

1 who were treated with dobutamine reported
2 significantly more ventricular tachycardia and
3 tachycardia than Natreacor patients.

4 So PRECEDENT was designed as a prospective
5 look at that subgroup. PRECEDENT then was a head-to-
6 head study comparing Natreacor to dobutamine, and the
7 focus of the study was on the relative effects of the
8 two agents on arrhythmogenesis via Holter monitoring.

9 PRECEDENT was ongoing at the time of the
10 NDA review and was not reviewed by the FDA until the
11 recent review of the NDA amendment, which is why I'm
12 showing it to you today. It was not designed to
13 answer specific questions that the agency had.

14 Next slide.

15 The objective of the trial then was to
16 compare the effects of dobutamine to Natreacor on
17 safety endpoints related to arrhythmogenesis and
18 heart rate in typical hospitalized patients with
19 decompensated heart failure.

20 Symptomatic hospitalized patients who
21 could undergo a 24-hour baseline Holter period without
22 being started on these agents were enrolled into the
23 trial. Patients could be treated with IV diuretics or
24 other oral therapies.

25 Toward the end of the baseline Holter

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1 tape, patients were randomized to treatments with
2 dobutamine, which was to be administered at a minimum
3 of five micrograms per kilo per minute, and the two
4 higher doses of Natreacor that were studied in the
5 previous NDA .015 and .03.

6 The randomization was stratified by
7 whether the patients had a known history of
8 ventricular tachycardia.

9 At the time that study drug was to be
10 started, the baseline Holter tape was removed, a
11 treatment Holter tape was placed, and study drug was
12 started, and then a 24-hour Holter tape was obtained
13 during the first 24 hours of treatment with these two
14 agents.

15 This was an open label study. However,
16 the Holter tapes were read at a COR (phonetic) lab at
17 Beth Israel Deaconess Hospital by Dr. Andrew Berger in
18 Boston. Dr. Berger was blinded to treatment group and
19 was blinded to whether the tapes were baseline or
20 treatment tapes.

21 All Holter endpoints then compared the
22 results of the full 24-hour treatment period against
23 each patient's own 24-hour baseline period.

24 The primary endpoints were PVCs,
25 repetitive beats, and average heart rate, and

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1 secondary endpoints included specific ventricular
2 topic events, such as VT, triplets, and couplets.

3 The next slide shows the baseline findings
4 during the 24-hour baseline tape. This is to show you
5 that there was significant ventricular ectopy
6 (phonetic) ranging from 110 to 192 PVBs per hour in
7 these patients, and significant incidence of VT events
8 during this time period, too. Mean heart rate was in
9 the low to mid-80 range, and there were no significant
10 differences between the population, between the
11 treatment group. Sorry.

12 Okay. Next slide shows the effect during
13 the 24-hour treatment period, and during this period
14 all measures of ventricular ectopy were significantly
15 increased with dobutamine compared to both doses of
16 Natreacor. So I'm only showing here the change in VT
17 because PVCs, couplets, triplets, they all go in the
18 same direction.

19 So during the first 24 hours of treatment,
20 dobutamine patients experienced the mean increase of
21 48 episodes of VT from baseline compared to actually
22 a significant decrease in the Natreacor, in the .015
23 Natreacor group from their own baseline tapes, and a
24 neutral effect at the higher dose.

25 The average heart rate during this entire

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1 24-hour treatment tape was increase by a mean of five
2 beats per minute compared to the baseline tape, and
3 the two Natreacor doses had a neutral effect, and all
4 of these, both of these endpoints were statistically
5 significant against both doses of Natreacor.

6 The last slide I'll show you from this
7 trial is that we applied existing pro arrhythmia
8 criteria to assess whether these increase in ectopy
9 were actually pro arrhythmia because there's such
10 variability of ectopy in this patient population.
11 There are no existing pro arrhythmia criteria for
12 heart failure specifically. So we applied these two
13 criteria that have been developed for anti-arrhythmic
14 drugs.

15 The relevant criteria requires that during
16 the evaluation period a patient having fourfold
17 increase in PVCs or the new onset of sustained VT, and
18 you see that 23 percent of the dobutamine patients had
19 at least a fourfold increase in ventricular ectopy
20 versus four percent or zero percent of the two
21 Natreacor doses, and these results were highly
22 statistically significant.

23 We also applied the CAPS criteria, which
24 was much more strict, requiring a tenfold or 1,000
25 percent increase in ventricular ectopy, and you see

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1 here that the dobutamine patients -- that ten percent
2 of the dobutamine patients had a tenfold increase in
3 ectopy, whereas no Natreacor patient experienced that,
4 and these data, again, were significant.

5 Okay. So in conclusion, based on the
6 efficacy and safety data presented here today, Scios
7 is recommending that the VMAC dosing regimen be the
8 standard dosing regimen for Natreacor. Based on the
9 VMAC trial, Natreacor is better tolerated than
10 nitroglycerine in the short term, and there's no clear
11 evidence of any long-term adverse sequelae compared to
12 nitroglycerine.

13 Symptomatic hypotension occurred with
14 similar incidence and severity and the maximum effects
15 on blood pressure were also similar between the two
16 agents. Natreacor does have a longer half-life than
17 nitroglycerine and does have a slower offset of effect
18 on blood pressure.

19 Symptoms associated with hypotension may
20 last longer than with nitroglycerine. However, there
21 were no differences in the severity of the events or
22 in the need for interventions.

23 The PRECEDENT study finally confirmed once
24 again that Natreacor is not arrhythmogenic and that
25 compared to a low to moderate dose of dobutamine,

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1 significantly more arrhythmias were caused by
2 dobutamine.

3 Last.

4 So you've seen this list a few times
5 today. We've gone through each item point by point.
6 We met the recommendations. We provided data to
7 address the concerns. Most importantly, your
8 consideration for the approval of Natreacor can now be
9 done with comparative safety data compared to the most
10 commonly used inotrope and comparative efficacy and
11 safety data compared to a commonly used IV
12 vasodilator.

13 Thank you for your attention.

14 CHAIRMAN PACKER: Okay. We'll open it up
15 for discussion. Ileana, do you want to start?

16 DR. PINA: Thank you.

17 That was very logically and well
18 presented.

19 I want to go to the hypotension issue
20 because that was something that was also brought up
21 during the original meeting here two years ago. If I
22 have a patient that I give a pre-load reducer, to
23 quote Dr. Young here, and they drop their blood
24 pressure, the first thing I think about is maybe their
25 volume. They're getting volume depleted. Maybe I've

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1 over diuresed them and it's time to give them some
2 volume.

3 That doesn't seem to be the case here
4 because I don't see diuresis happening. So if you
5 were going to give advice to a physician who's using
6 this drug who now we know what Jim would say about
7 dosing, and the patient gets hypotensive, what are
8 they to do?

9 DR. HORTON: If a patient becomes
10 hypotensive, the recommendations would be to
11 discontinue the agent until symptoms resolve and until
12 blood pressure stabilizes.

13 Now, in some cases, heart failure
14 specialists are comfortable with the idea of
15 decreasing the dose, especially if the patient maybe
16 has -- their blood pressure has just gone down, but
17 they're not considered hypotensive, and that has
18 actually been done on a number of patients in the
19 trial, and I would say that without symptoms that that
20 would be an acceptable way to address the dose as
21 well.

22 DR. PINA: And you would say that the
23 effects would last how many ours?

24 DR. HORTON: Well, the effects vary. The
25 blood pressure effects begin to come up within 15 to

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1 30 minutes, and appear to come up to where they're
2 going to go, which is basically where you'd want them
3 to be at approximately 60 minutes. Okay?

4 But the increase in blood pressure occurs
5 within the first 15 minutes, although the mean
6 increases that you observed there were small, only
7 four millimeters of mercury.

8 The duration of hypotension varies from 30
9 minutes to five hours, depending. It's kind of hard.
10 You have to really look at each case individually
11 because they're mild cases. Some are moderate. It's
12 helpful to look at the blood pressures during those
13 events.

14 DR. PINA: Following up with the question
15 of the volume issue, do you have any data to show that
16 the patients that did get the rather more severe
17 hypotension, in fact, had gotten more diuretics, in
18 fact, had diuresed more? Do you have that data?

19 DR. HORTON: No, we don't. We're not able
20 to actually show that in VMAC because there were so
21 few events. When you look at it within those events,
22 there doesn't appear to be a differences.

23 DR. PINA: All right. Let me go then to
24 the creatinine issue, which was another issue that had
25 been brought here. Do you feel that the creatinine

1 increase is another dose related secondary effect or
2 side effect?

3 It doesn't seem to be related to the blood
4 pressure.

5 DR. HORTON: Right. That's right.

6 DR. PINA: So what is happening at the
7 kidney? And is this dose related?

8 DR. HORTON: Right. That was definitely
9 clearly demonstrated in VMAC that it doesn't appear to
10 be related to hypotension when hypotension is
11 developing at the .01 dose. Okay?

12 I think that it is dose related, and it's
13 not entirely dose related, meaning that if you ever
14 get .015 or .03, you'll have an increased risk. Maybe
15 that is the case, but what we're only able to show
16 here is that when you start Natrecor at .015 or at
17 .03, there is a dose related incidence of increases in
18 creatinine compared to starting Natrecor at .01.
19 Okay?

20 When you go up on the dose of Natrecor,
21 having already tolerated the .01 dose, at least in the
22 few patients from the VMAC trial that did that, there
23 doesn't appear to be an association. But at the
24 higher doses, I think it's related to hypertension.
25 The tables that I showed you that showed you mild

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1 increases in creatinine that resolved over time and
2 more patients who met the increased creatinine
3 criteria were in patients who had developed
4 symptomatic hypertension with the .015 and the .03
5 dose.

6 DR. PINA: And the second part of my
7 question is: what's happening in the kidney? What is
8 the effect of Natrecor in the kidney vasculatures? It
9 is pre-glomerulus, post-glomerulus?

10 DR. HORTON: Well, that's a very good
11 question, and it's complicated because it's
12 complicated by pre-load as you're indicating. It's
13 also complicated by the direct effects of the
14 natriuretic peptides, which we know to be a
15 vasodilatory effect on the afferent of renal
16 circulation and a vasoconstrictive effect on the
17 efferent system.

18 So there should be an increase in CFR and
19 renal blood flow, and I'm not here to claim that
20 because we didn't do any of that in these trials and
21 in this particular patient population, although
22 there's a huge literature behind that which you can
23 look at.

24 But it may be the case that there is a
25 mild diuretic and a natriuretic effect. As long as

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1 you're not decreasing pre-load too low, and then any
2 positive effects may be abrogated by too large of an
3 effect on pre-loaded cell.

4 It's purely speculative because we haven't
5 looked at it in a nice, controlled trial.

6 DR. PINA: One last question or something
7 that you didn't bring up and we didn't see in VMAC,
8 but we saw in the other studies, and I think it's in
9 the PRECEDENT trial as well, and that's the lack of a
10 tachycardiac response to the blood pressure drop.

11 And I take care of enough heart failure
12 patients to know that they don't always have a nice
13 tachycardiac response to vasodilators, but I mean, it
14 does seem to be rather prominent. Why is that? Do
15 you have a mechanism?

16 DR. HORTON: You know, when we looked at
17 that in VMAC, it actually is very similar to what you
18 see with nitroglycerine in that -- in fact, when you
19 look at the patients -- let me just bring up that
20 slide.

21 DR. PINA: No, I realize that it's very
22 similar to nitroglycerine in VMAC, that you were also
23 dealing with the lowest infusion doses that you've
24 done in any of the other trials, but at the higher
25 infusion doses and at the doses that you used in

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1 PRECEDENT, which are more similar to your 325, 326
2 dosing, there was still no evidence of that
3 tachycardiac response even at the lowest blood
4 pressure.

5 And I wonder if you know scientifically
6 what the mechanism of that is, aside from saying that
7 heart failure patients don't respond as well.

8 DR. HORTON: Right. I don't know the
9 answer based on pure physiologic knowledge. I do know
10 that these patients, especially these days are on more
11 and more beta blockers, which may affect that as well.

12 DR. PINA: Are you aware of any data in
13 the atrial natriuretic peptide or feral (phonetic)
14 receptor resetting in animal models? Have you seen
15 that with DNP?

16 DR. HORTON: I am not aware of that.

17 DR. PINA: I'll be happy to hear from
18 anybody else

19 DR. HORTON: I don't know if anybody else
20 here. I don't know if any of the panel members are
21 aware of that. I'm not aware of that.

22 CHAIRMAN PACKER: Okay. Jeff and then
23 Marv.

24 DR. BORER: Ileana has, as I would have
25 expected, hit all of the key points that I think need

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1 to be hit here. I'd like to follow up the points she
2 made with some other questions.

3 You suggested you wanted to write a label
4 for this drug, assuming that it's approvable, that
5 follows the VMAC dosing regiment, but the VMAC dosing
6 regimen allows up-titration.

7 Now, I noted, as you said, that the
8 problems you have were in people by and large who
9 started on a higher dose rather than who were titrated
10 up to it, but then, again, statistical significance
11 notwithstanding, the events we're talking about are
12 very infrequent and were studied in very small
13 populations, and there really is no way to talk about
14 statistically significant differences between one
15 management strategy and another.

16 There does, however, seem to be a tendency
17 to more renal problems as the dose goes up for
18 whatever the mechanism is, and we just said we don't
19 know it.

20 So what would you think about the need to
21 limit the top dose in the label, and as a corollary to
22 that, if you believe that there might be some need at
23 this point before there is additional data and
24 assuming the drug is approvable with the data we have,
25 if you believe it would be reasonable to limit the top

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1 dose in the label because problems seem to occur above
2 that, and we don't know why and we don't know how
3 often they do, what if somebody needs more
4 vasodilatation than you can get with this drug?

5 Do you have any information specifically
6 about the combined effects of, say, nitroglycerine,
7 which as far as I can tell was studied only as a
8 comparator, or nitroprusside or what have you on top
9 of this drug, if it was believed by the individual
10 physician that more vasodilatation might be helpful?

11 Do we know anything about that? I'm going
12 to give you this whole laundry list, and then you'll
13 have to see if you can remember any of it, and then
14 answer. The --

15 CHAIRMAN PACKER: Do you want to give her
16 a chance?

17 DR. BORER: Yeah, I'll give you a chance,
18 and then we'll resume.

19 DR. HORTON: Thank you for allowing me to
20 think a little bit here.

21 First, just with the first part where you
22 were saying we don't think we know why there were
23 renal effects, renal effects with the higher doses.
24 I think we do know that. I think what I was trying to
25 show you there was that they were associated with

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1 symptomatic hypertension.

2 So I think if you can -- well, we think
3 that we've been able to do at VMAC is devise a
4 prescription for increasing the dose that would
5 prevent symptomatic hypertension in the few patients
6 who may benefit from the dose dependent hemodynamic
7 effects.

8 But clearly it's a benefit to risk
9 assessment. If you can do that in a way that is safer
10 than has been previously describe in the way the drug
11 has been administered, I think that's the way to go.

12 DR. BORER: Can I just interrupt you? I'm
13 going to say something that may sound sacrilegious
14 sitting on this panel here. I know a fair amount or
15 I should say the group here, and certainly the FDA,
16 knows a fair amount about pharmacologic effects of
17 drugs. Personally I'm not sure, however, how any of
18 those really specifically relates to clinical benefit.
19 I just know that the two seem to go together.

20 And when you talk about negative effects,
21 I think that that ignorance of mine is even greater.
22 I don't think you've shown in any defensible way that
23 the renal effects we've seen clearly are related to
24 hypotension, and that hypotension is the reason they
25 occur.

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1 It may be a contributor. It may be the
2 reason, but, you know, I don't think we know that
3 much, and therefore, I would challenge a statement
4 that says we know that it's hypotension and we have a
5 regimen to deal with hypotension. Therefore, no renal
6 problems.

7 I mean, what would you say to that?

8 DR. HORTON: Well, I think the best way to
9 answer the question is with data from the clinical
10 trial, and otherwise I couldn't speculate. So, you
11 know, we tried to look at those patients that had the
12 symptomatic hypertension, and that is clearly where
13 the majority of those events occurred.

14 So that's what we know.

15 DR. LINDENFELD: We've got an analysis
16 here that we just got at the last minute that suggests
17 there's no relationship between the renal function and
18 hypotension. I don't know if everybody saw this one.

19 DR. HORTON: Is that from the VMAC trial?

20 DR. LINDENFELD: I mean, Abe may want to
21 comment on this.

22 DR. HORTON: Yeah, let me just back up a
23 second because what I'm saying is that I agree with
24 that, but with the VMAC dose there is no association
25 of increases in creatinine with symptomatic

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1 hypotension. Okay?

2 The question is whether any increases in
3 creatinine that have been described in PRECEDENT trial
4 and other trials were dose dependent and why that
5 might be.

6 And they are dose dependent, and they
7 appear to be associated with hypotension, but it may
8 be more important since the standard recommended dose
9 would be the VMAC dose, is that there is no
10 association, and the few patients who develop
11 hypertension, there were no significant increases in
12 creatinine.

13 DR. BORER: But the VMAC dose is a
14 starting -- I mean, when you say the VMAC dose, are
15 you talking about .01 and we stop there or is it .01
16 with the capacity to titrate up because if the latter,
17 then the VMAC dose is just a starting point, and
18 people can go as high as they need to go, and we don't
19 know what happens there.

20 DR. HORTON: Right. Natrecor is not going
21 to be presented as a titratable drug per se. We think
22 that the VMAC dose should be the standard recommended
23 dose, and that it would be a safe and effective dose
24 in most patients.

25 DR. BORER: Okay.

1 DR. HORTON: In the few patients for whom
2 you all think you'd like to have better hemodynamic
3 effects, Natrecor is also an agent that you can use
4 for that, and what we've done is to simply provide you
5 with a prescription for how to do that so that you
6 don't do that too quickly and that you don't go up to
7 .2 micrograms per kilo per minute. We think the
8 maximum dose should be .03.

9 DR. BORER: Yeah, admitting that we don't
10 really know what happens kidney-wise at the high doses
11 really yet.

12 DR. HORTON: Right.

13 DR. BORER: Not that it necessarily does
14 bad things.

15 One more issue here. We're going to get
16 into this in the questions, and I don't want to make
17 much of it. There was short-term administration of
18 the drug. It's had to believe plausibly that what
19 happens six months later has anything to do with a few
20 hours of the drug six months before.

21 On the other hand, you know, the argument
22 for giving short-term medication without mortality
23 trials which are impossible to do is the chain of
24 survival argument, and if you believe that, and I do,
25 then you have to at least consider the possibility of

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1 chain of non-survival.

2 And, you know, there was no statistically
3 significant difference in the survival over six months
4 of the people who got the Natrecor versus the people
5 who got other agents, but the curves really weren't
6 superimposable. They were different by a little bit,
7 and they were different throughout the entire duration
8 of the follow-up.

9 Now, again, please understand I'm not
10 trying to draw firm conclusions from those kinds of
11 data, but you know, you see an increase in the number
12 of people who go on dialysis, a small increase, but an
13 increase. You see the increase in mortality. The
14 length of stay data were of interest to me in that,
15 again, don't make much of this, but, you know,
16 everything is sort of going in the same direction.

17 The p value of .164 for length of stays
18 that nominally have the same median value, which says
19 to me that the median isn't adequately describing the
20 data because the p value of .164 seems to be tending
21 in a certain direction. I'm assuming that that
22 tendency is in the direction of longer stay for
23 Natrecor. It could be exactly wrong and you'll tell
24 me.

25 So what do you think, if anything, that

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1 we're learning from these little smidgens of data that
2 suggest that the people who got Natreacor somehow in
3 some global sense maybe did just a teeny little bit
4 worse than the people you didn't get it?

5 DR. HORTON: The short answer to the
6 length of stay question is I don't know. We tried to
7 look for reasons for that. Clearly the dobutamine
8 patient population was sicker. That tended to carry
9 the increase. It's true that there's still a p value
10 of .1. There's no question. The means are not the
11 same as the medians, which is why we presented the
12 medians. The data are skewed. We did not correct for
13 or exclude any patients whose length of stay might
14 have -- this trial is just not large enough to look at
15 that.

16 But it's not an excuse. We wanted to look
17 to see if there was any real reason by this might
18 happen, and I think the answer to that is to look at
19 the overall safety profile, but I think my conclusions
20 would be different from yours.

21 You mentioned more patients with new
22 onset. There's not an increase in the need for
23 dialysis, nor in myocardial infarction, stroke, nor
24 increases in creatinine. So --

25 DR. BORER: Not in VMAC, but in your

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1 totality of data, it was three percent versus two
2 percent, small, but again, I'm looking at a lot of
3 little pieces that all go up.

4 DR. HORTON: Right, but the length of stay
5 was from VMAC where there were no differences. So,
6 you know, I'm just saying I don't know what the answer
7 is.

8 DR. BORER: Okay.

9 CHAIRMAN PACKER: Just to clarify the
10 mortality issue that Jeff just brought up, can you
11 tell us how many patients were in the analysis of six-
12 month mortality?

13 DR. HORTON: Yes, I can tell you that.
14 You mean how many patients were not excluded?

15 CHAIRMAN PACKER: How many patients were
16 in the analysis at the very beginning of the analysis.
17 In other words, how many patients were included in the
18 analysis?

19 DR. HORTON: Are you talking about in the
20 ISS population?

21 CHAIRMAN PACKER: Yes.

22 DR. HORTON: The big Kaplan-Meier group?

23 CHAIRMAN PACKER: That were in your
24 Kaplan-Meier curve.

25 DR. HORTON: Right. So that's 724

1 Natrecor patients and 443 control patients.

2 CHAIRMAN PACKER: Okay, and how many
3 patients had follow-up at six months?

4 DR. HORTON: Ninety-seven percent.

5 CHAIRMAN PACKER: Ninety-seven percent?

6 DR. HORTON: Yes.

7 CHAIRMAN PACKER: Okay. All randomized
8 patients were included in that analysis?

9 DR. HORTON: Yes.

10 CHAIRMAN PACKER: My understanding --

11 DR. HORTON: Sorry. All randomized and
12 treated patients were included in that analysis.

13 CHAIRMAN PACKER: That's not the same as
14 all randomized.

15 DR. HORTON: No, it's not.

16 CHAIRMAN PACKER: That's actually
17 important here because the reason that one randomizes
18 is to insure balance at baseline, and there were nine
19 patients randomized in VMAC that you excluded, that
20 did not get any randomized treatment, which you
21 excluded from the analysis of efficacy because they
22 didn't get randomized therapy.

23 But you also exclude them from the
24 analysis of safety. Now, one can understand why you
25 might want to do that for things like hypotension or

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1 creatinine or other reasons, but it's hard to
2 understand why you would do that for mortality since
3 the purpose of randomization is to insure balance, and
4 that means to insure that the patients were relatively
5 equal risk.

6 And the only reason for raising this is a
7 concern, is of the nine patients that were excluded
8 from the analysis of mortality in VMAC, and maybe
9 there were others randomized in other trials that
10 didn't get treatment that were also excluded from the
11 analysis, of the nine patients that were excluded, two
12 died within 24 hours of randomization, and both were
13 randomized to Natrecor.

14 DR. HORTON: Right. I do have an intent
15 to treat analysis if you'd like to see that.

16 CHAIRMAN PACKER: I would like to see
17 that.

18 DR. HORTON: It's slide 427.

19 So when all of the data are added in, it's
20 a six month mortality of 21 versus 25.2 percent versus
21 21.5, I believe, and 25.1 percent. So it's very
22 similar.

23 CHAIRMAN PACKER: Let me see if you can
24 help us out here. At one month there are --

25 DR. HORTON: There's a typo there.

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1 CHAIRMAN PACKER: The mortality, it isn't
2 quite -- can you help us out on this?

3 DR. HORTON: Yeah. It's 5.5 percent with
4 nitroglycerine versus 8.6 percent. That's a typo.

5 CHAIRMAN PACKER: So 5.5 percent
6 nitroglycerine, 8.6 percent on Natrecor. The
7 confidence intervals are stated, and at six months
8 it's 21, 22.6, and 25.2. This is all randomized?

9 DR. HORTON: Yes. So this differs in the
10 randomized and not treated group. The six-month
11 mortality is 20.8 versus 25.1.

12 CHAIRMAN PACKER: You previously suggested
13 that it may be an imbalance in baseline use of
14 inotropes.

15 DR. HORTON: Yes.

16 CHAIRMAN PACKER: Could explain some of
17 this. You took out the patients on inotropes in you
18 hospitalization analysis, but we didn't see how that
19 might have influenced an analysis on mortality. Do
20 you have that?

21 DR. HORTON: Yes, we do have that, and
22 that is slide 428, and it does appear that dobutamine
23 does affect both short term and long term. Patients
24 who are on ongoing dobutamine when study drug was
25 added does affect both short-term and long-term

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1 mortality. What you see here in the nitroglycerine
2 group, for example is that --

3 CHAIRMAN PACKER: I actually wanted the
4 analysis without dobutamine and dopamine.

5 DR. HORTON: Yes. That's the bottom part
6 here. This is with them excluded. The six-month data
7 is 19.4 and 21.5 percent. That's excluding patients
8 who are on dobutamine, and this is the majority of the
9 patients still since there were so few of them, but
10 they really do drive the mortality effect.

11 CHAIRMAN PACKER: And the confidence
12 intervals around the effect at one and six months, do
13 you have those?

14 DR. HORTON: We have them. We'll have to
15 get them written for you. We do have them.

16 CHAIRMAN PACKER: Steve?

17 DR. NISSEN: Yeah, I wonder if you could
18 put up slide 112. I want to talk with you about that.
19 the question I have relates to this issue of what I
20 think is a somewhat narrow therapeutic index for this
21 drug, and I was very struck by the fact that a dose
22 increase from .01 to .015 is really associated with
23 about a doubling of the risk of symptomatic
24 hypotension, and then there's even another large
25 increase when the dose gets higher.

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1 And so I had several questions that relate
2 to this that I think are important, and let me make
3 sure you understand why I am asking this question.

4 You know, one of the reasons that IV
5 nitroglycerine is very popular is that it has a very
6 wide range of doses. We give as little as ten
7 micrograms and I've certainly given as much a 1,000 or
8 more micrograms. So it's a drug that we know we can
9 use over a very broad range.

10 So whenever I see a drug with a narrow
11 therapeutic index, I worry. And so the next question
12 I wanted to ask is given the fact that I assume you
13 agree with me that it is a narrow therapeutic index,
14 what do we know about the pharmacokinetics of this
15 drug?

16 For example, how exactly is it metabolized
17 or eliminated? What kinds of patients might we have
18 to worry about as clinicians that might accumulate the
19 drug at greater levels because if presumably a 50
20 percent increase in dose is associated with a big
21 increase in risk of hypotension, then I've got to know
22 more about the variability in the kinetics here to
23 have comfort about this, and I wonder if you could
24 address that for me.

25 DR. HORTON: Yeah, I'd be happy to.

1 First, you know, during the 24 hour period in the
2 adjustable dose here -- now there were a few patients,
3 but the mean dose in that group was 0.013. So it's
4 somewhere in between the .01 dose and the .015. The
5 difference here is that those patients only went up
6 when their blood pressure was at least 100 and they
7 had tolerated the earlier doses.

8 That's not completely extrapolatable, but
9 it's useful information because these two doses, which
10 are, you know, 50 percent and 300 percent higher were
11 actually started at those doses, and you know, I think
12 that's critical, and it's going to be essential for
13 people to start at the lower dose.

14 Your comment about a narrow therapeutic
15 window is one way to look at it. The other way to
16 look at it is that this agent has a more predictable
17 effect, and there's a lot more variability in response
18 with the other agents.

19 So it just depends on what you're actually
20 looking for, and with regard to the question about
21 metabolism, the drug is metabolized by two pathways.
22 The first is that it's a receptor based mechanism of
23 action, and it's also receptor based clearance, at
24 least one part of it, and that there's a clearance
25 receptor, which is present ubiquitously throughout the

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1 body.

2 The other -- and at that point the peptide
3 is internalized and hydrolyzed and then the receptor
4 is then recycled back to the surface.

5 The other way that it's metabolized is by
6 neutral endopeptidases, which occur in the
7 intravascular lumen, again, throughout the whole body
8 and very small of it is excreted by renal filtration.

9 So the nice thing about that is that no
10 single organ failure would lead to you having to do a
11 dose adjustment or worry about any particular safety
12 concern because of the lack of clearance.

13 DR. NISSEN: The 18-minute half-life,
14 what's the standard deviation around that?

15 DR. HORTON: Do you know that?

16 We have our pharmacokineticist here.

17 Can you turn on the microphone, please?

18 DR. SANBOL: Yeah, Nancy Sanbol,
19 University of California, San Francisco.

20 And I worked up the pharmacokinetics and
21 did the PK/PD modeling.

22 Of course we didn't do it for the VMAC
23 study. They didn't collect concentrations here. So
24 I don't -- wasn't actually ready to answer your
25 question, but I do have some recollection from the

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1 prior data, and my recollection is it's a modest
2 variability. It's not bit. It's not necessarily
3 small, but it's modest, which is probably in the order
4 of about 30 percent in between subjects.

5 DR. NISSEN: All right. So we don't have
6 hard data we can look at today about --

7 DR. SANBOL: No. We were expecting more
8 to focus on a VMAC. So that something that wasn't
9 done here.

10 DR. NISSEN: Go ahead. I want to come
11 back when you're done.

12 CHAIRMAN PACKER: Yeah, I just want to
13 follow up and then Steve will go on. Eighteen minute
14 half-life in terms of residence in the blood stream,
15 but that seems to have relatively little relation to
16 the pharmacodynamic effect of the drug.

17 Nitroglycerine has a 19 minute half-life.
18 You know, the --

19 DR. SANBOL: I thought nitroglycerine's
20 half-life was much shorter than that. So I can't
21 confirm that. I believe it is quite a bit shorter.

22 CHAIRMAN PACKER: That's the
23 pharmacodynamic effect. I'm sorry. You're quite
24 right.

25 But anyway, what is the relation between

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1 the pharmacokinetic information you have and the
2 duration of effect of the drug?

3 DR. SANBOL: Yes. In fact, there is a
4 delay between, say, the peak concentration and the
5 peak effect, which is common with many drugs, and we
6 have seen this phenomenon here with Natrecor as well,
7 which accounts for the fact that when you get
8 concentrations immediately that are equivalent to what
9 you would see at steady state, you're not seeing the
10 peak effect immediately. You have to get much higher
11 concentrations that what you see at steady state to
12 get the equivalent effect early on, and that's why
13 this higher bolus dose was necessary.

14 And likewise, when you take the drug away
15 it takes more than the half-lives to account for the
16 diminution in effect, and we can incorporate that.
17 This is, you know, something we see all the time with
18 drugs. We incorporate it into our modeling.

19 DR. LIPICKY: Do you happen to remember
20 what the time source of that lag time is?

21 DR. SANBOL: I believe it's around 15 --

22 DR. LIPICKY: Twenty minutes or half an
23 hour?

24 DR. SANBOL: Maybe between 15 and 30
25 minutes.

1 DR. NISSEN: Well, I think we have some
2 very good sense of this from the duration of the
3 hypotensive episodes. I mean, you know, the duration
4 of the hypotensive episodes is rather consistent with
5 what we would expect.

6 I mean, you know, you look for, you know,
7 give half-lives for a drug to, you know, be
8 eliminated, and an 18 minute duration, five half-lives
9 is 90 minutes. In about 60 minutes, you know, most of
10 the hypotension is over.

11 So I think --

12 DR. KONSTAM: But, Steve --

13 DR. SANBOL: You know, if you're
14 interested, I can get an exact half-life of that delay
15 effect.

16 CHAIRMAN PACKER: Why don't we get that
17 information over the lunch break?

18 DR. SANBOL: Yes, okay.

19 CHAIRMAN PACKER: And just come back with
20 it.

21 DR. KONSTAM: But, Steve, you're not quite
22 right. I mean, seven of the patients just in terms of
23 the duration of symptomatic hypotension, seven of the
24 patients continued to have symptomatic hypotension
25 after two hours.

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1 DR. LIPICKY: Well, that depends on where
2 they went to. That depends on what the blood pressure
3 went down to.

4 DR. NISSEN: Marvin, that's exactly why I
5 asked the question about the pharmacokinetics.
6 Because if it's 18 minutes and there's a wide standard
7 deviation, and suppose there are some patients that
8 have a 30 minute half-life. Well, then five half-
9 lives for those patients is a lot longer.

10 And so the reason I need to understand
11 this is it helps me understand the safety issue.

12 DR. LIPICKY: Can I see if I can try to
13 address that? The duration of symptomatic hypotension
14 depends on how low the blood pressure goes. So that
15 it could last ten days if it went low enough, and it
16 would still have the same time course of return if you
17 didn't do irreversible harm that the pharmacokinetic
18 parameters would give you.

19 So the duration of symptomatic hypotension
20 doesn't tell you or you can't look at the
21 pharmacokinetics and get the direction of symptomatic
22 hypotension.

23 From the slope of return you can, and
24 there the time course for it to come back from
25 wherever it is roughly is in the 20 minute range, but

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1 there's a lag so that there's a time from the peak
2 plasma concentration until the time of the peak
3 effect.

4 But the time course of development of the
5 anti-hypertensive thing is consistent with the --

6 DR. KONSTAM: Well, Ray, if you look at
7 the slide that's their slide 106 that looks at --
8 there's no placebo. So it's nitroglycerine versus
9 Natrecor. At 120 minutes, the nitroglycerine group
10 has increased with symptomatic hypotension, has
11 increased their blood pressure by 26, whereas the
12 Natrecor group is 16.7.

13 Now, I take that to mean that, you know,
14 there's still something going on at two hours.

15 DR. HORTON: It's just the other thing to
16 remember though is that the nitroglycerine group
17 started out at about nine millimeters of mercury
18 higher. So you would expect no blood pressure to come
19 up higher.

20 MR. KONSTAM: I don't know. These are the
21 deltas.

22 DR. LIPICKY: No, if you look at that
23 table, 106, it looks like in an hour to an hour and a
24 half the Natrecor people are back to -- you know, are
25 at steady state, so to speak, and that's consistent

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1 with a half life of 20 minutes. Okay?

2 DR. NISSEN: If I may, okay, I think there
3 are going to be other people with questions about
4 this. So I'm really just kind of leading off with it,
5 but there are two reasons why I need to get a better
6 handle on this. One is that I think it's likely that
7 the drug is going to be used not exclusively in the
8 intensive care unit. So in a non-monitored, you know,
9 non-hemodynamically monitored setting where patients
10 are perhaps not watched as closely.

11 And I've been around long enough to know
12 that drugs given by infusion, that there is a
13 relatively high miscalculation and error rate, you
14 know, in busy hospitals. People calculate doses wrong
15 or maybe in hooking up the pump the nurse accidentally
16 gives a little more drug.

17 And so this issue of the therapeutic index
18 to me is very important because if something goes
19 wrong, how quickly can the patient rebound? So that's
20 what I'm trying to drive at here with this.

21 There is one other issue I want to put on
22 the table for everybody on the panel, and that is how
23 acute intravenous vasodilators are used to treat acute
24 congestive heart failure. Now, not everybody probably
25 does it the same, but I'll tell you how I do it, is I

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1 will give a drug like nitroglycerine to get a patient
2 out of the worst phase of acute congestive heart
3 failure.

4 I would much more commonly -- probably 20
5 of those patients will get nitroprusside for every one
6 that gets nitroglycerine, but that's another point
7 entirely, but if I use nitroglycerine, I'm going to
8 put them on it to get them better acutely, and then
9 when they're better, I'm going to give them an ACE
10 inhibitor.

11 And when the ACE inhibitor kicks in, and
12 it often kicks in like a bolt of lightning 20 or 30
13 minutes later, I quickly turn off the infused drug
14 because I know if I don't move quickly, I'm going to
15 produce a lot of hypotension, and I don't think I can
16 do that with this drug, and it makes me nervous.

17 Reassure me somehow that we're not going
18 to -- that when this gets out in the community, people
19 get put on the infusion, somebody gives them a pop of
20 an ACE inhibitor and their blood pressure goes down
21 and they stay down.

22 CHAIRMAN PACKER: Dr. Horton, let me ask
23 you to do this because I'm getting waves on this side
24 of the room to remind me that if we don't break now,
25 the cafeteria closes at two o'clock.

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1 So, Steve, I'm going to ask you to ask
2 that question one more time after the break.

3 DR. NISSEN: No problem.

4 CHAIRMAN PACKER: And we will come back
5 here and start again at -- we'll try at 2:15,
6 absolutely by 2:30.

7 (Whereupon, at 1:47 p.m., the meeting was
8 recessed for lunch, to reconvene at 2:15 p.m., the
9 same day.)

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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 (2:27 p.m.)

3 CHAIRMAN PACKER: Dr. Nissen was in the
4 middle of asking a question and making a point, and to
5 recreate that perspective, I'll ask him to make a
6 point once more, and we'll continue with the
7 discussion on safety.

8 DR. NISSEN: Okay. I'm going to phrase
9 the question maybe slightly differently, but let me
10 just say that I'm focusing in here on the dual issues
11 of a fairly narrow therapeutic index, and the fact
12 that if hypotension does occur, it's likely to be more
13 protracted than it would be with comparators like
14 nitroglycerine and nitroprusside.

15 And the point I was making, the question
16 I was asking was we have to transition patients from
17 intravenous therapy to oral therapy. It's something
18 that all of us have to do in acute heart failure all
19 the time, and the agent that we most often transition
20 to is an all or none drug. That is, ACE inhibitors
21 have a tendency when you give a dose basically to kick
22 in with great abruptness and maximal effect.

23 And so I want to get your sense of how
24 would we advise physicians about how to transition
25 from intravenous Natreacor to oral ACE inhibitors in

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1 the setting where if you turn off the Natreacor, the
2 effect does not go away for quite some time.

3 DR. HORTON: Right. Thank you.

4 Actually, it's really important to realize
5 that the four percent incidence of symptomatic
6 hypotension is what was described in patients in a
7 population where 60 percent of them were receiving ACE
8 inhibitors. This was 60 percent of the patients were
9 receiving an ACE inhibitor during study drug. Okay?

10 So you could expect that the incidence
11 would be lower if that were the case. The scenario
12 that you described also was one where you were more --
13 it sounded like an intensive care setting where you
14 were using an IV agent and then titrating to an oral
15 agent.

16 And I guess if I was you, I would envision
17 the half-life of the oral agent that you're giving and
18 stop or decrease the IV agent, you know, in concert
19 with you with what you're going to be expecting with
20 your oral agent.

21 But the main thing is that four percent of
22 patients develop symptomatic hypotension, and most of
23 them didn't even require the drug to be discontinued,
24 and the reason for that, we believe, was that the
25 cases were so mild that it just didn't seem necessary.

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1 There are several investigators in the
2 room if you'd like to give a better perspective on
3 that.

4 DR. NISSEN: Okay. That helps some.

5 CHAIRMAN PACKER: Marv, then Ileana.

6 DR. KONSTAM: Okay. You know, first of
7 all, I just wanted to challenge your comment about the
8 predictability of the effect because I don't think
9 we've seen any data regarding predictability. You
10 know, you haven't shown us, I don't think, the
11 distribution of effects across the population.

12 So when you say that your agent has a more
13 predictable hemodynamic effect than nitroglycerine,
14 you know, do you want to comment on that? Because I
15 would really challenge that you've show us that.

16 DR. HORTON: Yeah, and I wasn't trying to
17 say that Natrecor is more predictable than
18 nitroglycerine generally. I was responding to the
19 comment that one might go from ten micrograms per
20 minute to whatever you said, 400 or 1,000. So
21 clearly --

22 DR. NISSEN: At least 1,000.

23 DR. HORTON: So clearly one would only do
24 that with a drug that has a variable response.

25 DR. KONSTAM: Okay. the safety in the

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1 population in the preserved ejection fraction --

2 DR. HORTON: Yes.

3 DR. KONSTAM: -- I have to tell you that's
4 a population that I'd be worried about giving a
5 vasodilator. The numbers of patients obviously is
6 small. One specific question I have for you is you
7 indicated that, if I understand you, that none of the
8 patients with symptomatic hypotension went on to die,
9 and that doesn't seem to be correct.

10 DR. HORTON: None of the patients who
11 developed symptomatic hypotension in the first 24
12 hours was more likely to be due to study drug died
13 during the 30-day period.

14 DR. KONSTAM: Well, there is a patient who
15 had symptomatic hypotension and then died, and if the
16 patient -- according to the text, it's a patient with
17 restrictive myopathy.

18 DR. HORTON: Right. I'm not sure if that
19 was hypotension within the first 24 hours or not.

20 DR. KONSTAM: Well, it was symptomatic
21 hypotension within the first 11 minutes. I mean,
22 according to the narrative, the patient was treated
23 for 11 minutes before the infusion was stopped because
24 of a sudden decrease in blood pressure.

25 DR. HORTON: Right.

1. DR. KONSTAM: And the patient went on.
2 You know, she then got very sick and went on to die at
3 day ten.

4 I mean, I just point that out, what I
5 think is a correction of what you said.

6 DR. HORTON: Hold on.

7 We'll definitely look up that narrative
8 and see what happen and see what --

9 DR. KONSTAM: Do you want the patient
10 number?

11 DR. HORTON: It was a -- yeah, that would
12 be great. It was --

13 DR. KONSTAM: Three, five, seven, five,
14 oh, two.

15 DR. HORTON: Was it a Natrecor treated
16 patient?

17 DR. KONSTAM: Yeah. Three, five, seven,
18 five, oh, two. I mean it's right in the medical
19 reviewer's text. I don't know if the medical reviewer
20 wants to comment on that.

21 CHAIRMAN PACKER: The medical reviewer is
22 not here.

23 DR. KONSTAM: No? Well, so that's just a
24 point of information, , but I think that maybe you
25 could just expand on what we -- I applaud you, by the

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1 way -- I think I applaud you -- for studying patients
2 with preserved ejection fractions. In one sense I
3 applaud you, although, you know, I really worry about
4 getting vasodilators for that population, and I guess
5 I wouldn't want -- you tell me if you disagree with
6 this -- I wouldn't want to extrapolate any safety
7 conception that we have here to patients with
8 preserved ejection fraction as a group to say, well,
9 the safety data that we have applies equally to
10 patients who have preserved ejection fraction.

11 Given this one case, and given, you know,
12 the relatively small number of patients represented in
13 your population, would you agree with that?

14 DR. HORTON: What I've been able to
15 present you with is just the data we have observed in
16 the 65 patients with preserved ejection fraction in
17 this trial.

18 DR. KONSTAM: Now, I understand that, but
19 I just wonder what the conclusion is because my
20 conclusion is not that the drug is safe in people with
21 preserved ejection fractions. I have trouble reaching
22 that conclusion. I admittedly have a bias that it
23 might well not be safe in that population, and I just
24 want to say that.

25 I'm not sure that -- and it' relative to

1 your overall population, it's an extremely small
2 number of patients.

3 DR. HORTON: Yes.

4 DR. KONSTAM: You know, the only other
5 thing, just to go back to the mortality, I have
6 problems with including -- I don't have any problems
7 with looking at the entire data set to try to get a
8 point estimate of the mortality as opposed to any one
9 study. What I do have a problem with though is
10 including the PRECEDENT study in that analysis.

11 You know, we think that dobutamine might
12 well have excess mortality in certain circumstances.
13 You actually document it very beautifully in the
14 PRECEDENT study that dobutamine is pro arrhythmic, and
15 so I have a bid problem with saying I'm going to get
16 a point estimate on the control, you know, the drug
17 versus control effect on mortality and then include a
18 study where the control limb received dobutamine.

19 So I don't know whether you want to show
20 us what the data look like with that study taken out.
21 Is that possible?

22 DR. HORTON: We do have the risk ratio
23 calculated with that study taken out. It's slide 415.

24 CHAIRMAN PACKER: But I'm just wondering,
25 if I might. The vast majority of, I presume, the

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1 mortality data, if you take out PRECEDENT, comes from
2 VMAC not only because of its size, but because VMAC
3 had sicker patients in it than the earlier trial.

4 DR. KONSTAM: Maybe.

5 CHAIRMAN PACKER: I don't know.

6 DR. HORTON: Yeah, I think this gives you
7 a nice look at how the point estimates move around.
8 This, in fact, is the risk ratio, 95 percent
9 confidence intervals. This is what I showed you
10 earlier with a risk ratio of one.

11 If you exclude the PRECEDENT trial, which
12 was the dobutamine trial, the risk ratio goes to 1.1.
13 If you exclude VMAC, it goes to .9.

14 DR. KONSTAM: No, you wouldn't want to
15 exclude VMAC though.

16 DR. HORTON: No, I'm just -- yeah, the
17 answer to your question is this where the risk ratio
18 goes from one to --

19 DR. KONSTAM: So what is it if you just
20 exclude PRECEDENT?

21 DR. HORTON: This one right here. This is
22 325, 326, and 339 combined.

23 CHAIRMAN PACKER: And this is not all
24 randomized, right?

25 DR. HORTON: This is not all randomized.

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1 It's not an intent to treat.

2 CHAIRMAN PACKER: So it would be a little
3 bit more to the right if you included all randomized.

4 DR. HORTON: Probably.

5 DR. KONSTAM: And then what's the upper
6 boundary now, based on the way you said it before?
7 What upper boundary did you give?

8 DR. HORTON: Well, it looks like it's
9 about 1.4 to 1.5. Is that what it looks like to you?

10 DR. KONSTAM: One, point, four to 1.5.

11 DR. HORTON: I'm seeing it from the side.

12 DR. KONSTAM: Okay. You know, the only
13 final point, I share the other panelists' concerns
14 about, you know, clearly understanding the
15 relationship between the PK and the PD information,
16 and I don't know. I'm going to struggle at the end
17 about, for example, what is the appropriate dose to
18 approve based on the fact that the hypotensive effects
19 really start to appear when you get to higher doses.

20 So I don't know, and I'm concerned about
21 that. I wish I understood more about what's going on
22 about why patients -- and maybe Ray thinks I'm wrong
23 about this -- but why patients seem to have protracted
24 hypotension despite -- it seems to me out of
25 proportion to the 18 minute half-life, but maybe it

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1. isn't.

2. But I don't have a question associated
3. with that. I'm just worried about it a little bit.

4. DR. HORTON: I'm going to go back to the
5. blood pressure slide because I think you have to take
6. all of the data in totality, and it really looks like
7. most of the blood pressures are significantly back up
8. to where you want them to be by 60 minutes.

9. I mean, if you look, for example, at the
10. nitroglycerine patients, the blood pressure slide
11. tells you that the blood pressure is back up within 15
12. minutes with nitroglycerine, but yet there are three
13. patients whose episode lasts for three hours.

14. So there's lots of things going on with
15. CON meds. and hydration status and things like that.
16. So --

17. DR. KONSTAM: Yeah, I mean, I've got to
18. tell you my reaction. I mean I am fine with it. I
19. don't have a huge problem with it at the doses, at the
20. .01 dose. Where I start to -- and maybe Steve is
21. really making the same point. When you get to the
22. higher doses and if you're going to ask for an
23. approval range at those higher doses, and then, you
24. know, I think Steve nicely pointed out, you know, what
25. do we know about drug-drug interactions or the

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1 variation in plasma half life, and so I think that's
2 where I'm going to begin to get worried, particularly
3 when we talk about approving it at higher doses.

4 DR. NISSEN: Marv, can I give you a
5 hypothesis on the hypotension? Hypotension tends to
6 be self-reinforcing. Once you've been hypotensive for
7 a while, you know, you tend to get ischemic and other
8 things happen, and I think that that almost certainly
9 is why there's a difference between the PK and PD
10 effects.

11 I'm just guessing at it, but I'll bet you
12 that's right because, you know, hypotension that's
13 over in ten minutes, it's fine. But if it lasts for
14 a while, then people start to stay down for a while
15 even after the drug is gone.

16 DR. HORTON: I do have the answer to your
17 question about the patient that you described earlier.
18 That patient didn't have symptomatic hypotension.
19 They had asymptomatic hypotension.

20 DR. KONSTAM: Huh?

21 DR. HORTON: That patient was not
22 symptomatic. They had a decrease in blood pressure.

23 DR. KONSTAM: She was treated for 11
24 minutes before the infusion was stopped because of a
25 sudden decrease in blood pressure. The blood pressure

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1 dropped from 94 over 47 to 70 over 25, and you call
2 that a not symptomatic hypotension?

3 DR. HORTON: It's not my determination.
4 It's what the investigator reported.

5 DR. KONSTAM: Well, now you're worrying
6 me. That doesn't make me happy because now I'm
7 worried that there are other patients in there who had
8 really important hypotension that just weren't called
9 symptomatic hypotension. That sounds pretty important
10 to me, that one.

11 DR. HORTON: That's how the -- we followed
12 up on this. This was a death. This was a serious
13 adverse event. We clearly collected all of the
14 information on this patient, and it was, in fact, true
15 that that blood pressure of 70-something, the patient
16 was asymptomatic.

17 DR. KONSTAM: Well, let me just then --
18 you have raised the concern in my mind by saying that,
19 and I just wonder whether if that's the case, then it
20 might be worthwhile doing some kind of a post hoc
21 analysis vis-a-vis something called clinically
22 relevant hypotension. I don't know if you've done
23 that or worthwhile, but if that case wasn't identified
24 by the investigator as symptomatic hypotension, then
25 I worry about there may be other concerning cases in

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1 there that weren't identified.

2 DR. YOUNG: Could I address this from a
3 clinician's perspective?

4 DR. HORTON: Absolutely.

5 DR. YOUNG: And from looking at the
6 patients at the bedside that we were entering and then
7 looking at the data and also talking to the
8 investigators and whatnot, that as in every day when
9 we see these patients, there's a broad spectrum of
10 blood pressures that move up and down, and sometimes
11 the blood pressures will go down to 70, 75 or so, and
12 the case --

13 DR. KONSTAM: But, Jim, this was 11
14 minutes after starting the infusion.

15 DR. YOUNG: Yeah, and that case we ought
16 to look at to see exactly what it is particularly
17 because it seemed to be a restrictive process and
18 perhaps some of this diastolic dysfunction issue.

19 but if you looked at the return of the
20 blood pressures, Darlene said the vast majority of the
21 patients, you know, they were back, and they were up
22 there with reasonable levels within a 60 to 90-minute
23 period of time.

24 DR. KONSTAM: Yeah, like I say, I'm not
25 that worried at this dose, right?

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1 DR. YOUNG: Yeah.

2 DR. KONSTAM: I think extrapolating them
3 I'm going to be worried at the higher doses.

4 DR. YOUNG: Right, and I was going to
5 follow on saying that that is exactly what the issue
6 is, and just like other drugs that we're trying to
7 titrate either with or without hemodynamics, I think
8 a lot of decision is going to have to go into what
9 else is the patient on. Can other things be done?

10 We didn't even talk about the issue of the
11 concomitant vasodilators like the ACE inhibitors that
12 the patients could be taking that could also
13 contribute to this.

14 And so just like any clinician would, we'd
15 look for volume depletion and give volume or we'd make
16 a decision about the necessity of inotropes.

17 My perception from the hypotensive cases
18 from looking at it was pretty much, and we'll have to
19 look at that one case, pretty much that's what went on
20 from a clinician's perspective.

21 CHAIRMAN PACKER: If I understand it,
22 Marv, let me see if I -- a lot of the analyses that
23 we've seen that have been provided in an attempt to
24 reassure us that the hypotension doesn't carry any
25 sequela has been analyses that relate symptomatic

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1. hypotension to sequela, and Marv is raising the
2. question whether there is a group of patients who have
3. significant drops in blood pressure that are deemed
4. clinical significant, although not strictly
5. symptomatic that would shed additional insight as to
6. what the risks were of having hypotension, although
7. not accompanied by dizziness, but hypotension for
8. several hours.

9. DR. LIPICKY: Jim, can you tell me how you
10. would identify clinically significant hypotension if
11. it is not symptomatic?

12. CHAIRMAN PACKER: Well, Marv didn't jump
13. at this.

14. DR. LIPICKY: What would we look for?

15. CHAIRMAN PACKER: So I'll propose
16. something.

17. DR. LIPICKY: Yes.

18. CHAIRMAN PACKER: A drop in blood pressure
19. that -- let's see. The entry criteria was 90, if I
20. remember. Was it 100 or 90?

21. DR. HORTON: Ninety.

22. CHAIRMAN PACKER: Ninety. I would say
23. give me every patient with a blood pressure that was
24. either a drop in blood pressure that was symptomatic
25. or a drop in blood pressure that was less than 80.

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1 DR. KONSTAM: Well, I mean, there are ways
2 of getting at this. You could identify the patients,
3 you know, by some kind of magnitude of effect, and
4 then you could go in and review the --

5 DR. LIPICKY: No, but I'm asking for the
6 magnitude that becomes clinically meaningful.

7 DR. KONSTAM: Well, I would use that as a
8 screen. No, I wouldn't -- I'd use that as a screen.

9 DR. LIPICKY: Well, you've got to screen
10 by number.

11 DR. KONSTAM: Right.

12 DR. LIPICKY: So what number would you
13 screen for?

14 DR. KONSTAM: How about blood pressure
15 below 80? We could probably argue all day about
16 what's the right pressure to screen.

17 DR. HORTON: Right. Slide 104, please.

18 We actually saw this information in a
19 slightly different way. This just shows you the total
20 number of patients. This is the lowest blood
21 pressures that were observed in the first 24 hours,
22 and they were 13 percent and 14 percent of the patient
23 population in nitroglycerine and Natrecor, and those
24 were obviously not patients that developed symptoms.

25 There were also cases -- the problem with

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1 the blood pressure cutoff for this is that you can
2 have a patient whose blood pressure goes from 150 to
3 120 and develops what you think is symptomatic
4 hypertension, but it's really normal blood pressure.

5 CHAIRMAN PACKER: Right. So you could
6 have a criteria about that, too.

7 DR. HORTON: So we had a much larger, you
8 know, net to -- because we didn't want to exclude what
9 would be higher blood pressures if the patient
10 developed symptomatic hypertension.

11 CHAIRMAN PACKER: Also, the other thing
12 you don't have here is time. That is, it could be
13 that the drop in blood pressure below 80 is short-
14 lived for nitroglycerine versus long-lived, in part,
15 because of the phenomenon Ray mentioned, that with a
16 certain -- you know, the lower you go, the longer it
17 takes to come up and other factors.

18 Okay. Joann, yes.

19 DR. LINDENFELD: A quick question.
20 There's been some question about whether or not the
21 natriuretic peptides alter capillary leak or
22 filtration. Can you just to reassure me, can you tell
23 me something about the hemoglobin at zero and 24 hours
24 between the nitroglycerine group and the Natrecor
25 group? And were there differences?

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1 DR. HORTON: Unfortunately I can't because
2 we didn't collect that in this study.

3 DR. LINDENFELD: There's no --

4 DR. HORTON: We didn't collect any of
5 that.

6 CHAIRMAN PACKER: Okay. Ileana. Okay.
7 Ileana and then Alan.

8 DR. PINA: Going back to my trend of
9 thought on the advice you would give clinicians, the
10 patient gets better. You stop the drug. Now what do
11 you do?

12 And the reason I'm asking is going through
13 the deaths on both nitroglycerine and on all Natreacor,
14 there's a whole wide variation of patients. Some the
15 study drug gets stopped because of no clinical
16 improvement. Some the study drug gets stopped because
17 a patient has improved; there's clinical improvement,
18 and then the patient goes on to develop heart failure
19 and dies.

20 So what happens when the drug gets
21 stopped? Do you have any data on blood pressure, on
22 symptoms? Do you have any data on what patients get
23 put on afterwards? Because these are obviously
24 temporary treatments, and you're going to have to
25 substitute it with something, especially since the

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1 patients didn't diurese.

2 So you stop the drug. The volume is still
3 there. The weight hasn't come down, and now what do
4 you do?

5 DR. HORTON: You're talking about stopping
6 the drug in the case of --

7 DR. PINA: Well, whether there's
8 improvement or not improvement. There were various
9 reasons why the study -- why some of these patients
10 had, you know, so many hours of infusion. The patient
11 did better. The study was stopped or the infusion was
12 stopped.

13 DR. HORTON: Okay. So is your question
14 about the reasons why study drug was discontinued?

15 DR. PINA: No, no, no, no, no. What
16 happens when the drug gets stopped? What happens to
17 blood pressure? How long after totally stopping the
18 drug?

19 We know about hypotension.

20 DR. LIPICKY: Is there some kind of
21 rebound.

22 DR. PINA: It's just in the average
23 patient.

24 DR. HORTON: right. I'll go back to the
25 slide from the CORE safety presentation, which shows

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1 the blood pressure changes over two hours after drug
2 discontinuation. You don't want to see that?

3 CHAIRMAN PACKER: I don't think -- she
4 wants to know about --

5 DR. HORTON: Clinically what happens?

6 CHAIRMAN PACKER: -- as I understand it,
7 adverse events.

8 DR. PINA: Any adverse events that have
9 happened after stopping the drug.

10 DR. HORTON: No.

11 CHAIRMAN PACKER: Do you have any analysis
12 of AEs in VMAC, nitroglycerine versus nesiritide, in
13 the first 24 hours after stopping the infusion?

14 DR. HORTON: We don't have that analysis
15 specifically. We have analyses of adverse events
16 during specific time periods, during 48 hours, for
17 example, and during 14 days.

18 CHAIRMAN PACKER: But that's 48 hours in
19 people who took the drug for 48 hours.

20 DR. HORTON: Right, but then --

21 CHAIRMAN PACKER: But did you collect data
22 on AEs after the drugs were stopped?

23 DR. HORTON: Yes, we collected AE
24 information through 14 days.

25 CHAIRMAN PACKER: Okay

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1 DR. HORTON: And there are no differences.

2 CHAIRMAN PACKER: All AEs or serious AEs?

3 DR. HORTON: All AEs through 14 days,
4 serious adverse events through 30 days.

5 DR. PINA: All right. So can you tell us
6 about those?

7 DR. HORTON: Yeah. It's a 14-day period
8 of time. So usually patients have either been
9 discharged or have had the drug discontinued, and
10 again, there's no significant difference in any
11 adverse event. All adverse events are higher in
12 number because now there's a cumulative period of time
13 or most of the adverse events that you would expect to
14 occur in this population, but there is no significant
15 difference between Natrecor and nitroglycerine, and
16 that's during the entire 14-day period.

17 DR. PINA: All right. Another follow-up
18 question. When we were talking about the disposition
19 of the drug, we know about the endopeptidases, and you
20 said that there was a small percentage of the drug
21 that was eliminated through the kidney.

22 In patients who have impaired renal
23 function, which most of the heart failure patients do,
24 do you have any data about the dynamics, the
25 pharmacokinetics and the pharmacodynamics of the drug

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1 in that population.

2 In other words, should we be concerned
3 about longer term effects of the drug even after it's
4 stopped?

5 DR. HORTON: Right. We have two good
6 pieces of information there. We have first an animal
7 study in which we actually did a total ligation of the
8 renal arteries, and there was a reduction in clearance
9 by 30 percent, and that was with the complete
10 elimination of renal filtration.

11 Okay. So that leads you to believe that
12 it's not a big player in the clearance, and that's no
13 kidney function whatsoever and so that you would not
14 have to adjust the dose in the case of renal
15 dysfunction.

16 The other thing that we looked at is
17 patients that had creatinines greater than two just to
18 see if the adverse event profile was different, and in
19 previous studies -- in the original NDA we looked to
20 see if the efficacy profile was also different, and it
21 was not, indicating that there was not a difference in
22 pharmacokinetics or pharmacodynamics with renal
23 dysfunction.

24 CHAIRMAN PACKER: Alan.

25 DR. HIRSCH: Well, despite the magnitude

1 of the questions, again, I'll just flatter you by
2 saying it was a very well organized presentation.

3 DR. HORTON: Thank you.

4 DR. HIRSCH: Now, the question. I think
5 we've all been concerned about renal dysfunction, and
6 it sounds like it's one subgroup that we've all
7 analyzed, which is the higher dose group and possibly
8 those who are hypotensive.

9 There's one other group that I know as a
10 statistician I can't see a signal in, but as a
11 physician concerns me, and maybe you can help me,
12 which was the acute coronary syndrome group, which was
13 slide 133.

14 I think of, you know, every 34 patients I
15 treat with nitroglycerine, all patients may get a
16 headache, and so maybe they have a light higher ranged
17 of As for headache, but they don't go on dialysis. So
18 even a blip of two patients of 27 having achieved
19 dialysis concerns me, although I can't make a
20 statistical argument.

21 Now, there are many things that's
22 different about this population potentially, which I
23 alluded to earlier. An acute coronary syndrome
24 patient may have a different cardiac output, may have
25 neurohormonal activation, may be exposed to other

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1 medications, may go through contrast angiography, but
2 nevertheless, in the real world when the drug may come
3 and be used, there will be these patients, and there's
4 an awful lot of them in the United States, more and
5 more every year.

6 DR. HORTON: Right.

7 DR. HIRSCH: So I'm concerned that we may
8 be unmasking other high risk groups, and I wonder if
9 you can address that in some way for me.

10 DR. HORTON: Yeah, I'm not sure that this
11 has anything to do with the fact that they had an
12 acute coronary syndrome. There's no way for me to
13 answer that. I just have to go back to the total
14 database, which is that there was no difference
15 overall. There was a nuance at dialysis occurred in
16 two percent and three percent of the patients. So it
17 was actually this common in the study, but well
18 distributed across the groups.

19 What we could probably do is try to find
20 -- it's important to look at the narrative on that
21 patient as well. I can tell you that none of these
22 events that subsequently occurred in patients that had
23 acute coronary syndrome, the renal events, were felt
24 to be due to the -- as a consequence of the original
25 acute coronary syndrome. I could probably give you

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1. more information as far as when those things happened.

2 DR. HIRSCH: And in my review of the
3 narratives, I couldn't quite tell either. Sometimes
4 the narratives don't tell the whole story and all
5 you're left with is this little data blip, which may
6 require some additional monitoring.

7 One more question to go back to Ileana's,
8 which is just when the drug is stopped, I'm not
9 worried about hypotension, but I don't understand the
10 physiology completely. I have this drop in wedge
11 pressure. I have this slight fall in blood pressure.
12 The patient feels better. The drug is then stopped.

13 But there's no diuresis. What actually
14 happens that maintains homeostasis thereafter? Is
15 there intensification of other medications? Is there
16 a post infusion diuresis? Is there something that's
17 maintaining the patient feeling better that I can
18 explain?

19 It's a mystery to me.

20 DR. HORTON: It's not that there's no
21 diuresis. There's no significant difference in
22 diuresis to standard care.

23 DR. HIRSCH: Yeah. Well, fair enough.
24 Still a mystery to me.

25 DR. LINDENFELD: Just to come back to the

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1 point Alan made a little bit, how many patients do you
2 have total who had contrast? As we get into things,
3 I'm a little worried about this. You know, A&P may
4 make non-allogenic (phonetic) renal failure a little
5 bit worse. Do you have other -- do you know how many
6 patients you have, and do we know anything?

7 DR. HORTON: We don't have that.

8 DR. LINDENFELD: It would be worth
9 eventually knowing that, I think.

10 CHAIRMAN PACKER: Okay. Let me ask a
11 question. Patients who have a catheter in place tend
12 to be observed more carefully and perhaps treated more
13 carefully than patients without a catheter. Was there
14 a difference in the AE profile between the patients
15 who were catheterized and patients who were not?

16 DR. HORTON: Let me show you that
17 information. If you look at slide 324, that is the --
18 it's more of a busy slide here to answer all of these
19 questions, but, in general, the pattern was similar.
20 There was, you know, more headache. Most things were
21 pretty similar. Symptomatic hypotension occurred in
22 two percent and six percent. Non-sustained BT, extra
23 systoles were all basically the same.

24 There's not a -- if you look at the p
25 values, the only thing that's significantly different

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1 in the headache in the nitroglycerine group.

2 CHAIRMAN PACKER: Okay. Let's see. Just
3 getting back to the question about setting the
4 infusion off, how long do you think patients should be
5 observed after the infusion is stopped?

6 DR. HORTON: I would say that for at least
7 two hours after the infusion is stopped.

8 CHAIRMAN PACKER: And you come up with two
9 hours based on?

10 DR. HORTON: Based on the half-life and
11 what we know of the offset of effects from VMAC.

12 CHAIRMAN PACKER: Did any patient develop
13 symptomatic hypotension or developed asymptomatic
14 hypotension after the infusion was stopped, within the
15 first four hours after the infusion was stopped?

16 DR. HORTON: There may have been. I don't
17 know the answer to that. There might have been. I
18 don't know the answer specifically, but I can imagine
19 a situation where blood pressure might have been
20 stopped because of a decrease in blood pressure and
21 then the patient may have later -- you know, in that
22 same episode they would have been considered either
23 asymptomatic or symptomatic hypotension.

24 CHAIRMAN PACKER: Okay. I think that's
25 important information that we need to -- but we're not

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1 going to get it today -- but the division needs to see
2 in terms of whether there's any delayed hypotensive
3 effect.

4 DR. HORTON: I don't think the reason for
5 that is because of delayed hypotension. I think it's
6 a question of when the drug was stopped. It's the
7 same effects on blood pressure overall which we've
8 seen, which were mild, which are no different than
9 nitroglycerine, but I don't think it -- it doesn't
10 make any sense that it would be a delayed drop in
11 blood pressure after the drug was discontinued. I
12 think it's all just part of the same profile.

13 CHAIRMAN PACKER: Okay. There are data in
14 the literature similar to what Joann was referring to
15 ant a natriuretic peptide has effects on capillary
16 permeability. Does nesiritide have effects on
17 capillary permeability?

18 DR. HORTON: Well, that's a very difficult
19 thing to study. As you know, we've not studied it
20 directly, and I can't say one way or another. Who
21 knows? Maybe it has to do with why dyspnea improves,
22 because of movement of fluid back into the
23 intravascular space. Maybe it has to do with --

24 CHAIRMAN PACKER: I thought the effect was
25 an increase in permeability.

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1 DR. HORTON: It goes both ways.

2 CHAIRMAN PACKER: No, no. I understand it
3 goes both ways. The question is whether the flux is
4 increased.

5 DR. HORTON: Right, and the answer is I
6 don't know, but it would depend on where the pressure
7 gradient would be. So if you're decreasing the
8 pressure, you would expect for that to go from the
9 alveoli into the intravascular space, for example, but
10 it --

11 CHAIRMAN PACKER: Yeah, I understand that
12 because, although we're very fond of wedge pressure
13 measurements, what the patient feels is very
14 incompletely and very indirectly and very poorly
15 correlated with changes in wedge pressure as your own
16 data indicate, and additional effects of the drug on
17 other factors. Pulmonary dyspnea receptors or
18 permeability might have an effect on how people feel.

19 DR. HORTON: I mean, I might just add that
20 the data on even capillary permeability with A&P is
21 very small studies. It's unclear what it means. I
22 don't think it's --

23 DR. HIRSCH: It's hard to interpret, but
24 one of the problems in the current last ten-year area
25 is we often have a relative lack of physiologic human

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1 data for almost any compound we look at as compared to
2 the previous ten years, and I also was very concerned
3 about the where is the volume going question when
4 there's no overall obvious, clear cut, unambiguous
5 naturitic diuretic effect.

6 Just to say it out loud though, you know,
7 it could all be venodilation. In other words, the
8 primary mechanism of action here would permit a
9 potential liter of fluid to pool in the leg veins,
10 which would in a sitting patient permit them to feel
11 less dyspneic, and the supine catheterized patient
12 pool blood less well in the leg.

13 In other words, the venodilatory effect
14 could explain this. I think so.

15 CHAIRMAN PACKER: Yeah, right. Okay. Any
16 other questions on safety? If not, we'll proceed.
17 We've asked Dr. Abraham to keep his comments brief,
18 and he has said he will do so as best as he can.

19 DR. ABRAHAM: Well, thank you very much.

20 Dr. Packer, Committee members, I spoke
21 with you two years ago at the first advisory committee
22 meeting for Natrecor, and some of what I will say
23 today I said then, except that now with VMAC and with
24 PRECEDENT, we have more evidence, we have more
25 confidence, and we have a substantial body of

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1. comparative information between Natreacor and
2 nitroglycerine, and Natreacor and dobutamine, that
3 demonstrates a favorable benefit-risk profile for the
4 drug.

5 What I'd like to do with this brief
6 presentation is to review the current status of acute
7 heart failure. We'll then take a look at the
8 demonstrated benefits of Natreacor in the context of
9 the known physiology of the natriuretic peptides, and
10 in this regard, maybe some of the questions that have
11 been raised will become a little bit more clear.

12 I'll then summarize the demonstrated risk
13 of Natreacor and make a few comments from the
14 clinician's perspective regarding some of the issues
15 or questions raised about hypotension.

16 We'll then review candidates for
17 treatment, and I'll try to bring us all together in a
18 summary.

19 Well, this slide reviews the current
20 status of acute heart failure in the United States.
21 As you all know, heart failure represents a major and
22 growing public health concern. In fact,
23 hospitalization for heart failure represents the
24 number one DRG discharge diagnosis for those over the
25 age of 65 years. Estimates have placed the total

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1 direct cost of heart failure care in excess of \$38
2 billion, and clearly nearly two thirds of this
3 staggering economic cost may be attributable to the
4 in-patient management of decompensated heart failure.

5 Now, current therapies are effective, but
6 as you all know, they may be limited by a variety of
7 adverse events, such as the risk of malignant
8 ventricular arrhythmias associated with the positive
9 inotropic agents. Thus, I would suggest that there is
10 a need for alternative therapies.

11 In this regard, one should appreciate that
12 no new intravenous drugs have been approved for the
13 management of decompensated heart failure in over a
14 decade. Thus, another option or another agent is
15 warranted.

16 Now, in this regard, it should really come
17 as no surprise that a natriuretic peptide has been
18 developed and now proven to be effective for the
19 treatment of heart failure.

20 When one looks at the next slide, which
21 summarizes the physiology of the natriuretic peptides,
22 you will see that these agents, in fact, in many ways
23 represent the ideal counter-regulatory hormone in the
24 setting of heart failure.

25 Now, please remember that the natriuretic

1 peptides, and there are a family of them, including
2 ANP, BNP, CNP, DNP, and urodilatin, represents a
3 family of peptide hormones. These are endogenous
4 substances produced by the body in response to
5 myocardial failure, and they represent one of the
6 body's defenses against cardiac failure.

7 Now, I won't review this slide with you in
8 any detail, but suffice it to say that when one looks
9 at the overall experience, both experimental and in
10 human clinical trials with these agents, natriuretic
11 peptides demonstrate favorable effects on the heart,
12 on the kidney, and on the vasculature, and have a
13 marked effect on other neurohormonal mechanisms as
14 well, such as reducing plasma aldosterone levels, and
15 in some studies they've been demonstrated to exert a
16 sympatholytic effect, which may explain in part some
17 of their effects on heart rate.

18 Now, on this background, the next two
19 slides review the proven benefits of Natrecor. These
20 two slides will review what was presented earlier and
21 synthesized in the presentation from Dr. Lipicky, and
22 the VMAC and PRECEDENT data presented by Dr. Horton.

23 As you have seen, Natrecor produces a dose
24 dependent decrease in the pulmonary capillary wedge
25 pressure and in systemic vascular resistance, and in

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1 this regard, Natreacor may be viewed as a balanced
2 vasodilator.

3 In addition, Natreacor has been shown to
4 produce significant symptom improvement at three
5 hours, as shown in the VMAC trial, and at six hours in
6 the study 325, and this has been looked at
7 specifically for improvement in dyspnea and
8 improvement in global assessment.

9 Natreacor produces a dose dependent
10 increase in cardiac output and stroke volume, with no
11 increase in heart rate, and in particular, and as
12 addressed earlier, there is no direct inotropic
13 effect, and there is no increase in cyclic AMP, and I
14 think we all believe that these effects are
15 undesirable, and Natreacor, like other natriuretic
16 peptides, does not possess them.

17 Next slide.

18 In addition, Natreacor has demonstrated no
19 increase in tachyarrhythmias, either atrial or
20 ventricular. It has been demonstrated to have a more
21 rapid hemodynamic onset of effect or improvement
22 within 15 minutes compared to nitroglycerine or
23 placebo, as demonstrated in the VMAC trial.

24 And finally, Natreacor has been show to
25 have sustained or to produce sustained reduction in

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1 pulmonary capillary wedge pressure through at least 48
2 hours. As you also saw, this sustained improvement in
3 hemodynamics has been associated with the sustained
4 symptom improvement demonstrated at 24 hours when
5 compared to nitroglycerine in the VMAC trial.

6 Now, as you heard and spent much time
7 discussing today, there are some known risks of
8 Natreacor therapy, and I think really, in sum, there is
9 one of major interest, and that is the dose dependent
10 risk of hypotension, which has been demonstrated with
11 this drug.

12 The Natreacor experience taken as a whole
13 suggest that hypotension, in fact, is mild or moderate
14 in severity in the vast majority of cases, and that
15 there were no significant adverse sequelae associated
16 with this incidence of hypotension.

17 Now, I'll come back to the concept in a
18 moment, but I think it's fair to say that really all
19 agents currently used for the management of
20 decompensated heart failure have some risk of
21 associated hypotension. Hypotension risk is sort of
22 part and parcel for the treatment of these patients,
23 and when these patients become hypotensive, at least
24 hypotensive enough to produce clinical concern,
25 clinically we respond to that. We withdraw drugs, we

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1. treat them with volume expansion or intravenous
2 pressure agents, and this is really part of the
3 treatment of patients with advanced heart failure.

4 So in this way, Natreacor does not differ
5 from contemporary therapy. Compared to
6 nitroglycerine, the risks of hypotension associated
7 with Natreacor were similar. You saw that, and no
8 significant difference was seen in time of onset,
9 severity, the maximum effects on systolic blood
10 pressure, or need for intervention.

11 However, as you saw, the duration of the
12 hypotensive episode was longer.

13 Well, now, let's just briefly discuss
14 patients who would be candidates for treatment with a
15 drug like Natreacor, and this really is a clinician's
16 view of the management of acute heart failure.

17 Now, some of you will appreciate that what
18 is shown on this slide is an adaptation of Lynn Warner
19 Stevenson's paradigm for the management of these heart
20 failure patients where they are judged to be wet or
21 dry or warm or cold.

22 And what I would like you to focus on is
23 the large group of patients who fall under the
24 category that is wet and that has inadequate
25 perfusion, although not frank cardiogenic shock. I

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1 would suggest and, in fact, can support through many
2 benchmarking experiences with hospitalized patients
3 with heart failure that this represents the typical
4 heart failure patient.

5 For example, if one looks at data from the
6 University Health System consortium, you will see that
7 90 percent of patients admitted to the hospital with
8 heart failure are wet, and about 60 percent of them
9 are judged to have inadequate perfusion while not in
10 cardiogenic shock. These patients who on average may
11 have a pulmonary capillary wedge pressure of about 25
12 millimeters of mercury and a modest reduction in
13 cardiac index are typical of the patients enrolled in
14 the Natreacor trials and typical of patients admitted
15 to the hospital with decompensated heart failure.

16 So in summary, candidates for treatment
17 with Natreacor include those patients who are
18 hospitalized with decompensated heart failure,
19 specifically those who are volume overloaded and not
20 in cardiogenic shock. Again, the typical patient who
21 is hospitalized for heart failure.

22 In addition, shown on the next slide there
23 are some special considerations which I think really
24 demonstrate a need for additional drugs in our
25 pharmacological armamentarium.

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1 For example, there are other situations
2 which would favor the use of a vasodilator, for
3 example, over an intravenous positive inotropic agent.
4 Decompensated heart failure patients with tachycardia,
5 with hypertension but decompensated heart failure, and
6 those with a history of or current malignant
7 ventricular arrhythmias may be better treated with an
8 intravenous vasodilator than a positive inotropic
9 agent.

10 Now, finally I'm going to conclude by
11 looking at the contemporary intravenous treatment of
12 acutely decompensated heart failure because I think
13 when one discusses benefit-risk, it's important to
14 discuss it in the context of available therapies,
15 essentially answering the question: why another agent
16 for the management of acutely decompensated heart
17 failure?

18 Now, let me take you through this somewhat
19 animated slide by showing you first how it's set up.
20 There are six drugs that are reviewed on the slide,
21 six drugs that are used commonly, five of these drugs
22 used commonly for the treatment of heart failure, and
23 Natreacor, which is investigational. From left to
24 right, these drugs are IV diuretics, the positive
25 inotropic agents, dobutamine and Milrinone, the

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1 nitrovasodilators, nitroprusside and nitroglycerine,
2 and then finally Natreacor.

3 And what we'll eventually look at are some
4 of the limitations of therapies with these agents.

5 Now, let's advance to the next slide
6 because the next point I'd like to make is that four
7 of these six agents are FDA approved for this
8 indication, that is, for the treatment of acutely
9 decompensated heart failure in patients who have
10 established heart failure.

11 Now, one agent, nitroglycerine, is, in
12 fact, approved for the treatment of heart failure in
13 the setting of acute coronary syndromes but not for
14 the indication of decompensated heart failure in a
15 chronic heart failure patient.

16 And finally, Natreacor is investigational.

17 Well, now, let's first look at the risk or
18 limitation profile of the agents which are approved
19 for this indication. Here you can see, and I won't
20 take you through this in any detailed fashion, but
21 what I hope that you will appreciate is that there are
22 shortcomings to all available therapies for the
23 treatment of acutely decompensated heart failure.

24 We'll come back to hypotension in a
25 minute, but notice that in some instances some of

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1 these adverse effects are particular to certain
2 classes of medications. So the limitations from top
3 to bottom include hypotension, ventricular
4 arrhythmias, tachycardia, neurohormonal activation,
5 the production of toxic metabolites, electrolyte
6 abnormalities, renal dysfunction or sodium retention,
7 the development of tolerance to treatment and the lack
8 of demonstrated symptom relief associated with these
9 treatments.

10 For example, you'll see that the positive
11 inotropic agents, dobutamine and Milrinone, are
12 associated with risk for ventricular arrhythmias.
13 Nitroprusside, for example, is uniquely associated
14 with the risk for toxic metabolites, such as
15 thiocyanide, such as cyanide or thiocyanate.

16 Now let's look at our two comparator
17 agents from the VMAC trial: nitroglycerine and
18 Natreacor. You'll see here that when staff against
19 contemporary therapy for the management of acutely
20 decompensated heart failure, the limitations of
21 Natreacor fare pretty well in comparison.

22 I do also want to focus your attention on
23 the top line because it brings us back to that issue
24 of hypotension, and you'll see that really all of the
25 drugs, perhaps with the exception of dobutamine, have

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1. been associated with some significant incidence of
2 hypotension, and in selected patients we've all seen
3 hypotension even in association with treatment with
4 dobutamine.

5 There's a lot going on during the
6 treatment of patients with acutely decompensated heart
7 failure. The picture is pretty cloudy, but the bottom
8 line here is that any of these agents can produce
9 hypotension. As shown in the VMAC trial, the
10 incidence of hypotension associated with Natreacor is
11 very comparable to that seen with the agent
12 nitroglycerine.

13 Now, the other point i want to address
14 with this slide is a point that came up earlier, and
15 that was concern about the doses of nitroglycerine
16 used in the VMAC trial. Well, in fact, it's
17 interesting that while one might suggest that these
18 doses were subtherapeutic, as you saw from the adverse
19 event data in the VMAC trial, there certainly was some
20 pharmacological effect as we saw a relatively
21 significant instance of GI distress and headache and
22 other adverse events, including hypotension associated
23 with the use of this agent in the VMAC trial.

24 Well, finally, I'd just like to make a
25 couple of comments about how we treat these patients,

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1 and, again, this is from the clinician's perspective.
2 And I'm going to do that on the background of our
3 approach to treating patients with chronic systolic
4 heart failure.

5 This slide lists some of the published
6 clinical practice guidelines for the management of
7 chronic systolic heart failure. You'll see that there
8 are many, and the reason for that is that the
9 management of chronic systolic heart failure has been
10 well defined in numerous large scale randomized
11 controlled trials.

12 Let's look at the story with acute heart
13 failure. This slide lists all of the published
14 guidelines which tell us how to take care of patients
15 with acutely decompensated heart failure. There are
16 none, and the reason that there are none is because
17 our database is lacking.

18 In this regard, I would suggest that the
19 Natrecor experience in general and the VMAC trial in
20 particular provides one of our best insights into the
21 management of patients with acutely decompensated
22 heart failure.

23 Well, let's try to bring this all together
24 with a summary. I hope that throughout the course of
25 today it's become apparent that Natrecor is a safe and

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1 effective intravenous therapy for patients with
2 acutely decompensated heart failure.

3 Natrecor has an excellent benefit-risk
4 profile when viewed alone, and particularly when
5 viewed in the context of other therapies used for this
6 indication. It has predictable hemodynamic effects
7 associated with a rapid onset of effect. It's easy to
8 use and can be used safely in patients without
9 invasive hemodynamic monitoring.

10 And finally, again, from the clinician's
11 view, I believe that Natrecor would be a useful
12 addition to our armamentarium for the treatment of
13 acutely decompensated heart failure.

14 Thank you for your attention.

15 CHAIRMAN PACKER: Does anyone in the panel
16 have any pressing comments or questions?

17 If not, thank you. Thank you very much,
18 and we'll go on to the questions. I am not going to
19 read the introduction except to remind the Committee
20 that they have not seen a presentation today of data
21 contained in the original NDA, which had 721 patients
22 in it, 505 on nesiritide.

23 We have been focusing today on 489
24 additional patients, 204 treated with nesiritide, and
25 the questions posed to us, and we should look at this

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1 not based only on the data seen today, but on the
2 totality of the data available with nesiritide in the
3 NDA, is, one, consider the pulmonary wedge pressure.

4 Due to the results of VMAC, and
5 specifically this refers to VMAC, demonstrate that
6 compared with placebo, nesiritide decreased wedge
7 pressure.

8 And, Ileana, we'll ask you to begin with
9 each of these.

10 DR. PINA: My answer to the first question
11 is yes. Compared to placebo, nesiritide lowers blood
12 pressure.

13 Do you want me to go on?

14 CHAIRMAN PACKER: No. I want to pause
15 here for a moment.

16 Does anyone disagree?

17 Okay. One, two, considering VMAC and
18 earlier studies, was there a benefit on pulmonary
19 wedge pressure associated with the use of nesiritide
20 when compared with placebo?

21 DR. PINA: Yes.

22 CHAIRMAN PACKER: Does anyone disagree?

23 How about when compared with
24 nitroglycerine?

25 DR. PINA: No, except for the first few

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1 hours where the wedge pressure drops more rapidly with
2 nesiritide.

3 CHAIRMAN PACKER: I'm confused. The --

4 DR. PINA: It says considering would serve
5 benefit with the use of nesiritide when compared to
6 nitroglycerine.

7 CHAIRMAN PACKER: Well, maybe we should
8 say was there an effect on.

9 DR. PINA: Yes.

10 CHAIRMAN PACKER: I don't want to mince
11 word. The word "benefit" has certain connotations
12 which we do not want to get into. Was there a
13 directionally favorable effect on pulmonary wedge
14 pressure?

15 DR. PINA: Yes.

16 CHAIRMAN PACKER: Compared to
17 nitroglycerine?

18 DR. PINA: Yes.

19 CHAIRMAN PACKER: All right. Does anyone
20 disagree?

21 Steve.

22 DR. NISSEN: Well, I guess I have a little
23 bit of a problem here in that I really think that
24 nitroglycerine was very under dosed in VMAC, and so
25 it's hard for me to interpret it. I guess I would say

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1 at the doses compared, yes. But I don't know that as
2 a class or as a drug compared to nitroglycerine.

3 DR. LIPICKY: We should have written this
4 more carefully. You're 100 percent correct. We
5 learned that all day yesterday.

6 CHAIRMAN PACKER: Well, what would you
7 like to hear from us, Ray?

8 DR. LIPICKY: I've heard all I need to.

9 (Laughter.)

10 PARTICIPANT: Next question.

11 CHAIRMAN PACKER: On this question.

12 DR. LIPICKY: I meant on this question,
13 not --

14 (Laughter.)

15 CHAIRMAN PACKER: I think it would be fair
16 to summarize the discussion to date to say that there
17 is no comfort on the part of the committee that the
18 way that nitroglycerine was dosed represents an
19 optimum regimen for the use of nitroglycerine in these
20 patients. In fact, there is evidence that it was not,
21 in fact, an optimal regimen.

22 Having said that --

23 DR. LIPICKY: Well, that's fine. It's
24 just that nobody told people to use it improperly.

25 CHAIRMAN PACKER: That's right.

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1 DR. LIPICKY: It's just that whoever was
2 doing the studies didn't know what they were doing.

3 CHAIRMAN PACKER: I think the implications
4 that the --

5 (Laughter.)

6 DR. LIPICKY: Sorry.

7 CHAIRMAN PACKER: I think the implications
8 of this, and I welcome any disagreement from the
9 Committee, is that if we assume that nitroglycerine
10 were placebo, this would give additional evidence that
11 nesiritide was more effective than placebo.

12 DR. LIPICKY: Right. This would --

13 CHAIRMAN PACKER: If we assume that
14 nitroglycerine was an effective drug and dosed the way
15 that presumably it could have been dosed, not
16 necessarily should have been dosed, but could have
17 been dosed, and if the sponsor were asking for a claim
18 vis-a-vis nitroglycerine, we would probably respond
19 very differently to this question.

20 DR. LIPICKY: Correct. That's correct.

21 CHAIRMAN PACKER: Anyone disagree?

22 Okay. Question 1.3, is demonstration that
23 an agent decreases pulmonary wedge pressure sufficient
24 for its approval as a therapy for acute heart failure?

25 Ileana.

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1 DR. PINA: I would have to say no.

2 CHAIRMAN PACKER: Okay. Does anyone
3 disagree?

4 DR. KONSTAM: Well, I can't exactly
5 disagree, except I will say that it comes close for
6 me. I would be satisfied in terms of demonstrating
7 efficacy for short term administration for patients
8 with recently decompensated heart failure and elevated
9 wedge pressure if I had a drug that convincingly
10 reduces wedge pressure and does no harm or does a very
11 acceptable level of harm. That would satisfy me.

12 CHAIRMAN PACKER: Wait a minute, Marv.
13 I've got a question. You say an acceptable level of
14 harm.

15 DR. KONSTAM: Well, I interpret this
16 question vis-a-vis efficacy. It's an efficacy
17 question.

18 DR. LIPICKY: Yeah, correct. This would
19 assume that all other things are equal, that is, all
20 adversity and all morbidity and all mortality are
21 okay, and it's just that pulmonary capillary wedge
22 pressure changed significantly.

23 DR. KONSTAM: Yeah, and I guess, you know,
24 there's no evidence to show that it makes people
25 exsanguinate, and that's how it's lowering wedge

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1 pressure or something like that.

2 Assuming that's what it's doing, yeah, I'm
3 happy with that.

4 CHAIRMAN PACKER: Would you feel the same
5 way for cardiac output?

6 DR. KONSTAM: I don't see that question
7 here, no.

8 CHAIRMAN PACKER: I'm asking.

9 DR. KONSTAM: I don't have to feel the
10 same way for cardiac output. I'm not sure that I
11 could make as strong a case for cardiac output. I
12 might, but it would be a more complicated discussion.

13 CHAIRMAN PACKER: Steve.

14 DR. NISSEN: If the question is only
15 efficacy --

16 DR. LIPICKY: Yes.

17 DR. NISSEN: Okay. If that's the only
18 question you're asking --

19 DR. LIPICKY: The only question we're
20 asking.

21 DR. NISSEN: -- then maybe heresy, but I
22 would be more than satisfied. A drug that produced
23 clinically significant reductions in pulmonary
24 capillary wedge pressure, and I think I know what
25 those are, I would be considered to be efficacious

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1 even if there was no other efficacy data.

2 CHAIRMAN PACKER: Steve, what is
3 clinically significant decreases in wedge pressure
4 when we don't know whether a decrease in wedge
5 pressure is clinically significant?

6 DR. NISSEN: I guess the problem is that
7 the other endpoints that one could measure, like
8 symptoms and dyspnea, are very difficult to measure,
9 and so I don't want to set as a bar something which I
10 think is sufficiently fuzzy and difficult to measure.

11 And so I guess what I'm trying to say is
12 that those of us that treat a lot of patients with
13 heart failure, you know, know that if you bring the
14 pulmonary capillary wedge pressure down, you make
15 patients better. I think that's just unquestionably
16 the case.

17 DR. LIPICKY: Steve, we're not shy in
18 setting incredible hurdles. You know, it was like for
19 chronic congestive heart failure. The hemodynamics
20 were not sufficient. We had no idea what you had to
21 measure to find out whether people feel better, but
22 the rule sort of has become feel better, live longer,
23 or both.

24 And pulmonary capillary wedge pressure
25 doesn't achieve any of those things.

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1 DR. NISSEN: Okay, but let me just argue
2 with you a minute about that and tell you that there's
3 a well recognized lag between improving hemodynamics
4 and improving symptoms. I mean even chest X-ray.

5 DR. LIPICKY: So what?

6 DR. NISSEN: All the other things

7 DR. LIPICKY: You're just saying it's
8 hard.

9 DR. NISSEN: But I mean --

10 DR. LIPICKY: It's hard to find out people
11 with chronic congestive heart failure feel better,
12 too.

13 DR. NISSEN: I understand.

14 DR. KONSTAM: May I respond to that? I
15 guess I still think that a drug that produced no harm
16 and had a very --

17 CHAIRMAN PACKER: First of all, there is
18 no such drug that produces -- that has no risk. So
19 there's always a risk to benefit relationship.

20 DR. NISSEN: Agreed.

21 DR. KONSTAM: But this is an efficacy
22 question. You're asking the efficacy point.

23 CHAIRMAN PACKER: Then I'll ask the
24 question a different way.

25 DR. KONSTAM: Well, can I respond to Ray?

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1 You know, I want to respond to Ray's question.

2 I guess what I'm saying, and I think Steve
3 is saying the same thing, is that in the setting of
4 acutely decompensated heart failure for short term
5 administration, for me pulmonary capillary wedge
6 pressure is an extremely good surrogate because I
7 think I know enough about the pathophysiology of
8 pulmonary edema to know that it's caused by an
9 elevation of pulmonary venous pressure, and therefore,
10 a drug that I know reduces pulmonary venous pressure
11 to me is a useful agent.

12 DR. LIPICKY: Right, but --

13 DR. HIRSCH: Well, just to make it more
14 difficult then, then let me just chime in for the
15 opposite so that we don't have any possible perception
16 of consensus.

17 It's certainly very easy to lower wedge
18 pressure one millimeter, two millimeters of mercury,
19 and I know I can do that with many drugs. I think as
20 time has moved on, I would like to think that what I'm
21 seeing with my eyes and hearing with my ears can be
22 measured in a questionnaire, and I think actually this
23 sponsor has done it.

24 DR. LIPICKY: But excluding today,
25 yesterday there just was no data set that allowed one

1 to conclude that what everybody knows is true, and
2 that is that when pulmonary capillary wedge pressure
3 goes down, people feel better.

4 CHAIRMAN PACKER: You still don't know
5 that. You don't know that. All you know --

6 DR. KONSTAM: I know that it causes
7 pulmonary edema.

8 CHAIRMAN PACKER: All you know -- there
9 are many factors that determine pulmonary edema.
10 Wedge pressure is one of them. Pulmonary arterial
11 resistance is a major determinant of pulmonary edema,
12 and there are drugs that -- tulazoline in the old days
13 -- that dropped pulmonary arterial resistance.

14 DR. KONSTAM: Your point. So let me just
15 -- but what weighs against --

16 CHAIRMAN PACKER: Sure.

17 DR. KONSTAM: So your argument is purely
18 correct, okay, but what weighs against it is that it's
19 very, very difficult in the setting of acute severe
20 decompensated heart failure, and we can go on and on
21 about why this is true, to demonstrate symptomatic
22 benefit.

23 DR. HIRSCH: Weren't you the person that
24 said the sickest patients could have the greatest
25 benefit?

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1 CHAIRMAN PACKER: But, Marv, this sponsor
2 did that.

3 DR. KONSTAM: Yeah, it took them nine
4 years to do it, and they did it, but that's not what
5 the question is asking.

6 CHAIRMAN PACKER: It took them six months,
7 and then did it.

8 DR. KONSTAM: Okay, all right. I voted.

9 DR. LIPICKY: What took them nine years
10 was everything changed in the middle.

11 CHAIRMAN PACKER: Okay. Let me ask the
12 question in a different way. The reason that the
13 sponsor designed VMAC the way it did was because it
14 was advised to do so. The division, based on -- in
15 conferring with the sponsor, said that you need to
16 show something more than hemodynamics. They didn't
17 say what they needed to show. They said that you
18 needed to show something that was clinically relevant,
19 and the sponsor went out and designed the trial where
20 the primary endpoint was a clinical -- a measure of
21 clinical symptoms, and the sponsor, based on things
22 that we've already heard, appears to have achieved
23 that.

24 Was the advice the division gave wrong?
25 Because the advice they give to one company they tend

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1 to repeat to other companies.

2 DR. PINA: Milton, is it not in the
3 guidelines of this Committee and the guidelines that
4 you wrote that demonstration of a hemodynamic benefit
5 is good, but it's not sufficient; that it should be
6 accompanied with something else?

7 CHAIRMAN PACKER: Forget about guidelines.
8 The world changes every single day. What do you think
9 now? If the next time Ray meets with the sponsor who
10 wants to develop a short-term intravenous treatment
11 for heart failure and the sponsor says, "You know, I
12 went to a nesiritide hearing, okay, and I learned a
13 lot," what did they learn?

14 The question, they want to do it. They
15 have a drug that lowers wedge pressure. It beats
16 placebo. I don't know by how much because I don't
17 know what a clinically relevant drop in wedge pressure
18 is, and no one can tell me that.

19 DR. KONSTAM: Well, Milton, maybe if we
20 voted on the question they would learn the panel's
21 feeling and we could move on to the next question.

22 DR. HIRSCH: Right. You'll need to poll
23 us and see the range of opinions.

24 CHAIRMAN PACKER: Let's do it. Clarify it
25 first, yes.

1 DR. NISSEN: I just want to clarify
2 something. I mean, not every single thing in medical
3 practice can be proven in the way that I think is
4 being asked for here, and let me just try and help a
5 little bit, why I'm a little more comfortable than
6 maybe some other people are.

7 In 20 years of doing this, you know, I
8 monitor a very large number of patients with
9 hemodynamic monitoring, probably more than almost any
10 physician you know, and so many hundreds, perhaps
11 thousands of time I've looked patients in the eye,
12 walked in their room, seen their wedge pressure at 30,
13 the patient is gasping for air, you know, sometimes
14 frothing pink froth from their mouth from their
15 pulmonary edema, and they look like they're going to
16 die any minute, and I've hung an intravenous
17 vasodilator, sometimes nitroglycerine, and titrated up
18 the dose of the drug, watched their wedge pressure
19 come down, and watch the patient go, "Ah, that's a lot
20 better."

21 Now, I know; I know that's not
22 scientifically proven, but I can tell you that anybody
23 who's ever been there, who's ever treated a patient in
24 pulmonary edema with a vasodilator and watched them
25 get better in front of your eyes as their wedge

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1 pressure went down believes and I believe it.

2 DR. HIRSCH: But then if you follow that
3 line further, we don't need any clinical trials. We
4 will at some point as we evolve have to know what
5 threshold of wedge pressure gets that sigh of, "Ah,
6 thank you, sir." Unless we collect that data
7 prospectively, we'll never answer the question.

8 DR. KONSTAM: Can I just follow on what
9 Steve is saying? The population -- the reason this is
10 important is that the population that Steve is
11 describing is not represented in this study. Okay?
12 So in this study we're looking at wedge pressure
13 changes, and we're looking at dyspnea changes. I'm
14 not at all sure that in this population that the
15 dyspnea scores are being driven by the change in wedge
16 pressure, but I do think that the population of
17 patients that Steve just described is extremely hard
18 to study in the way that this group was studied, and
19 so then what we have to say is, well, then we can't
20 approve a drug in that population because we can't
21 study them.

22 You know, I think what Steve and I are
23 saying is that we believe that lowering of wedge
24 pressure acutely is a very good surrogate for at the
25 least clearing up pulmonary edema in somebody who is

1 in cardiogenic pulmonary edema.

2 Now, to --

3 CHAIRMAN PACKER: If someone comes in with
4 a wedge pressure decrease, you will approve that for
5 the treatment of pulmonary edema?

6 DR. KONSTAM: Well --

7 CHAIRMAN PACKER: Because you're saying
8 that there is a relationship between wedge pressure --
9 Steve is saying that -- there is a relationship
10 between wedge pressure and dyspnea and pulmonary
11 edema, but not between wedge pressure and dyspnea in
12 the patients studied in VMAC.

13 So where are we going here?

14 DR. LIPICKY: Well, look, Milton. Why
15 don't you just vote with yeses and noes because, you
16 know, this is a whole surrogate business, and we've
17 heard people who believe. You can't shake their
18 belief. You just have to ignore them. That's all.

19 (Laughter.)

20 CHAIRMAN PACKER: Gee, I thought a
21 discussion might be useful. Maybe not.

22 All right. Ileana, you voted no.

23 DR. PINA: I voted no.

24 CHAIRMAN PACKER: Okay. Well, where do
25 you want to start? Ralph, why don't you start?

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1 DR. D'AGOSTINO: No. The answer is no.

2 CHAIRMAN PACKER: The question is: is it
3 sufficient for approval?

4 DR. D'AGOSTINO: Right.

5 CHAIRMAN PACKER: Ralph said no.
6 Steve?

7 DR. NISSEN: Yes.

8 DR. LINDENFELD: Yes.

9 DR. BORER: No, and just one comment. I
10 believe that the issue of the magnitude of the effect
11 is important, and since I have no idea what magnitude
12 is important, I think it's important to have some
13 clinical indicator of benefit.

14 CHAIRMAN PACKER: I vote last.

15 DR. GRABOYS: No.

16 DR. HIRSCH: No.

17 CHAIRMAN PACKER: Michael?

18 DR. ARTMAN: I think it's necessary, but
19 not sufficient. So I would say no.

20 DR. KONSTAM: Yes.

21 CHAIRMAN PACKER: And I vote no.

22 DR. LIPICKY: Wait. Necessary but not
23 sufficient becomes a yes?

24 CHAIRMAN PACKER: No, no. We have three
25 yeses and seven noes.

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1 Consider symptoms. What influence did the
2 assessment of invasive hemodynamics in some subjects
3 have on evaluation of symptoms?

4 Ileana?

5 DR. PINA: We're talking about the VMAC
6 trials specifically?

7 CHAIRMAN PACKER: Yes, specifically, I
8 think.

9 DR. PINA: That's a hard one because we
10 saw the improvement in symptoms primarily in this
11 group, and we sat here and talked about was there
12 something confounding the analysis of symptoms, and
13 I'm right up there with realizing how very, very
14 difficult it is, and it does give me some sense of
15 comfort when I see that the non-catheterized group is
16 feeling better at 24 hours and the things are sort of
17 moving in the same direction.

18 Maybe it's the strength of the signal;
19 maybe it's that patient's catheterized came in later
20 in the trial because they finished the non-
21 catheterized portion first and people got better at
22 not letting the patient in on what the hemodynamics
23 were doing, and so there was a better dissociation
24 between the patient's sense of how they were doing and
25 how they were feeling.

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1. So I have to say that I think that there
2 was some influence, but I don't know exactly where to
3 put the finger on it.

4 CHAIRMAN PACKER: Okay. Well, the problem
5 is there's all sorts of ways of grading this. I'm
6 just going to have everyone respond. We're just going
7 to go down the line and just have everyone respond:
8 no influence, a little influence, or a lot of
9 influence.

10 There's no other way of doing it.

11 DR. PINA: I would probably say a little
12 influence.

13 CHAIRMAN PACKER: Okay, and we start on
14 this side. Marv, why don't you start? None, a
15 little, a lot?

16 DR. KONSTAM: A little.

17 DR. ARTMAN: A little.

18 DR. PINA: A little.

19 DR. GRABOYS: A little.

20 DR. BORER: I have no idea.

21 DR. LINDENFELD: A little.

22 DR. NISSEN: I really don't know.

23 DR. D'AGOSTINO: A little.

24 CHAIRMAN PACKER: A little.

25 Okay. Do the result of VMAC demonstrate

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1 that compared with placebo, nesiritide improved
2 symptoms?

3 DR. PINA: Again, it's only in the
4 catheterized group that I saw that to my satisfaction.

5 CHAIRMAN PACKER: So is the answer yes or
6 no?

7 DR. PINA: The answer is, yes, in the
8 catheterized group.

9 CHAIRMAN PACKER: Okay. Let's have some
10 discussion.

11 Ralph.

12 DR. D'AGOSTINO: I mean, I understand
13 where you're coming from in looking at the data, but
14 you do have to take the company, the sponsor, for how
15 they put their study together. They didn't do this
16 after looking at the data. They had a protocol,
17 specified analysis, an endpoint, and they achieved
18 what they set out to do, and there were no
19 inconsistencies in the data in terms of looking at
20 subsets.

21 If we ask them to show significance in
22 both of the groups, that's a different question in the
23 sense of sample size than what they actually set out
24 to do. So I think you really want sort of the courage
25 of our convictions, that we've been telling people to

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1 set up your primary endpoint, do your analysis
2 accordingly. If you show significance, then show
3 consistency, and that's what they did.

4 CHAIRMAN PACKER: Okay. I guess we can
5 have some more discussion or we can take a vote there.
6 I guess there are three possibilities. One is yes or
7 no or yes in a subgroup, which is what --

8 DR. LIPICKY: Well, I would not like the
9 latter part, but maybe it's yes, no, or sort of.

10 CHAIRMAN PACKER: Yes, no, or sort of is
11 okay with you?

12 (Laughter.)

13 DR. LIPICKY: It's a strength of evidence
14 thing. Okay? And I think that there is a sort of
15 category. I mean, that's the easiest --

16 CHAIRMAN PACKER: We had a previous
17 question that was no, a little, a lot. Is this
18 parallel to that?

19 DR. LIPICKY: This is parallel to that.
20 We could have raised it, and we probably should have,
21 was what is the strength of evidence, but then that's
22 harder to answer. So --

23 DR. KONSTAM: Is this going to appear in
24 the packet insert sort of?

25 (Laughter.)

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1 DR. LIPICKY: So it's yes, no, or sort of.

2 CHAIRMAN PACKER: Okay. Yes, no, or sort
3 of? Ileana, can you choose one?

4 DR. PINA: Sort of, sort of.

5 CHAIRMAN PACKER: Sort of, and Marv, we'll
6 begin with you.

7 DR. KONSTAM: I don't know what sort of
8 means. So I'm just going to say yes.

9 DR. ARTMAN: I'll say yes.

10 DR. HIRSCH: Always respect the primary
11 endpoint. Yes.

12 DR. GRABOYS: Sort of.

13 DR. BORER: Unequivocally yes.

14 DR. LINDENFELD: Yes.

15 DR. NISSEN: I'm going to offer a comment
16 here and say that to me it would not be fair to raise
17 the bar after the game is over, and so this was the
18 pre-specified endpoint. It wasn't met, and I think
19 it's really got to be yes.

20 DR. D'AGOSTINO: Yes.

21 CHAIRMAN PACKER: And I'll vote sort of.

22 We have three sort ofs? What is it?
23 Three sort ofs, okay.

24 Question 2.3, consider VMAC and earlier
25 studies. Was there a symptom benefit associated with

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