I just wanted to say one more  
21 thing, Ray. The reason I made the comment about the  
22 high bar is that if they had treated these patients  
23 the way contemporary --

24 DR. LIPICKY: They should have changed the  
25 standard. That's the only thing.

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1 DR. NISSEN: No, no, no. Just hear me out  
2 for a second. If you take a group of patients -- if  
3 they had taken a group of patients 50 percent of whom  
4 were on ACE inhibitors --

5 DR. LIPICKY: I understand, but that  
6 shouldn't allow you to accept \$100,000 for a million  
7 dollar watch.

8 DR. NISSEN: All right.

9 DR. LIPICKY: Okay?

10 ACTING CHAIRMAN BORER: Okay, but we don't  
11 all agree it's only \$100,000, but it doesn't matter.

12 We've given you the best that we can do,  
13 which is a resounding 50 to 50.

14 Are there any other comments from the  
15 committee? If not, we'll conclude the meeting.

16 (Whereupon, at 3:22 p.m., the Advisory  
17 Committee meeting was concluded.)

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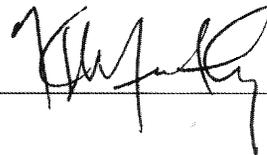
This is to certify that the foregoing transcript in the  
matter of: Meeting of the Cardiovascular and Renal  
Drugs Advisory Committee

Before: DHHS/PHS/FDA/CDER

Date: October 11, 2001

Place: Bethesda, MD

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