

1 fifth clinical trial in which Natreacor has
2 demonstrated efficacy when compared with placebo in
3 treatment of congestive heart failure.

4 This trial also addressed questions of how
5 Natreacor might compare with nitroglycerine, which is
6 a standard, short acting, intravenous vasodilator used
7 for heart failure, but which up until now has never
8 been evaluated in a clinical trial.

9 Next slide.

10 Dr. Horton has overviewed the study design
11 and many of the characteristics of the patients in
12 VMAC. I will present more baseline data and then
13 review the primary and several other subsidiary
14 endpoint results.

15 Next slide.

16 As noted by the check marks on the bottom
17 of this slide, Dr. Horton has described how VMAC was
18 specifically designed to address the agency's
19 questions outlined in the 1999 action letter. Again,
20 these issues included questions about pharmacodynamics
21 and further clarification of some efficacy and safety
22 issues.

23 I will present information regarding the
24 yellow highlighted points on this slide.

25 Next slide.

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1 This slide demonstrates some important
2 baseline characteristics noted in the treatment groups
3 at the beginning of the three-hour placebo controlled
4 period. Generally there were not significant
5 differences in any of the parameters between groups,
6 and in particular, between Natreacor and placebo.

7 However, fewer males and fewer individuals
8 with a significant ventricular tachycardia history
9 were in the nitroglycerine group at study initiation.

10 Next slide.

11 It is also important to note that the
12 properties of patients receiving intravenous diuretics
13 within six and 24 hours of study was similar in all
14 groups, but fewer nitroglycerine patients had received
15 intravenous vasoactive medications within 24 hours.

16 Also, fewer nitroglycerine patients were
17 continued on dobutamine or dopamine during study
18 period.

19 Next slide.

20 For the most part, all treatment groups
21 were well balanced with respect to baseline
22 hemodynamics. Indeed, there was no significant
23 difference between the groups with respect to PCWP,
24 pulmonary artery pressure, pulmonary vascular
25 resistance, blood pressure or heart rate.

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1. Furthermore, the mean PCWP of 28
2 millimeters of mercury in the catheterization group
3 indicates the patients were severely volume
4 overloaded.

5. Next slide.

6 This now very important and interesting
7 slide shows how nitroglycerine was dosed over 24 hours
8 in the catheterized and non-catheterized strata. The
9 pink line represents catheterized and the light blue
10 line non-catheterized patients.

11 We see that at the 15 minute mark, the
12 mean nitroglycerine dose was about 20 micrograms per
13 minute in both catheterized and non-catheterized
14 patients. Note, however, that when the investigators
15 knew what was happening with hemodynamics, there was
16 an increase in nitroglycerine dose by the three-hour
17 time point.

18 Consequently, there is a significant
19 difference in the dose of nitroglycerine in the two
20 strata at that point. The catheterized group received
21 a mean dose of 42 micrograms, whereas the non-
22 catheterized patients received a mean dose of 30
23 micrograms per minute at this mark.

24 This slide also demonstrates that during
25 the 24-hour time period, again, when the investigators

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1 knew what was happening with hemodynamics, the
2 nitroglycerine dose increased to even higher levels,
3 almost 60 micrograms per minute.

4 This implies that in the non-catheterized
5 arm when systolic blood pressure is known but central
6 hemodynamics are not, nitroglycerine was not up-
7 titrated.

8 Next slide.

9 The Natreacor fixed dose group received a
10 bolus of two micrograms per kilogram, followed by an
11 infusion of 0.01 micrograms per kilogram per minute.
12 For the Natreacor adjustable dose group, all having
13 hemodynamic monitoring, physicians had the opportunity
14 to increase Natreacor doses at specified intervals with
15 predetermined dose increments. We might discuss how
16 that relates further to the double dummy study design.

17 Nonetheless, it turns out that the median
18 Natreacor dose at all time points was 0.01 microgram
19 per kilogram per minute, and the mean dose at 24 hours
20 was 0.013 microgram per kilogram per minute.

21 Interestingly, in the 62 adjustable dose
22 patients, 35 actually continued to receive 0.01
23 microgram per kilogram per minute fixed dose. This
24 suggests that this dose seems sufficient in these
25 catheterized patients.

1 Next slide.

2 Before specifically reviewing the primary
3 and subsidiary endpoints of VMAC, it is important to
4 remember that this study was designed to demonstrate
5 efficacy when compared to placebo plus standard care,
6 with safety to be generally assessed by comparing
7 nitroglycerine to Natreacor plus standard care.

8 Next slide.

9 As stressed, in VMAC Natreacor or control
10 agents were added to standard therapies as deemed
11 appropriate by the investigator. The primary
12 endpoints were three-hour mean change in PCWP and
13 catheterized subjects and three-hour patient dyspnea
14 self-assessment in all subjects.

15 Secondary endpoints were to compare
16 hemodynamic and clinical effects of Natreacor versus
17 intravenous nitroglycerine, and where the onset of
18 effect on PCWP, patient dyspnea self-assessment, and
19 24-hour PCWP.

20 Next slide.

21 The first primary endpoint, mean change in
22 PCWP at three hours shows significant reduction by
23 Natreacor compared to placebo at all time points.
24 Indeed, the onset of response to Natreacor is rapid,
25 with a significant decrement noted first at 15 minutes

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1 and a peak reduction noted at about one hour with this
2 change maintained out to the three-hour placebo
3 controlled mark.

4 Next slide.

5 This slide adds in the nitroglycerine
6 cohort. Interestingly, the only point at which
7 nitroglycerine is significantly better than placebo is
8 at two hours.

9 Also, Natreacor showed a significant
10 reduction in PCWP compared to nitroglycerine at all
11 but the two-hour mark.

12 Next slide.

13 The second primary endpoint, patient
14 assessed change in a seven point dyspnea scale at
15 three hours, is shown here as the aggregate
16 improvement, which is shown above the zero line or no
17 change and worsening shown below the line. This
18 evaluation of dyspnea was prospectively defined to
19 allow the combination of data from both the
20 catheterized and non-catheterized patients.

21 Improvement with Natreacor was
22 statistically significant compared to placebo, and the
23 gradations of improvement were tested for proportional
24 change.

25 Next slide.

1 In contradistinction to Natrecor,
2 nitroglycerine did not demonstrate statistically
3 significant improvement when compared to placebo.

4 Next slide.

5 This slide demonstrates the systolic,
6 diastolic and mean pulmonary artery pressures during
7 the three-hour placebo controlled period paralleled
8 the PCWP changes seen previously.

9 There was a rapid and significant
10 reduction in Natrecor group measurements at 15
11 minutes, and this was sustained over three hours.
12 Natrecor group values were significantly lower than
13 placebo at all time points and compared to
14 nitroglycerine, significantly less except for the
15 diastolic pulmonary artery pressure at one and two
16 hours.

17 For nitroglycerine versus placebo, only
18 the one hour diastolic pulmonary artery pressure was
19 statistically significant. Pulmonary and vascular
20 resistance also fell significantly for both Natrecor
21 and nitroglycerine compared to placebo at the one hour
22 mark with Natrecor maintaining significance at the
23 three hour endpoint.

24 Next slide.

25 If we continue to monitor PCWP over 48

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1. hours, the data show that Natreacor not only
2 significantly lowered PCWP faster than nitroglycerine,
3 but maintained the significant effect compared to
4 nitroglycerine for 24 hours.

5 Natreacor produces sustained lowering of
6 PCWP for at least 48 hours, with no evidence of
7 decreasing effect.

8 Next slide.

9 This slide recapitulates the 48-hour PCWP
10 observation seen on the previous one, but added in is
11 the nitroglycerine dose required to maintain this
12 effect. Remember that the Natreacor dose was for the
13 most part fixed.

14 Next slide.

15 Systolic blood pressure reduction with
16 Natreacor and nitroglycerine should be counterpoised to
17 the degree of PCWP fall during the three-hour placebo
18 controlled period.

19 Note that for a comparable reduction in
20 blood pressure, Natreacor versus nitroglycerine,
21 Natreacor more effectively and consistently reduced
22 pulmonary capillary wedge pressure.

23 Next slide.

24 Now, I would like to take you back for a
25 moment to the primary endpoints of this trial. Again,

1 they were PCWP and dyspnea assessment at three hours
2 and placebo control.

3 I want to specifically address what we
4 know and can infer about the relationship between
5 these two measurements based on the data. I'll start
6 with a question that has been specifically raised
7 about the Natrecor database, that is, what effect does
8 physician assessment of invasive hemodynamics have on
9 patient dyspnea self-assessment.

10 In other words, does the presence of a
11 pulmonary artery catheter influence de facto physician
12 or patient assessment of dyspnea severity?

13 Next slide.

14 Remember that in study 324 a significant
15 decrement -- a significant improvement in dyspnea
16 scale was noted when Natrecor was compared to placebo
17 without any background therapy. But as alluded to,
18 the issue of potential influence of the hemodynamic
19 monitoring on symptom reporting was raised.

20 Next slide.

21 Let me answer this concern directly.
22 First, consider what VMAC did to avoid this perceived
23 potential for influence. As Dr. Horton explained,
24 VMAC took several steps to prevent this. Unlike in
25 the earlier Natrecor trials, there was no physician

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1 assessment of symptoms effect in VMAC at all. These
2 were patient self-assessments.

3 The Committee has raised the concern that
4 a physician assessed dyspnea scale in patients
5 undergoing hemodynamic monitoring would influence the
6 patient self-assessment. Thus, in VMAC the patients
7 had the first and the last word about their symptoms.

8 Furthermore, the patient was asked to fill
9 out his dyspnea scale sheet without coaching before
10 hemodynamics were recorded for the primary endpoint.

11 Furthermore, caregivers were instructed to
12 avoid discussion of hemodynamics in front of or with
13 the patient.

14 Next slide.

15 Additionally, to address this issue, a
16 test for interaction between treatment and catheter
17 use was done with an ANOVA demonstrating no
18 significant interaction at a p equal .24, and a
19 polychotomous logistic regression analysis also not
20 significant at a p equal .29.

21 Why then might some think from the VMAC
22 data that there is a potential for an influence?
23 Perhaps it may be the findings detailed on the next
24 slide.

25 At three hours Natreacor leads to a

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1 statistically significant improvement in dyspnea in
2 catheterized patients versus placebo with standard
3 care, but in non-catheterized patients, the greater
4 improvement of symptoms with Natreacor versus placebo
5 is not significant.

6 As mentioned, one interpretation of this
7 finding is that the catheterized patients were aware
8 of their hemodynamic status, and their responses
9 regarding dyspnea tainted by this information.
10 Looking at the rest of the data proves interesting,
11 particularly when remembering the pathophysiology of
12 compensative heart failure and dyspnea and the fact
13 that concurrent standard care was allowed in this
14 protocol.

15 Next slide.

16 Here Natreacor led to a statistically
17 significant improvement in symptoms and global self-
18 assessment in patients who were not hemodynamically
19 monitored at the 24-hour observation point. Remember
20 that this significance was observed during a double
21 blinded comparison with nitroglycerine coupled to
22 standard care.

23 Importantly and interestingly, the
24 catheterized patients did not have significant changes
25 in dyspnea scale or global patient self-assessment

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1 when Natreacor was compared to nitroglycerine cohort at
2 this time point.

3 In summary, VMAC so far is the largest and
4 first trial in an acute congestive heart failure
5 population to show efficacy of a new agent when added
6 to standard care. Indeed, standard care was left to
7 the discretion of the investigator and may have
8 included intravenous diuretics, dobutamine or
9 dopamine.

10 Furthermore, as we believe this trial
11 population represents a broad spectrum of patients
12 hospitalized for congestive heart failure, the
13 observations take on added importance.

14 Patients clearly were severely ill with
15 all being New York Heart Association Class IV at the
16 time of the study start. We specifically did not
17 exclude patients with acute coronary syndromes,
18 congestive heart failure with preserved ejection
19 fraction, patients with atrial or ventricular
20 arrhythmias, or even patients who had renal
21 insufficiency or failure.

22 Furthermore, the trial design maximizes
23 double blinded empiric symptom assessments while
24 minimizing influence of hemodynamic measurement.

25 Next slide.

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1. From a hemodynamic standpoint, Natreacor
2 turned out to be more effective than nitroglycerine in
3 this protocol. Its onset of action was rapid with
4 significant effects on PCWP noted at the 15 minute
5 mark. Compared to nitroglycerine, Natreacor's effects
6 were greater over 24 hours of effusion, and the
7 sustained PCWP and BP reductions suggest no diminution
8 of effects within this time period.

9. As Dr. Horton will demonstrate, there was
10 no greater level of symptomatic hypotension in
11 patients treated with Natreacor than in those treated
12 with nitroglycerine. Particularly attractive is the
13 fact that Natreacor proved effective with its simple to
14 give, bolus, fixed dose strategy.

15 With this administration protocol we have
16 demonstrated the drug is clearly better than placebo
17 and, at the very least, as useful as nitroglycerine
18 with respect to hemodynamics.

19 And with the predictable hemodynamic
20 effect observed with a single dose, we demonstrated
21 no need for invasive hemodynamic monitoring in
22 patients meeting the trial entry criteria.

23 Finally, there was a significant
24 improvement in dyspnea with Natreacor compared to
25 placebo at the three-hour primary endpoint mark.

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1 Next slide.

2 And so, in conclusion, the VMAC trial
3 demonstrated that fixed dose Natreacor is an effective
4 vasodilator in acutely decompensated congestive heart
5 failure patients and leads to meaningful clinical
6 benefit in a broad range of acutely ill patients.

7 Also important is the fact that Natreacor
8 was well tolerated and safe, as you will see, as given
9 in this study.

10 Dr. Horton will, indeed, next address the
11 safety issues.

12 Thank you very much.

13 CHAIRMAN PACKER: Okay. We'll pause here
14 for Committee questions. Again, I'll ask the
15 Committee to confine their questions to the specifics
16 of the presentation.

17 And I want to start with Ileana in a
18 moment, but before doing that, what I'd like to do is
19 bring up a question which was raised in all of or by
20 many of the individuals during the clinical trial
21 design discussion.

22 And I want to get it up front and center
23 so that we can work this out and get our questions
24 focused on this. What I want to do is focus on the
25 primary endpoint of dyspnea at three hours and the

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1 specifics of the analyses of that endpoint, and I want
2 to focus on that first.

3 And I'm going to ask Ileana and then I'm
4 going to ask Ralph to focus on that, and just let's
5 get this up front and center and focus on this.

6 So Ileana.

7 DR. PINA: Very nice, as usual. Very
8 elegant.

9 DR. YOUNG: Thank you.

10 DR. PINA: If I look at the separation of
11 the nitroglycerine-Natreacor-placebo for all subjects
12 at three hours, it seems that that difference is
13 driven by the patients who felt moderately better, and
14 that the patients who felt marked better were nearly
15 identical in the placebo and in the Natreacor group,
16 and in fact, that the nitroglycerine patients felt --
17 there were more patients who felt moderately better,
18 but of course, we're comparing to placebo just as a
19 point of fact.

20 DR. YOUNG: Right.

21 DR. PINA: And then, again, a bit of a
22 different, but probably not significant in the
23 minimally better.

24 So it seems to be driven by that
25 moderately better group, and it seems to be driven by

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1 the catheterized patients, again, in that moderately
2 better group.

3 What would you think? Why would you think
4 that the catheterized patients would have this
5 improvement in the dyspnea score?

6 DR. YOUNG: It's a great question, and
7 those of us that deal with the dyspnea decompensated
8 congestive heart failure struggle with knowing exactly
9 the pathophysiology of the dyspnea resolution in these
10 individuals.

11 I think a couple of things can be said.
12 First of all, specifically about the analysis, the
13 analysis was done two ways, one, a parametric analysis
14 and the other a non-parametric, and the reasons for
15 that, I think, have been discussed in the documents.

16 The overall dyspnea scale group reached
17 statistical significance by both of those analyses,
18 however.

19 Now, when you split the cath. group out
20 from the non-cath. group, that's when you lost
21 significance on either analysis.

22 Now, also your question deals with the
23 proportion of change within each one of those
24 subgroups, and that tails back to an earlier question
25 that was asked about, gee, how do we know how much

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1 dyspnea improvement to predict and exactly how do we
2 use or create a scale to measure this, and I think
3 this is very hard to do.

4 We did have some data though from 325,
5 which had a five point ordinal scale and gave us a
6 little bit of information about how to power up on
7 things and gave us some insight. The scale was
8 modified a little bit based on the 325 experience.

9 Now, getting back to your specific
10 question about the proportionality of changes within
11 these groups, I think those groups narrow down and
12 become smaller, and we can't make too much out of that
13 and, rather, need to make more out of the group that
14 either got better or didn't change and got worse.

15 And specifically why there may be a
16 difference between the catheterized and the non-
17 catheterized limb may relate to the time period and
18 course of events that is occurring.

19 In some senses it's unfair to parse out
20 the cath. and the pre-cath. parts at the three-hour
21 endpoint since we specified all patients, but you
22 know, everybody's going to do it, and we're going to
23 look at it.

24 On the other hand, at the 24-hour mark,
25 you know, we can say, "Well, it's not fair to parse

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1. out those two groups either there." But when we do
2 parse them out, we see the non-cath. patients become
3 improved from a significant fashion.

4 So if you see how medicines are given and
5 what's happening with those patients, perhaps that's
6 the answer to your question.

7 DR. PINA: Do we have any data whether
8 those catheterized patients -- and I've asked this
9 before about the diuretics. Our patients tend to feel
10 better when we give them diuretics and the diurese
11 (phonetic). Did they get more diuretics in all the
12 groups, realizing the investigator is standing there
13 looking at the wedge pressure? Did that group end up
14 with more diuretics early?

15 DR. YOUNG: Yeah. If we go to -- and I'm
16 getting like Dr. Packer. I have to look at --

17 (Laughter.)

18 DR. YOUNG: Let me see Slide 244. Thank
19 you, Steve. Sorry. Two, forty-four. I think we
20 might could address your point.

21 Here we see diuretic use during the
22 placebo control period, and so what is occurring here
23 -- actually let me go on to 246. Give me -- all
24 right. Here this addresses the specific question
25 about the median intravenous furosemide dose that had

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1 occurred over the 24-hour interval.

2 And if you'll look over here, it appears
3 that there is no difference in the median diuretic
4 doses that were given, and if you look at the
5 catheterized subjects over here, I believe that that
6 will address and will answer your question.

7 But the median doses of diuretics was
8 pretty good in this trial. It was not, I think, a
9 particularly small dose that these patients were
10 seeing.

11 Let me see 246.

12 DR. PINA: Yeah. Do you have it broken
13 down for those first three hours?

14 DR. YOUNG: Yeah.

15 DR. PINA: Since that is where the dyspnea
16 is formatted.

17 DR. YOUNG: Yeah, we can go back over
18 there.

19 The other thing that I think is
20 interesting is, again, if you look over the first 24
21 hours here and focus on the nitroglycerine group
22 versus the Natreacor groups here, and we've split out
23 both the total group and then the group with the fixed
24 dose Natreacor here, you see that more patients
25 received diuretics in the nitroglycerine group than in

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1 the Natre. groups over here. There was a trend and
2 some statistical significance here.

3 And I think that's an interesting
4 observation to add into potential efficacy for this
5 drug.

6 Let's go back to that three-hour period,
7 and I believe it was 244.

8 DR. PINA: Yeah, but that's not broken up
9 into --

10 DR. YOUNG: This is the placebo control
11 period for three hours, but you're right. It's not
12 broken up like you had asked. So this is more the
13 proportion of patients that were receiving the drug.

14 Well, I guess down here is the proportion
15 of patients receiving diuretics during that placebo
16 controlled period, and what you see is one group
17 versus the other prior to that three-hour primary
18 dyspnea endpoint didn't receive diuretics more than
19 another.

20 DR. PINA: I mean they look similar. It
21 would be interesting if you had the data to break it
22 down between the catheterized and the non-catheterized
23 because, again, there's an investigator that's looking
24 at numbers and knowing exactly where those patients
25 are and may be very willing to give extra diuretics at

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1 that point to lower it because I just -- the way you
2 did your dyspnea evaluation, there shouldn't have been
3 an interference with knowledge of hemodynamics and the
4 assessment score.

5 DR. YOUNG: Well, theoretically.

6 DR. PINA: Theoretically.

7 CHAIRMAN PACKER: Yeah, let's focus on
8 that for a moment, Ileana, just so we can -- because
9 all of us have pretty much common questions on this.
10 Just to clarify, we fully recognize that the primary
11 sponsor pre-specified analysis was an overall analysis
12 of both strata.

13 But it is fair, in fact, mandatory for
14 this Committee and for the division to look at what
15 contributes to that and particularly if one has
16 conducted a trial which is stratified based on
17 catheterization. There are lots of reasons to
18 stratify, but when you have, in fact, deemed it
19 appropriate to stratify and it is important to look at
20 whether the strata respond similarly or not, in
21 determining whether it is appropriate to combine the
22 data, you can pre-specify that the data should be
23 combined, but after you do your primary analysis and
24 find something that would be encouraging, you then
25 have to go and see whether, in fact, some of the

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1 assumptions that you've built into a combined analysis
2 are reasonable and valid.

3 And, Ileana, let me hold for a moment
4 because we're turning to a statistical issue and turn
5 to Ralph to pursue this.

6 Yes.

7 DR. D'AGOSTINO: Could you pull up 91 in
8 our presentation?

9 CHAIRMAN PACKER: Five, ninety-one.

10 DR. D'AGOSTINO: Another way of viewing
11 that is that you could say I have a stratification,
12 but my hypothesis is and my pre-specified analysis is
13 I'm going to do the overall analysis, and then after
14 I do that, I look for consistency within each of the
15 strata, the cath. versus the non-cath., and not
16 necessarily statistical significance in each of them.

17 And I think it would be worth it to sort
18 of pursue this a bit because they've rated some of the
19 questions also about the clinical significance.

20 The test that they used, they have an
21 analysis of variance test. They have basically a two-
22 by-two table, cath. versus non-cath., drug versus
23 placebo, and they used a test for interactions to see
24 if the effect is basically the same. Is the drug
25 working in both groups?

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1. That test for interactions is a terrible
2 test. It has very power poor. So even though it says
3 "except no interactions," you don't know whether to
4 believe it.

5 So I think what you have to do is sort of
6 look to see what they actually see. Now, one of the
7 groups has a p value of .03, and the other is -- one
8 of the comparisons -- and the other is a .410. So the
9 thing that I would ask is: is it consistent? Are you
10 seeing a consistent effect?

11 And then I would ask the question that was
12 raised earlier about what are some of the numbers
13 attached to this. This was a scaled value. You did
14 the normal distribution test. It would be equivalent
15 to the T test here.

16 Do you see the effect sizes being the same
17 in these two groups?

18 One of the comparisons is based on a
19 fairly large sample size, and the other is based on
20 half of that or something. You have 123 -- I have to
21 keep flipping back and forth -- versus 80. So to see
22 a worse significance in the group that has the -- the
23 stratum that has the smaller sample size is not that
24 upsetting.

25 But do you see basically the same effect?

1 And do you have any data on that? What were the mean
2 values that were associated with that?

3 Do you see what I'm driving at, Milt?
4 It's more than a question of just do you have an
5 interaction test. You have an interaction test, but
6 when you look at those two, you see significant
7 differences, but that's not pre-specified. That was
8 post.

9 So what you really want to ask is: are
10 you seeing the same effect? Do you think that
11 basically the two strata are telling you the same?

12 And visually they're probably telling you
13 the same, and you can explain the differences of
14 statistical differences maybe by sample size, but I
15 think it's their argument as opposed to my argument on
16 how to look at that, and I'd like to hear them say
17 something about it, and I'd also like if they have
18 that data, do they know something about the effect
19 sizes that are going on.

20 CHAIRMAN PACKER: Ray, did you want to add
21 something before the sponsor responds?

22 DR. LIPICKY: Well, no, I don't want to
23 add anything, I guess, except to emphasize that the
24 sample size that was used for the entire trial was
25 based on a guess, the treatment effect that would be

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1 observed, and that's how the thing was sized.

2 The trial was not designed to be able to
3 answer the question was the catheterized population
4 going to have a treatment effect and is the non-
5 catheterized population going to have a treatment
6 effect.

7 So I guess the question that really is
8 being asked, if I can use what I think is Peto's
9 terms: is there a qualitative interaction? Is the
10 treatment effect in the other direction, or is there
11 a quantitative effect, or is the effect sort of the
12 same?

13 Go ahead. I've said something wrong.

14 DR. D'AGOSTINO: Well, the data says
15 there's no interaction. So the question is are we
16 convinced enough that the direction by looking at
17 it -- the statistical procedure in Peto's vocabulary
18 would say don't go any further. You don't even have
19 a discussion of interaction.

20 DR. LIPICKY: Well, right, but we know the
21 test isn't very sensitive. So did it go in the wrong
22 direction? It didn't go in the wrong direction. It's
23 a matter of the p value changed.

24 DR. D'AGOSTINO: And I think the direction
25 is pretty much the same. It's just visually, and the

1 question I'm asking for more sort of comfort: do we
2 see effect sizes looking the same?

3 And I'm not -- just point estimates. No
4 statistical test because the statistical test has
5 already been done, but are we comfortable that things
6 are working in the same direction?

7 It's a very weak test for interaction, the
8 sort of are they in the same direction. They're in
9 the same direction. Now let's take a step further and
10 ask quantitative are we seeing the same type of
11 effect? Are the point estimates looking the same?

12 DR. LIPICKY: Well, the point estimates
13 aren't, right? I mean, the difference just looking at
14 the grafts is about 20 percent and the other one is
15 smaller.

16 DR. D'AGOSTINO: Those are standard.

17 DR. LIPICKY: No, this is proportion of
18 subjects.

19 DR. D'AGOSTINO: Yeah, but they have
20 scales.

21 DR. LIPICKY: But that wasn't looked at.
22 That isn't the data that we're looking at here.

23 DR. D'AGOSTINO: That's what the test was
24 though. Those p values are dealing with -- you did a
25 normal distribution test, right? Yeah, you did a

1 normal distribution test. So that's what the p values
2 are from the normal distribution test. This may be a
3 visual to help you, but it's an analogue to the non-
4 parametric. It's a Wilcoxon test, which basically
5 turns the numbers into ranks.

6 CHAIRMAN PACKER: Let me see if I can
7 focus this discussion, and, Bob, I'm going to ask you
8 to comment. But I think this Committee in the past,
9 prior to this meeting and specifically in January of
10 1999, raised the concern, the possibility that
11 hemodynamics, knowledge of hemodynamics might
12 influence the assessment of symptoms. We based that
13 based on data that were obtained in earlier studies
14 with this drug that were done far less carefully than
15 this trial.

16 But, in fact, it is curious that one can
17 look at these data and say that perhaps some of the
18 concerns that we had were justified. We, I think, all
19 recognize that the directional effect -- hold on, Ray
20 -- the directional effect in both groups is not
21 qualitatively different, and that the test for
22 interaction is not significant, albeit a lousy test.
23 I don't want to use that. I think the official term
24 is "low power" test, but it's sort of a similar
25 connotation.

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1. Here's the question. The question is: if
2 you believe that the knowledge of hemodynamics drives
3 this analysis -- I'm not saying that that's true -- if
4 you believe that the knowledge drives the finding on
5 symptoms, because you believe that knowledge of
6 hemodynamics somehow was conveyed to the patient in
7 some way, and let's not speculate as to how that might
8 have happened, then, in fact, what the sponsor did
9 here in this trial was, in fact, optimize the
10 possibility of a result because what they did -- and
11 I'm not saying what they did was right or wrong, but
12 it is important to understand that there are many
13 companies that are developing IV drugs, and they want
14 to hear what, in fact, we have to say today.

15 And what the company did was they did a
16 trial that had a hemodynamic component and a non-
17 hemodynamic component, and assuming there was a trend
18 in the non-cath. patient and then a particularly
19 striking trend in the cath. patient with a combined
20 analysis, the hope would be that it would reach a pre-
21 specified level.

22 DR. D'AGOSTINO: Yeah, the statistical
23 analysis will never reveal that.

24 CHAIRMAN PACKER: Right. It won't.

25 DR. D'AGOSTINO: I mean, the statistical

1 analysis will ask are they consistent.

2 CHAIRMAN PACKER: Right.

3 DR. D'AGOSTINO: And get to the question
4 of can you anticipate and can you live with subsets
5 not producing exactly the same.

6 CHAIRMAN PACKER: But what it does do is
7 it raises the question as to whether sponsors would be
8 encouraged in the future to do a VMAC-like trial with
9 cath. and non-cath. in the hopes that the -- in other
10 words, if there is unblinding, and I don't know if
11 there is; if there is unblinding, that the response in
12 the cath. patient would drive the analysis. The
13 result, that the non-cath. patients will trend in the
14 right direction.

15 DR. D'AGOSTINO: But could you ask that
16 they have to show it in both groups? I mean --

17 CHAIRMAN PACKER: You could ask that, but
18 we're not nearly there yet in the --

19 DR. D'AGOSTINO: No, but I'm just saying
20 as a way of addressing that question.

21 CHAIRMAN PACKER: Right, but I just want
22 to raise that as a possibility because we see the
23 trends that are, quote, consistent, and I don't want
24 to suggest that it's otherwise than that.

25 DR. YOUNG: Thank you.

1 CHAIRMAN PACKER: Let us ignore for a
2 moment the lower powered interaction test because no
3 one knows what that means.

4 DR. YOUNG: okay.

5 CHAIRMAN PACKER: But just think for a
6 moment that, in fact, if you really thought there was
7 an element of unblinding based on these data -- and
8 I'm not saying there is, but if you thought so -- that
9 it would be strongly -- this would strongly encourage
10 sponsors to always have a cath. component of a symptom
11 trial in the hopes that if there was some unblinding
12 and great attempts were made not to do so, that that
13 would drive the symptom assessment to a p value less
14 than .05 with the hope that the symptom assessment in
15 the non-cath. patients would go along for the ride
16 sort of, and that the combined analysis would reach a
17 nominal p value of .05.

18 I don't want to say that's right or wrong.
19 I just want to hear what the Committee thinks.

20 Bob.

21 DR. TEMPLE: Well, Milton, obviously if
22 you believe or have reason to believe that the
23 symptoms in the cath. patients are driven by bias,
24 then there's no point in doing the symptom score in
25 those people at all because there's no way to deal

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1 with that.

2 The question is how strong the evidence
3 that that's what's going on here is, and of course,
4 that's unanswerable. The interaction tests aren't
5 good enough. The numbers are too small. This sort of
6 variation is easily visible in all kinds of trials,
7 and I want to ask people how come it doesn't work for
8 nitroglycerine the same way because it's the opposite
9 effect there.

10 Now, does that -- that seems pertinent.

11 DR. YOUNG: Is that question to me?

12 DR. LINDENFELD: Just a point of
13 clarification, Jim. The patients that were non-
14 catheterized, were they asked to lie flat at 15
15 minutes, 30 minutes, an hour, two hours, and three
16 hours?

17 Again, I just wonder if some of the bias
18 here couldn't be that the patients that had a catheter
19 in had to lie down flat for all of these measurements,
20 and they would be much more dyspneic at that time as
21 opposed to the ones who never.

22 DR. YOUNG: Yeah, they were.

23 DR. LINDENFELD: You know, and that's
24 something that I think ought to come out of this. If
25 we're not going to have catheters in, maybe that's

1 something one ought to do to increase the sensitivity
2 of this test.

3 DR. YOUNG: They were in bed, but there
4 was no a pre-specified.

5 DR. LINDENFELD: And they were probably
6 sitting at 45 degrees reading the newspaper.

7 DR. YOUNG: And also the commentary, you
8 know, there's a lot of interpretation here that people
9 can put to the data in all of these trials. I take a
10 little bit of a different view. I don't think that
11 the catheterization procedure per se or the physician
12 investigator, knowing the hemodynamics necessarily
13 influences the results that we're seeing.

14 I think, on the other hand, we're seeing
15 something different. I think the broad spectrum of
16 heart failure is just that. It's a spectrum, and in
17 fact, if you look at very subtle, always not
18 statistically significant, but subtle differences in
19 who got a catheter put in and who didn't, I think
20 that's where perhaps the difference lies between the
21 catheterized and the non-catheterized group.

22 We also know that wedge drives symptoms,
23 in part. You know, the amount I don't think we can
24 quantify. There's a whole lot of things going on in
25 these heart failure patients though, and what we're

1. doing quickly here is dropping the wedge, bringing it
2. down. We don't know what the wedge did in the non-
3. cath. patients. We know what it did in the cath.
4. patients, and it did come down.

5. So I think it's a more complicated issue.
6. You know, Milton and I can sit on either side of the
7. fence about the influence, and I think it's fair game.

8. CHAIRMAN PACKER: Ileana.

9. DR. PINA: Jim, I tend to agree with you
10. that the population that got catheterized -- we said
11. this before -- tends to be a sicker group. It was
12. also a group that in some of them they had a higher
13. Natrecor dose because you could adjust it in the
14. catheterized group, and you couldn't in the other.

15. DR. YOUNG: Right.

16. DR. PINA: So is it possible -- I'm sorry?

17. DR. HORTON: Not during the first three
18. hours.

19. DR. PINA: So that probably would not
20. interfere.

21. I have to agree with you about the
22. spectrum of patients, but I just think that this was
23. a sicker group. Maybe this sicker group when you made
24. them feel somewhat better felt the difference. The
25. other group --

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1 CHAIRMAN PACKER: No, those were the
2 patients least likely -- oh, I'm sorry. More likely.

3 DR. PINA: They would feel something
4 better, and the other group had more acute coronary
5 syndrome, and again, I wonder how much that influenced
6 in how they felt better, but again, this is all just
7 extrapolation.

8 DR. YOUNG: To answer that question, acute
9 coronary syndrome group was small, but again, if you
10 look at the non-cath. group at that 24-hour mark, I
11 mean, that raises my eyebrows, too, and says, "Huh,
12 maybe all of the cath. guys got their benefit up front
13 and then it took longer for the non-cath. patients to
14 get their benefit down the road," but you were still
15 giving therapies to everybody and so it washes things
16 out a little bit.

17 And I think that hypothesis is a
18 reasonable one, too.

19 DR. PINA: It might be they were a small
20 group, but the non-catheterized patients had
21 substantially more peripheral edema, which is, again,
22 a little against that hypothesis.

23 CHAIRMAN PACKER: Ralph.

24 DR. D'AGOSTINO: One of the questions I
25 asked the previous speaker is in terms of all these

1 groups, I think there are so many subgroups floating
2 around and potential subgroups to look at, and none of
3 them can we hope to find statistical significance, but
4 consistency, and you know, here we're seeing one here,
5 and I'm looking at it purely from a statistics point
6 of view. We're not saying sort of the motivation or
7 the set-up that may have changed it.

8 But I think that trying to dice the data
9 down and trying to look at statistical significance is
10 a hopeless task. I mean, do we see consistency?

11 If you have explanations, a priori
12 explanations, which it seems like you have, you know,
13 that's part of the concern, but you're going to see,
14 I think, some bizarre things as you go through these
15 subgroups, but is there sort of general consistency?

16 I wouldn't subject them to formal
17 statistical tests.

18 CHAIRMAN PACKER: No, I think that, Ralph,
19 the only reason we're having this discussion isn't
20 because this is your typical sort of subgroup that
21 comes out.

22 DR. D'AGOSTINO: Exactly, and I understand
23 that.

24 CHAIRMAN PACKER: Right. This was a pre-
25 specified concept that emerged from the January 1999

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1 meeting with reasons why -- and, in fact, the sponsor
2 sensitive to that concern.

3 DR. D'AGOSTINO: No, I understand that.

4 CHAIRMAN PACKER: -- bent over backwards
5 to construct their design, one, to include non-
6 catheterized patients at all, and two, to take great
7 pains to make sure that those assessing the symptoms
8 or dyspnea would not have knowledge of the
9 hemodynamics.

10 So that, in fact, this was --

11 DR. D'AGOSTINO: No, I understand that.
12 Some of the conversation after this has been trying to
13 look at subgroups, and I think it's right, but I think
14 that it's not going to probably be more than your
15 discussion of why these two groups are here and what
16 the concerns are.

17 CHAIRMAN PACKER: Okay. Maybe I can
18 ask -- yeah, Ray.

19 DR. LIPICKY: Independent, I think, of the
20 outcome of this discussion, if I were in the future
21 asked for advice on this sort of thing, if people's
22 pockets were big, I would say they ought to have
23 catheterized patients; they ought to have non-
24 catheterized patients, and sample size in both should
25 be adequate, and if they didn't have deep pockets,

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1 they should have all non-cath.

2 And I think it's only in that way that you
3 can get the answer you want, and the problem here is
4 a sample size problem, and you can argue about the
5 subgroup forever and not be able to tell.

6 CHAIRMAN PACKER: Because remember we're
7 not just discussing this NDA. We're discussing some
8 general principles as to what kind of data we would
9 like to see, and so I want the Committee to think of
10 that, take that perspective in thinking about this
11 particular issue.

12 It's a very important issue. The sponsor
13 knew they were sensitive to it. They designed the
14 trial in order to address the issue. They have the
15 data that they have. We need to make an assessment of
16 these data in a manner which is not only consistent
17 with our thinking now, but consistent with guidance we
18 think is appropriate in the future.

19 DR. LIPICKY: So don't blame it on the
20 sponsor. We were part of this, and we did not think
21 that there had to be a plan for how to handle that,
22 and that's our fault.

23 CHAIRMAN PACKER: No, no, no. There was
24 no blame here. It is just simply an observation, and
25 you know, we need to think it through.

1. Jeff.

2 DR. BORER: You'll stop me if I'm straying
3 too far here. I must tell you I think that they look
4 pretty good as they are, but about dyspnea. However,
5 there were some collateral issues that might have
6 provided support given the fact that dyspnea is just
7 a symptom, and there are confounders, et cetera, et
8 cetera.

9 And I'd like to ask a little bit about
10 that. In the initial NDA there was a suggestion that
11 urine volume was lower in the group that was treated
12 with Natreacor than those who weren't. I didn't see
13 any data about urine volume here, and I understand
14 that there's an obvious confounder that concomitant
15 use of diuretics, et cetera, et cetera.

16 But do we have any sense of whether this
17 agent did what putatively it would do, which is to
18 increase natruresis.

19 DR. YOUNG: I think it would be unfair to
20 impugn too much from the database. This was a large
21 clinical heart failure trial, and up front we knew
22 that we couldn't run a GCRC type of study that is
23 necessary to quantify electrolyte changes and urine
24 volumes and urine function.

25 However, we did see fewer diuretics

1 prescribed over the course of events. The edema
2 resolution, the tachypnea improvement; weight changes
3 were the same in the groups though on top of
4 underlying diuretics.

5 DR. LIPICKY: Correct me if I'm wrong.
6 The original NDA actually showed that there was some
7 salt and water retention in the 24 hours.

8 DR. HORTON: No, no. The original NDA
9 showed in 325 during --

10 CHAIRMAN PACKER: It was neutral, right?
11 Please.

12 DR. HORTON: Thank you for recognizing me.
13 I'm sorry I was interrupting.

14 CHAIRMAN PACKER: Okay.

15 DR. HORTON: In 325 during the six-hour
16 placebo controlled period where diuretics were
17 withheld, there was actually a significant increase in
18 urine output with Natreacor compared to placebo.
19 That's in the original NDA, but it's during only the
20 six-hour placebo control period.

21 CHAIRMAN PACKER: I'm a little bit
22 confused. If I remember in January of 1999, there was
23 a considerable discussion on the issue as to whether
24 this agent was a natriuretic, and in fact, there was
25 a joke that was made -- some people laughed -- that,

1 in fact, there did not appear to be any net
2 natriuretic response.

3 The one member of the Committee who I
4 don't think is on the Committee anymore said, "If
5 there is no natruresis, why did you call it what you
6 called it?"

7 And the response of the company was, "It
8 is B type natriuretic peptide. The company didn't
9 call it that."

10 And then the response of the same person
11 on the Committee is, "Well, you did call it Natrecor,
12 which implies that there was natruresis."

13 I thought the net result of all of that
14 discussion was that there was no net positive or
15 negative if one looked at the totality of the data.
16 Is that not correct?

17 DR. LIPICKY: That's my recollection, but
18 you may be correct that 325 said something different,
19 but there were six other, seven other studies to look
20 at, and they weren't very consistent.

21 DR. HORTON: There were only two other
22 studies in which -- three other studies in which urine
23 output was collected. One was a 307 study where you
24 showed the dose dependent effects, and in that study
25 there was both diuresis and natruresis.

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1 In the 24-hour infusion study in which
2 diuretics were not withheld, there was no difference
3 between Natreacor and placebo.

4 In 325, during the placebo controlled
5 period when diuretics were withheld, there was a
6 difference, but during the 24-hour period when then
7 standard care agents could be given, there was no
8 difference over the 24-hour period.

9 DR. PINA: Are you talking about 325?

10 DR. HORTON: Three, twenty-five.

11 DR. PINA: I'm sorry. You're talking
12 about 325.

13 DR. HORTON: Yes.

14 DR. PINA: Was the placebo period the zero
15 to six hour?

16 DR. HORTON: Yes.

17 DR. PINA: The initial six hours? I've
18 got the volumes here.

19 DR. HORTON: Yeah. It was a statistically
20 significant effect. I believe the p value was .01,
21 and the differences in the .015 and the .03 groups
22 from placebo were approximately 180 milliliters and
23 approximately 240 milliliters during just the six-hour
24 period of time.

25 But I think in sum -- and there's also

1 ample literature that shows that this is a natriuretic
2 peptide, but the issue is that in typical patients
3 where you're not withholding medications, Natrecor is
4 not a diuretic. It is not nearly as potent at all as
5 any of the agents that really were designed to do that
6 and whose primary mechanism of action is to do that.

7 So when you add on lasix, you don't see an
8 effect.

9 DR. PINA: Maybe I'm a bit confused, but
10 with the 325 data that I have here from the agency,
11 the negative -- it actually was positive for
12 nesiritide at .03 with the .015 infusion. There was
13 97 -- this is mean --

14 DR. LIPICKY: Just after 24 hours you're
15 only --

16 DR. PINA: It says zero to six-hour data.
17 Stable, and I refer everybody to page 62 of the
18 assessment of 325 in the agency book. The fluid
19 intake mean was 97. The urine output in mLs per hour
20 was 91.7, with a minus 2.6, and with the higher dose
21 nesiritide at .03, there was a bit more diuresis at
22 about 9.8.

23 And the control was even worse, 29.7. So,
24 yeah, comparatively a bit more, but still not a frank
25 diuresis

1 DR. HORTON: That's correct.

2 DR. LIPICKY: But, Jeff, why did you want
3 to know?

4 DR. BORER: Well, for two reasons really.
5 First, because the issue was flagged in the NDA that
6 was discussed at the meeting at which I wasn't present
7 a couple of years ago, but in addition, because I am
8 convinced by the dyspnea data, together with some of
9 the other information we have, but I wanted some
10 information as to whether there was more collateral
11 evidence to support the dyspnea results, and urine
12 volume would have given me that.

13 We don't have it; we don't have it.
14 that's all.

15 DR. PINA: I think we have it for 24
16 hours, and there's no difference.

17 DR. HORTON: Yes.

18 DR. PINA: There's no difference in that,
19 and there's also one problem. There's no difference
20 at all in respiratory rate. One would like to see a
21 slight change in respiratory rate if people's dyspnea
22 was really --

23 DR. YOUNG: Respiratory rates start at
24 about 23, but that's good because that goes along with
25 a wedge of 28.

1 DR. PINA: No difference.

2 DR. YOUNG: Right, and then they fall in
3 a similar fashion.

4 CHAIRMAN PACKER: Let me take up some from
5 what Jeff has brought up. Jeff has asked the question
6 in an attempt to determine how much he and the
7 Committee should feel comfortable with the dyspnea
8 assessment at three hours. That was part of the
9 reason that you asked the question.

10 Jim has put forward to the Committee that
11 regardless of what misgivings or uncertainties the
12 Committee may have about the comparison of placebo and
13 nesiritide at three hours, there is a comparison of
14 nesiritide and nitroglycerine at 24 hours, which is
15 statistically significant and primarily driven by the
16 result in non-catheterized patients.

17 How helpful is this? How helpful is this?
18 Does this convince you that the initial thing was a
19 place of chance or do you think that this is helpful?

20 DR. BORER: Well, I think we're trying to
21 dissect the data to a level to which we should not be
22 going. I think the number of patients that were
23 studied was relatively small. We're dealing with a
24 symptom, a subjective symptoms that's very difficult
25 to quantify. The best we can do is get an overall

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1 sense of what happened to the group as a whole, I
2 believe.

3 And I think that the data at three hours
4 are highly suggestive that the drug is doing
5 something. The data at 24 hours are consistent with
6 that. I don't think that the case is made that
7 Natreacor had the greater effect than nitroglycerine
8 did no dyspnea because of the reasons that were
9 actually raised in the statistical review from the
10 FDA, but it doesn't matter. It went the same way.

11 Nitroglycerine is an active comparator
12 that we believe is good for people with heart failure
13 certainly to lower pulmonary pressures and make them
14 feel a little better, we think. Maybe it doesn't do
15 that, but you know, the data are in the same
16 direction.

17 So I find the 24-hour data supportive of
18 the three-hour data, and I think the three-hour data
19 are pretty good for the total group of patients that
20 were studied. I really think we are asking too much
21 of the data to look at subgroup and sub-subgroup and
22 whatever for all of the reasons that Ralph has pointed
23 out.

24 DR. D'AGOSTINO: Let me just reiterate
25 that, you know, we did ask the question. They wrote

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1 it down, and we did ask the question. This is their
2 primary endpoint; this is their primary analysis, and
3 they performed it exactly as they said they were going
4 to.

5 Now, if there were design problems which
6 you can psych out, that's one thing, but if you've
7 asking for the consistency of the data, they've shown
8 it here. I believe those two subgroups, catheterized
9 versus non-catheterized, are going to be consistent,
10 and they've shown consistency across other pieces.

11 The 24-hour readings are nice also, but if
12 the 24-hour readings went sort of in the other
13 direction and weren't statistically significant, I
14 don't think that that would necessarily be an
15 indictment of this analysis.

16 You know, it's nice to see it all falling
17 in the same way, more and more confirmation, but this
18 primary analysis, I think, is where we really should
19 focus the main attention.

20 CHAIRMAN PACKER: Let me just ask for the
21 remainder of time that we have, again, let's just
22 focus on this issue. Then we're going to go on to
23 whatever other issues anyone wants to talk about.

24 Any other discussion on the assessment of
25 dyspnea either compared with placebo or compared with

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1 nitroglycerine at any point in time.

2 I'm sorry. Yes.

3 DR. HORTON: Sorry. I just wanted to
4 respond to Dr. Pina's question earlier about
5 diuretics, and it gets back to the question of is
6 there a reason why there would be no differential
7 effect in non-cath. patients, but there would be with
8 the cath. patients other than study drug itself or the
9 knowledge of hemodynamics?

10 And if you look within the six-hour period
11 of time beforehand, in the catheterized patients, I
12 have this data, but I'll just say it quickly. In the
13 catheterized patients, about 25 percent of them got an
14 IV diuretic before any time between time zero up to
15 six hours before the start of study drug versus 40
16 percent of the non-cath. patients.

17 And that gets back to your observation
18 that the non-catheterized patients had more overt
19 evidence of frank fluid overload with pulmonary edema.
20 It makes sense.

21 But the other reason, the other point that
22 I just wanted to make is that there's also a reason
23 why there could have been a statistically significant
24 effect at 24 hours in non-cath. patients between
25 Natreacor and nitroglycerine, but not in the cath.

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1 patients, and that has to do with the dose of
2 nitroglycerine that was being administered. At higher
3 doses, possibly more effective, and there would be no
4 differentiation between the two treatment groups.

5 And then the last point since tachypnea
6 was mentioned, we can bring up slide 278. We looked
7 at tachypnea. There were decreases in respiratory
8 rates overall, not distinguishable from placebo, but
9 clearly that effect would be greater in patients who
10 are actually tachypneic, of which approximately 60, 65
11 percent of them were tachypneic.

12 And there is at least a trend in the right
13 direction that the mean respiratory rates were coming
14 down greater with Natreacor than placebo, plus-minus
15 against nitroglycerine.

16 Thank you.

17 DR. PINA: Jeff, to go back to your point
18 at the 24-hour, you were asking about the urine
19 volume. Even though the adjustable dose Natreacor
20 patients received less diuretics overall -- am I
21 correct with that, Dr. Horton?

22 DR. HORTON: Yes.

23 DR. PINA: That the adjustable dose
24 received less diuretics overall?

25 DR. HORTON: Sorry. I'll check that.

1 That's a different question.

2 DR. PINA: Well, that's at least what the
3 document says here.

4 The negative urine output between the
5 nitroglycerine and all Natreacor group was nearly
6 identical.

7 DR. YOUNG: Sure, and I'm not surprised.

8 CHAIRMAN PACKER: Marv.

9 DR. KONSTAM: Could we see data regarding
10 dyspnea at baseline across the different groups?

11 DR. YOUNG: That was on that slide that
12 was just up there, I believe.

13 DR. KONSTAM: Is that right?

14 DR. YOUNG: Wasn't it?

15 The mean respiratory rate was 23 --

16 DR. KONSTAM: No, no, dyspnea, dyspnea.

17 DR. YOUNG: Oh, dyspnea scale. Oh, oh.
18 Do you want me --

19 DR. HORTON: The dyspnea assessment itself
20 was a change from baseline.

21 DR. KONSTAM: No, I understand, but there
22 is information on the subject.

23 DR. HORTON: Yes. We had the physician
24 assess the patient at screening to qualify them for
25 the study, and then the patient did that as well. We

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1 have that data.

2 DR. KONSTAM: Well, I have a table from
3 the medical review that says, you know, dyspnea at
4 rest, dyspnea while sitting, dyspnea while lying,
5 dyspnea where --

6 DR. YOUNG: That was the baseline
7 quantification, and that tool is not the same as --

8 DR. KONSTAM: I understand.

9 DR. YOUNG: -- the change from baseline.
10 The way the dyspnea scale was done was that, but
11 you're asking about quantification of that to go --

12 DR. KONSTAM: The question I have is did
13 the patients across the different groups look the same
14 at baseline.

15 DR. LIPICKY: Well, the table you're
16 referring to was that Dr. Karkowsky challenged the
17 fact that all patients with dyspnea get rest, and he
18 produced that table. That table is accurate, but how
19 it should be interpreted was talked about earlier,
20 what dyspnea at rest means.

21 DR. KONSTAM: Yeah. I mean, just what
22 concerns me about -- I mean, that's what I wanted to
23 put up because what concerns me about it is the
24 different groups look a little different

25 CHAIRMAN PACKER: The FDA review in

1 reference to that raised the possibility that another
2 way of analyzing a primary endpoint would have been to
3 use the baseline symptoms as a covariate. Karkowsky
4 specifically suggested that simply because there may
5 or may not have been meaningful differences in
6 baseline symptom severity --

7 DR. KONSTAM: Just looking at the numbers,
8 I mean, within the catheterized group, the placebo and
9 the Natrecor groups look different at baseline. So I
10 wonder what we're going to do about that, if anything.

11 DR. LIPICKY: Well, nothing has been done.
12 Do you want to do something?

13 DR. KONSTAM: I want to just show it.

14 CHAIRMAN PACKER: Can we just see those
15 data again?

16 DR. HORTON: I'm sorry. We don't have
17 them.

18 DR. KONSTAM: I mean, in the medical
19 review it's on page 24 of the medical review, Table
20 15.

21 DR. HORTON: I have the baseline activity
22 based dyspnea assessment in catheterized patients
23 showing that if you look at the top three groups,
24 which are at rest, 93 percent of the Natrecor-
25 nitroglycerine patients, 93 percent of Natrecor -- oh,

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1 sorry. This is during the active control period. I
2 need to find the placebo control. Sorry.

3 DR. KONSTAM: I mean, I can read you the
4 numbers.

5 DR. LIPICKY: But then what do you want to
6 do? Because there hasn't been a covariate analysis
7 done. No one has done a quantitative assessment of
8 how that should occur. So what can we do?

9 DR. KONSTAM: Well, if, in fact, the
10 groups look different --

11 DR. D'AGOSTINO: But you did take
12 differences, right? The analysis is on difference.

13 DR. KONSTAM: No, I understand the
14 analysis.

15 DR. D'AGOSTINO: I mean, that's like a
16 covariate analysis.

17 DR. KONSTAM: Yes, but biologically it
18 could be very important because if you're not that
19 dyspneic at rest, then you can't get much more
20 dyspneic. Okay. So although mathematically I
21 understand your point, but clinically, if the patient
22 groups look different --

23 DR. D'AGOSTINO: Well, the covariate
24 analysis isn't going to be that much more clever
25 actually in dealing with that.

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1. DR. YOUNG: I guess, Marv, your argument
2 is it's similar to wedge pressure. If the wedge
3 pressure isn't quite as high, it's not going to fall
4 as much

5 DR. KONSTAM: Right, right. But this may
6 be even more so. Like if somebody asked me if at
7 three hours was I better, I hope that I would say no
8 because I'm not dyspneic to begin with

9 DR. LIPICKY: Well, let me ask you the
10 obvious, Marv, because I don't have the table in front
11 of me. Is the disparity at baseline in favor of
12 finding a dyspnea?

13 DR. KONSTAM: Yeah, I mean, so in the --

14 DR. LIPICKY: So it says that the baseline
15 characteristics made it more likely, you would find
16 that the Natrecor --

17 DR. KONSTAM: Right. At baseline in the
18 catheterized group, just looking at the catheterized
19 patients, the --

20 DR. LIPICKY: Well, but that's not there
21 because we can't draw a conclusion from that even when
22 we look at the dyspnea score. So that doesn't help me

23 DR. TEMPLE: Would you say that again?

24 DR. LIPICKY: Well, if what Marvin is
25 going to do is to try to convince me that the baseline

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1 qualifications make the interpretation of the result
2 difficult, if we're saying we can only pay attention
3 to the dyspnea score in both catheterized and non-
4 catheterized patients, which is what was said, then
5 reading me the numbers for catheterized patients isn't
6 going to influence me.

7 DR. KONSTAM: Well, okay, but the problem
8 is that that's the way the table is broken up

9 DR. LIPICKY: Well, that's a problem. I
10 mean, that means that the way that table is
11 constructed doesn't help you or me. It only confused.

12 DR. KONSTAM: Right, but also the
13 discrepancy is evidence in the catheterized and not
14 the catheterized patients. Okay? The discrepancy is
15 suggested if you look at the numbers in the
16 catheterized, but not in the non-catheterized
17 patients, and that's the same direction as we see the
18 results.

19 DR. TEMPLE: Could you just say what the
20 observation is and what the implications? You think
21 which group is sicker?

22 DR. KONSTAM: It looks like the Natreacor
23 group -- among the catheterized patients, just by
24 their numbers, it looks like the Natreacor group looks
25 a little sicker at baseline. If you just look at the

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1 percent of patients who were dyspneic while sitting,
2 you know, which one could question: does that then
3 give that group a better opportunity to improve?

4 DR. LIPICKY: Well, I question that that's
5 true.

6 DR. KONSTAM: Okay. I'm not trying to
7 make too big a deal about it. I'm not trying to draw
8 conclusions from it. Okay? That wasn't my intent.
9 I just wanted to just throw it in and say it does look
10 like the groups look a little different at baseline
11 and let people conclude what they want. It's hard to
12 do that without looking at the data.

13 DR. TEMPLE: Suppose you look at the two
14 top groups. I mean, maybe you know, but at rest while
15 sitting and at rest while lying flat look similar to
16 me. I mean, I guess I don't know which is worse.

17 PARTICIPANT: Rest while sitting is worst.

18 DR. TEMPLE: Rest while sitting is worst
19 than lying flat? Oh, because it would be apnea.
20 Well, if you add them up, it's not clear how different
21 they are.

22 DR. HIRSCH: I think it's impossible to do
23 the analyses at this point with this data set, and I
24 see the same trend, and one could hypothesize that --

25 DR. D'AGOSTINO: Well, I don't think it's

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1 impossible. I think that it's in some sense beside
2 the point. I mean, you know, these groups were
3 randomized. They do have some imbalanced. A lot of
4 the imbalances in the nitroglycerine group for some
5 strange reason as opposed to the treatment versus --
6 Natreacor versus the placebo, and the change is a
7 certainly power way of looking at this data.

8 DR. HIRSCH: But, Ralph, I think for
9 future study design it raises the question of how to
10 minimize confounding variables if another company
11 wants to do such a thing. So that the control
12 condition is natural and common as possible.

13 DR. D'AGOSTINO: No. I mean, I think in
14 terms of where we're going with these, you know,
15 possible recommendations it's quite useful, and that
16 also is the terms of should you do catheterized or
17 non-catheterized patients, or should you show
18 significance in both.

19 What I was commenting on was I thought
20 that we were raising questions with another possible
21 analysis of this data. I mean, I'm sure I can find an
22 analysis where you're not going to get significance at
23 all if you give me a long enough time, and that's what
24 I'm afraid of.

25 CHAIRMAN PACKER: Okay. I really want to

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1 move this process along. There's a lot of stuff to
2 cover, and let me just -- you know, we've covered one
3 part of Jim's presentation. There's a lot of things
4 we can cover.

5 Why don't we start all the way at this end
6 and move forward. Ralph, any additional comments?
7 Steve?

8 DR. NISSEN: Jim, I have a series of sort
9 of interrelated questions, and the hypothesis to be
10 tested here was that this agent was effective in the
11 background of standard of care, and so I'm interested
12 in exploring with you this whole issue of standard of
13 care.

14 Now, as I understand this, these were
15 Class IV patients, dyspneic at rest with acute
16 decompensation; respiratory rates in the low to mid-
17 20s; a pretty sick group.

18 In my experience, if a patient like that
19 comes in the emergency room, before I've answered my
20 page, someone has given them a big slug of IV
21 furosemide, and I'm very troubled here by slide number
22 73, if you want to put that up, because it suggests
23 something about this study was somehow biased toward
24 not providing standard of care.

25 I mean, here is only 30 percent of the

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1 Natrecor patients got an IV diuretic within six hours
2 before they began these infusions, and only a little
3 more than half got an IV diuretic within 24 hours
4 before.

5 And so it looks to me like somebody was
6 withholding diuretic therapy, withholding standard of
7 care therapy in order to set these patients up for the
8 drugs to be used, and I need to understand what
9 happened here to be able to properly interpret the
10 data.

11 DR. YOUNG: You hit right smack dab on an
12 incredibly important thing that we're dealing with
13 right now. You know, there are no guidelines for how
14 to treat these patients. There are none. We think
15 we've got a lot of ideas. There's a lot of teaching.
16 There's a lot of evidence that has been generated from
17 huge amounts of clinical experience and whatnot, but
18 the key is the gradation of the heart failure patient,
19 the time at which you're seeing them, whether this is
20 an acutely presenting patient with acute fulminant
21 pulmonary edema and tachypnea or whether this is
22 somebody, as the majority of patients in this trial
23 represent, the gradual deterioration that has occurred
24 over several months.

25 And I would submit to you that this is, in

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1 fact, the real world practice of how decompensated
2 heart failure gets treated and how patients move
3 along.

4 Plus, interestingly enough, personally I
5 don't think clinicians use enough IV diuretics, and
6 they will revert to high oral doses frequently before
7 intravenous bolus.

8 So I'm not particularly bothered. I think
9 this fits pretty much with my perception of what
10 standard care is.

11 DR. NISSEN: Well, I don't know, Jim. I
12 mean, it might be true in small community hospitals
13 and so on, but I looked at your list of investigators,
14 and they're a pretty sophisticated bunch of people,
15 and it just to me, you know, having worked for many
16 years in a coronary care unit treating such patients,
17 as you know, I just to me find it inconceivable that
18 so few patients would receive IV diuretics in the day
19 before enrollment in the protocol.

20 In a similar vein, along a similar line of
21 thinking, I look at the titration of IV
22 nitroglycerine, and I thought to myself as I looked at
23 this, "What would happen in my coronary care unit if
24 I came in the morning after a patient was enrolled
25 with congestive heart failure and one of my fellows

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1 left a patient with a wedge pressure in the mid-20s
2 and the patient was on 50 micrograms of IV
3 nitroglycerine.

4 Well, you know, me pretty well. You know
5 that the fellow would get skewered, that I'd reach
6 into my pocket, pull a quarter out, and ask them to
7 call their mother and have her come pick him up and
8 take him home.

9 And so it looks to me like there was some
10 investigator bias here toward not treating the
11 congestive heart failure, and that has a lot of
12 influence on how we interpret the data in this
13 context.

14 DR. YOUNG: Well, let me answer those two
15 questions in several ways. First, where is it that
16 you work, Steve?

17 (Laughter.)

18 DR. NISSEN: As many of you know, we're at
19 the same institution as Dr. Young.

20 DR. YOUNG: So I know you're kind of a
21 nitrate kind of guy, and I understand that.

22 (Laughter.)

23 DR. YOUNG: And I understand the
24 perspectives, and Steve and I actually agree a lot
25 about these issues. The facts are people do give

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1 aggressive nitrate dosing in decompensated congestive
2 heart failure, and people like you, people that run
3 coronary care units, a lot of people at this table
4 that do a lot of this, myself included, but there are
5 a couple of things that are important.

6 Number one, the anecdotes of the gram,
7 like you mentioned earlier this morning, those we tend
8 to remember, and yet when you look at ordinary
9 practices across the country and across the pool of
10 how nitroglycerine is used, we see a very different
11 thing.

12 If you look at the literature, for
13 example, well, since 1996, between '96, May 15th of
14 this year, there were 35,000 articles published on
15 congestive heart failure, many by people up here on
16 this panel.

17 There was a couple thousand published on
18 nitrates and heart failure, and 245 published on
19 intravenous nitroglycerine that dealt in one fashion
20 or another with heart failure, and in fact, there's a
21 lot of consistency.

22 Most people recommend starting at five or
23 ten mics. per minute and up-titrating all the way up
24 to several micrograms, but if you look at the average
25 doses that are in a lot of these studies, they're 40,

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1 60, maybe 80.

2 So again, we come back to individual
3 practices versus the way people are using this drug
4 generally.

5 DR. NISSEN: One short follow-on question.
6 In the group in which the bag of nitroglycerine
7 contained placebo, do we know how much nitroglycerine
8 they would have gotten had there been nitroglycerine
9 in that bag?

10 DR. YOUNG: That was a very perceptive
11 question that you asked, and we were trying to get
12 that data. I'm not entirely certain that we have it
13 yet.

14 DR. HORTON: We're still doing it.

15 DR. NISSEN: Do you understand why I'm
16 asking this?

17 DR. YOUNG: Yes.

18 DR. HORTON: Yes.

19 DR. NISSEN: Because I want to get inside
20 the mind of the investigators, and if they were really
21 actively titrating the nitroglycerine, then what
22 should have happened is those people should have ended
23 up on a boat load --

24 DR. YOUNG: Right. My hypothesis is that
25 those patients, their dose is, in fact, impacted.

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1 DR. HORTON: If I could, I'd like to
2 address your concerns about this table because I think
3 some of it is a technicality because it comes down to
4 how the analysis was done because, first of all,
5 patients might have been randomized and treated very
6 quickly, and so they wouldn't have gotten an IV
7 diuretic for the six fours. If they had -- sites were
8 different. There were 55 sites. If they had a
9 smooth, you know, well oiled clinical research
10 machine, they may not have given the IV diuretic or
11 they might have written the order and it simply might
12 have not been given by the time the study drug was
13 started.

14 The second thing is that's just an
15 analysis within six hours. It might have been six
16 hours and five minutes. It might have been eight
17 hours. So if you had given an IV diuretic and said,
18 "Well, I'm not going to give another one for seven
19 more hours or for six and a half hours," they already
20 got it at eight hours or whenever. That wouldn't show
21 up within the six-hour time point, and you do have 60
22 percent of the patients receiving an IV diuretic
23 during that time period.

24 The other thing that's on this slide is
25 that there were some patients who were getting other

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1 IV vasoactive medications, and that may have been the
2 investigator's primary agent to treat the
3 symptomatology of that particular patient, and they
4 just simply may not have gotten an IV diuretic on top
5 of that, depending on what their overall -- also, 90
6 percent of patients were on oral diuretics, and that
7 might have been an explanation for why some didn't
8 make the threshold for getting an IV diuretic.

9 DR. NISSEN: I still think that -- I heard
10 everything that you said, but I still think that
11 what's going on here is that investigators are
12 involved in protocols like this. They want the drug
13 to work. They're rooting for you, and I think that
14 may have subtle effect and maybe some not so subtle
15 effects on how they practice medicine.

16 And that's important for us to understand,
17 and if the effect was that they never thought that
18 they were doing you a favor by not giving so much
19 concomitant medication so your drug would have more of
20 an opportunity to look good, then that does influence
21 how we are to interpret the results.

22 DR. YOUNG: But that's why it was double
23 dummied.

24 DR. LIPICKY: What data could they have
25 collected or what design feature of the trial could

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1 they have put in place so that your question could be
2 addressed?

3 DR. NISSEN: I'll have to think about it.
4 That's a tough question.

5 DR. LINDENFELD: Just to get back to the
6 dyspnea one more time, I understand the primary
7 endpoint is three hours, but maybe you can help me
8 understand why the dyspnea score versus placebo wasn't
9 any different at any of the other time periods
10 measured.

11 Just, you know, we think this is a
12 reflection of the difference in wedge pressures, and
13 the difference was almost exactly the same between
14 placebo and Natreacor at the 15 minute, 30 minute, one
15 hour, three hour, and yet dyspnea is only significant
16 at three hours.

17 That bothers me.

18 DR. YOUNG: Yeah. Let me --

19 DR. LINDENFELD: Excuse me. The same is
20 true of global assessment. There's only one time
21 period when any of these are significant compared to
22 placebo, and that's three hours. It was measured five
23 other times.

24 DR. YOUNG: Yeah, and let me tell you what
25 my perception is, and it relates to comments earlier

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1 about what is happening as we resolve pulmonary edema,
2 lowering pulmonary artery pressures, and particularly
3 the time progress that we're seeing with the
4 concomitant medications, and that's my interpretation
5 of the data.

6 A three-hour mark is perhaps the earliest
7 that we would anticipate seeing any significant
8 improvement in dyspnea. We got, I think, some
9 information from some of the other trials. So that's
10 my perception as to why that is occurring.

11 CHAIRMAN PACKER: There is an alternative
12 hypothesis, of course.

13 DR. YOUNG: Sure, chance.

14 CHAIRMAN PACKER: No. The alternative
15 hypothesis is that since hemodynamics were measured
16 before three hours, you took great pains to measure
17 symptoms before hemodynamics at each point in time,
18 but, of course, at three hours there was knowledge.
19 There was knowledge almost exclusively held by the
20 investigator or coordinator of the hemodynamic changes
21 in the hours preceding three hours, and I'm not saying
22 that that's the answer, but that's --

23 DR. YOUNG: No, but it's an alternative
24 hypothesis.

25 CHAIRMAN PACKER: But that's an

1 alternative hypothesis.

2 DR. LIPICKY: That information would have
3 accumulated for those four measurements and just
4 become operative for the fifth?

5 CHAIRMAN PACKER: No. The concept is that
6 if one knew that the drug lowered wedge pressure for
7 the preceding two hours, then the assessment of
8 symptoms at three hours --

9 DR. LIPICKY: That's what I was saying.

10 CHAIRMAN PACKER: -- actually proceeds
11 hemodynamic --

12 DR. LIPICKY: But since it was known at 30
13 minutes and one hour, that would not have affected the
14 two-hour dyspnea score, only the three-hour --

15 CHAIRMAN PACKER: No, it would have
16 affected the two hours. I thought there was a
17 progressive trend.

18 DR. LINDENFELD: It's possible short-term
19 memory was poor.

20 (Laughter.)

21 CHAIRMAN PACKER: Okay. Joann, any
22 additional comments?

23 DR. LINDENFELD: Not right now.

24 CHAIRMAN PACKER: Jeff?

25 DR. BORER: No. Actually my questions

1 will relate to safety, which comes later.

2 CHAIRMAN PACKER: Tom, Alan, Ileana?

3 DR. PINA: Yeah, Jim. Can we get away
4 from the three-hour dyspnea? Can I go on and ask him
5 something else, Milt?

6 CHAIRMAN PACKER: Oh, sure.

7 DR. PINA: If you were now giving a
8 clinician advice as to how to use this drug, and most
9 people don't use catheters, as you and I well know,
10 and you told them, "Here's the fixed dose," because
11 that's the data that you have, is a fixed dose, how
12 would you tell them to monitor the patient?

13 DR. YOUNG: I can do that, again, based on
14 a compendium of the experience with respect to safety
15 that Dr. Horton will present later, and based on the
16 observations made in the safety protocol, first of
17 all, what patients to pick. Pick a WET (phonetic)
18 patient with heart failure due to a broad spectrum of
19 causes. Somebody who has a blood pressure that's
20 reasonably well preserved, obviously volume overload
21 on physical exam therefore, put them in a telemetered
22 setting, whether that's in an ER or CDU, whether
23 that's up on a floor, and monitor them in telemetry
24 with intravenous administration of the medication.

25 The way that we started VMAC, I think

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1 that's going to keep people out of trouble, and I
2 think one would reasonably expect to see the benefits
3 and the side effects that we saw in a proportion that
4 we do in VMAC.

5 DR. PINA: Will you use your blood
6 pressure as a surrogate for lowering the wedge?
7 Because you can't follow urine output.

8 DR. YOUNG: Well, I would look at the
9 patient globally. Now, we're talking about or
10 protocol.

11 DR. PINA: Now, I'm talking -- I'm talking
12 about --

13 DR. YOUNG: You know, a doctor at the
14 bedside --

15 DR. PINA: Right.

16 DR. YOUNG: -- taking care of a heart
17 failure patient.

18 DR. PINA: Right.

19 DR. YOUNG: And I would do the things that
20 we ordinarily do in a non-catheterized patient. I
21 would look at the vital signs, tachycardia, blood
22 pressure, tachypnea response, physical examination,
23 how much congestion they had, and see how the patient
24 was doing, and I'd also ask them, gee, was his
25 shortness of breath getting better, and just follow

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1 along that way.

2 I would not titrate the drug unless I
3 wanted to get a bigger blood pressure response. So
4 specifically to your question about how I would manage
5 a non-catheterized patient, that would be it:
6 telemetered setting with those guidelines.

7 DR. PINA: And if you told them to up-
8 titrate the drug, how would you do the up-titration?

9 DR. YOUNG: Well, I'd tell them to go slow
10 and use the doses that we had defined in VMAC. I'd
11 have to ask them, "Gee, if you want to up-titrate the
12 drug, what is it you want to do?"

13 And if it's lowering the blood pressure,
14 in particular, I think that it's going to work and
15 work very nicely and be safe. And I'd tell them to
16 use the same protocol that we did in VMAC.

17 CHAIRMAN PACKER: Michael, anything?

18 Okay. Marv.

19 DR. ARTMAN: I have a real issue with this
20 dyspnea scale. You know, it just seems to me like
21 we're putting a lot on something we can't really
22 measure, and it just seems like to use this, ask
23 patients if they're mildly, moderately, or markedly
24 better, or minimally, moderately, markedly better, you
25 know, I just think that I don't know how well that's

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1 been validated. I don't know if it accurately
2 reflects anything, and it sort of biases against
3 getting worse because these patients, already 50
4 percent of them have dyspnea at rest, and if they get
5 any worse, they're going to be intubated, and they're
6 not going to be on your study.

7 So I think it sort of biases against going
8 in the wrong direction, and if you look at the
9 patients that were -- you know, the differences in
10 this, we're getting back to this non-catheterized
11 versus catheterized group, and the patients in the
12 placebo group in the non-catheterized group did
13 better, and that obviated the difference between the
14 study drug and the placebo group.

15 And I think the reason they got better is
16 because they started out a little bit worse. Fifty
17 percent of those patients had dyspnea while sitting at
18 rest, whereas only 30 percent of the placebo patients
19 had dyspnea while sitting at rest.

20 So, you know, I think we're splitting
21 hairs here, and I don't think we can make much out of
22 this whole dyspnea assessment.

23 CHAIRMAN PACKER: We're going to get into
24 a question that the division asks of us as to how
25 important the clinical status assessment is, and we

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1 need to open that discussion.

2 DR. ARTMAN: Well, I've made my position
3 known on that.

4 CHAIRMAN PACKER: Right, but I think that
5 that's a very important question. The sponsor was
6 told that assessment of some measure of clinical
7 benefit was important, and they, in fact, went forward
8 and specified that as a primary endpoint that needed
9 to be met in order for this trial to be considered
10 positive.

11 If we think that that guidance to the
12 sponsor is inappropriate, we'll bring it up during the
13 response to the questions.

14 Marv.

15 DR. KONSTAM: You know, Jim, I guess you
16 didn't show the cardiac output data unless I'm --
17 cardiac output data?

18 DR. YOUNG: I did not.

19 DR. KONSTAM: Yeah. You know, I wondered
20 if you could comment on it because it looks like there
21 wasn't much effect on cardiac output, and you might
22 want to put it up, if you want to.

23 DR. YOUNG: Yeah, let me talk to it, and
24 we can show it.

25 DR. KONSTAM: Well, go ahead. Show it if

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1 you want to show it.

2 DR. YOUNG: The cardiac output did not
3 increase in VMAC as much as it did in the higher doses
4 in the other studies. You're correct about those
5 observations.

6 And the reason for that was choosing the
7 wedge pressure to go after and to drop. Here you see
8 -- I can't see back here. Is this 24 hours or three
9 hours?

10 Okay. Here we have during the placebo
11 controlled period with nitroglycerine, Natreacor, and
12 placebo. The changes that occurred in mean right
13 atrial pressure here, but specifically to your
14 question, cardiac index here.

15 And so we do see the cardiac index going
16 up here with Natreacor, falling and tailing down at the
17 three-hour mark here.

18 This is also why the pulmonary vascular
19 resistance fell at this particular mark, if you
20 remember that other slide.

21 I think this is a product of the dose that
22 we choose, and, again, the issue about cardiac index
23 is as a clinician, based on the compendium of the data
24 we have about Natreacor, if I'm after a cardiac output
25 increase and I want to use this drug, then it would

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1 require up-titration.

2 DR. KONSTAM: Well, let me just share with
3 you that when we reviewed the data in detail last
4 time, you know, it struck me that the cardiac output
5 effects weren't that dramatic either. I know they
6 were more than here, and we're not going to have an
7 answer, but maybe you could just comment.

8 Subjectively, I would have expected a pure
9 vasodilator with a significant effect on wedge
10 pressure here to have more of an effect on cardiac
11 output that we're seeing here, and that was my
12 subjective pressure last time for what it's worth.

13
14 DR. YOUNG: You know, again, based on my
15 experience with the drug and in unblinded experiences
16 and whatnot, and you know, knowing the nuances of
17 saying, gee, nitroglycerine is a pre-load reducing
18 agent more than an after-load reducing agent,
19 nitroprusside more after-load than pre-load.

20 Perhaps I would put this agent into a bit
21 more pre-load reducing than I would after-load
22 reducing, and that's how I would look at the global
23 hemodynamics.

24 DR. KONSTAM: Can I just ask to remind us
25 is it clear from preclinical data or other that the

1 agent has no direct effect on the heart, cardiac
2 contractility?

3 DR. YOUNG: We do not believe, based on
4 any of the basic science data that's been presented
5 that it's an inotrope at all, and it doesn't cause --

6 DR. KONSTAM: Or negative inotrope.

7 DR. YOUNG: Or negative. And it doesn't
8 cause tachycardia.

9 DR. HORTON: Would you like me to respond?

10 Bill Abraham actually did a study in
11 explanted myocardium from transplant patients and
12 showed that compared to isoproterenol that there was
13 no effect on contractility either positively or
14 negatively with Natreacor, no effect on positive or
15 negative DPDT.

16 DR. PINA: I just want to also make the
17 point that this was not a population of a low output.

18 DR. YOUNG: Correct.

19 DR. PINA: This population had 2.2 output.

20 DR. YOUNG: Two, point, two meters per
21 minute per meter squared.

22 DR. PINA: So this is different than that
23 continually decompensating deteriorating heart failure
24 patient whose cardiac index is dropping. This is by
25 and large a volume overloaded population.

1 DR. YOUNG: Correct, which we might argue
2 may be the most common, but that would be an argument.

3 DR. HIRSCH: Just in follow-up, what is
4 the effect of BNP, again, on normal myocardia or more
5 normal myocardia, not explanted human hearts?

6 DR. HORTON: On contractility, I don't
7 know the answer to that. I don't think it's been
8 studied.

9 CHAIRMAN PACKER: Any other comments from
10 any other members of the Committee on any of Dr.
11 Young's data that he's presented?

12 If not, I'll thank you very much, Jim.

13 DR. YOUNG: Thank you.

14 CHAIRMAN PACKER: I'll ask the Committee
15 if their preference is to take a break now and get
16 something to eat or to proceed to the presentation of
17 safety. What is your pleasure?

18 Why don't we do this, since there seems to
19 be no preference? My preference would be to try to
20 get through safety and take a break and do Q&A. Does
21 anyone strongly object to that or mildly object to
22 that?

23 Okay. Let's do that.

24 (Pause in proceedings.)

25 CHAIRMAN PACKER: Dr. Horton, can you just

1 describe that? Just put that into the record.

2 DR. NISSEN: Just as a matter of record,
3 I had requested the doses of nitroglycerine that would
4 have been used had there not been placebo in the bag,
5 and I think you'd agree that they're essentially
6 identical to the doses that were used in which
7 nitroglycerine was actually in the bag. So there was
8 no difference.

9 CHAIRMAN PACKER: And, Steve, what do you
10 make of that?

11 DR. NISSEN: I think that the
12 investigators were really not titrating according to
13 hemodynamics. I think they were just ignoring it
14 because otherwise you would have expected when there
15 was placebo in the bag for those doses to have been
16 escalated.

17 And I must say it tends to confirm my
18 hypothesis here that the investigators were really
19 laying off of standard therapy.

20 CHAIRMAN PACKER: Okay. Dr. Horton,
21 please.

22 DR. HORTON: Thank you, Dr. Packer.
23 Shall I get started?

24 CHAIRMAN PACKER: Yes, please.

25 DR. HORTON: Okay, great. Thank you.

1 By now you know a great deal about the
2 patient population in VMAC and the efficacy profile of
3 Natreacor. The remaining questions pertain to safety.
4 I will answer these questions with the VMAC data, with
5 some safety data from the whole program, and from the
6 PRECEDENT trial, which was a head-to-head safety study
7 comparing Natreacor to dobutamine.

8 The next slide outlines what I'll cover.
9 We'll start with general adverse events focusing
10 mainly on the VMAC trial, followed by the effects on
11 blood pressure and hypertension, again, primarily from
12 VMAC, effects on creatinine and VMAC, serious adverse
13 events from the entire program, followed by the events
14 that occurred in VMAC, specifically including
15 readmissions, length of stay, major events that were
16 reviewed by the Data Safety Monitoring Committee, and
17 mortality through six months.

18 We'll then cover the safety of two
19 different patient subgroups, those with preserved
20 systolic function and with acute coronary syndromes,
21 and then we'll end with a brief review of the
22 arrhythmia data from the PRECEDENT trial.

23 Let's start with general adverse events
24 from the VMAC trial. Here's a summary of the adverse
25 events that were reported during the three-hour

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1 placebo controlled period in the nitroglycerine,
2 Natreacor, and placebo groups. More nitroglycerine
3 patients generally reported any adverse event, and you
4 can see that the events of headache, hypotension, and
5 abdominal pain were reported significantly more
6 frequently in nitroglycerine patients.

7 There was no event that was reported more
8 frequently with Natreacor than nitroglycerine during
9 this time period.

10 It's also important to just note that
11 symptomatic hypotension was rare during the first
12 three hours, occurring in two nitroglycerine patients
13 and one Natreacor patient.

14 The next slide summarizes the adverse
15 events that were reported during the first 24 hours
16 of treatment with these two active agents. Recall
17 that now during this period the placebo patients had
18 crossed over to therapy with either Natreacor or
19 nitroglycerine.

20 Again, significantly more nitroglycerine
21 patients reported any adverse event compared to
22 Natreacor, and this appear to be driven primarily by
23 the reporting of headache. Headache occurred in
24 significantly more nitroglycerine patients at 20
25 percent versus eight percent with Natreacor.

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1 Abdominal pain, interestingly, was also
2 significantly more common in nitroglycerine patients,
3 and this is a consistent finding at different time
4 points throughout the trial.

5 During these first 24 hours, symptomatic
6 hypotension was similarly reported with these two
7 agents, occurring in five percent of nitroglycerine
8 patients and four percent of Natrecor patients. And,
9 again, there was no adverse event that was reported
10 more commonly with Natrecor.

11 Other important events that are typically
12 meaningful in this patient population, such as
13 ventricular tachycardia and angina were not reported
14 more commonly. They were reported very similar with
15 the two agents.

16 I guess this is particularly important
17 since not only did the trial include patients with
18 acute coronary syndromes, but this was 489 patients,
19 most of whom had ischemic cardiomyopathy.

20 Now, let's review the effects on blood
21 pressure itself.

22 Next slide.

23 Dr. Young already showed you the graph on
24 the left, which summarizes the effects of systolic
25 blood pressure through three hours, where the blue

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1 line is placebo, the yellow line is Natreacor, and the
2 green line is nitroglycerine.

3 Both agents were associated with mild, but
4 significant, decreases in blood pressure compared to
5 placebo at different time points, and both agents were
6 significantly decreased from placebo by about five
7 millimeters of mercury at three hours.

8 The graph on the right shows the effects
9 of systolic blood pressure through 24 hours in all
10 patients. Here the placebo patients have crossed over
11 to active therapy, and through 24 hours, you see that
12 there were no significant differences in the change in
13 systolic blood pressure between these two agents.

14 The next slide summarizes the greatest
15 effects on blood pressure through the first 24 hours.
16 So, first of all, you see that the mean baseline blood
17 pressure with the two agents was similar.

18 The mean lowest blood pressure at any time
19 point during the first 24 hours was also similar, and
20 the range there shows that the lowest blood pressure
21 was 60 and 49 in the two groups in that one patient.

22 When you look at the number and percent of
23 patients who fall into these blood pressure
24 categories, that is, where their lowest blood pressure
25 at any time point fell during the first 24 hours, you

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1 see that there are no significant differences in the
2 number and percent of patients who fall within these
3 blood pressure categories.

4 Not surprisingly, the maximum decrease in
5 blood pressure and the maximum percent decrease are
6 also similar with the two agents.

7 What about the offset of effect on blood
8 pressure?

9 I explained earlier that blood pressure
10 was frequently measured for the two-hour period after
11 discontinuation of infusion in all of these 489
12 patients. Well, first you see that at the time of
13 discontinuation, both agents are associated with a
14 mean decrease in blood pressure from baseline of eight
15 millimeters of mercury.

16 Through the two-hour period following
17 discontinuation, you see that there are really no
18 significant changes in blood pressure with either
19 agent and no evidence of rebound during this period.

20 Okay. What about the offset of effect on
21 blood pressure after symptomatic hypotension? The
22 next slide demonstrates the serial blood pressures
23 that were obtained for the two-hour period after the
24 onset of symptomatic hypotension, and this is only in
25 the 12 nitroglycerine patients who developed

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1 hypertension and the 15 Natreacor patients who
2 developed symptomatic hypotension.

3 The protocol instructed investigators to
4 discontinue the drugs at the onset of symptoms and to
5 restart the agents once symptoms had resolved or once
6 blood pressure had stabilized, but in some cases the
7 investigators chose to decrease the dose.

8 So what these blood pressures reflect are
9 increases in blood pressure that occurred mainly after
10 either an interruption or a dose reduction.

11 The mean baseline blood pressure, there's
12 a few points on this slide. The mean baseline blood
13 pressure in these patients who developed symptomatic
14 hypotension tended to be higher in nitroglycerine
15 patients. However, the blood pressure at the onset of
16 the vent was very similar.

17 These data do demonstrate that the
18 increase in blood pressure with Natreacor is more
19 slowly than that which is observed with
20 nitroglycerine, especially after these dose changes.
21 However, there was evidence of an increase in blood
22 pressure within the 15 to 30 minute period. It
23 appears here that the peak increases with
24 nitroglycerine during this time period do occur within
25 15 to 30 minutes, whereas the peak increases with

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1 Natrecor during this time period is more around 60
2 minutes.

3 Another way to look at duration is to
4 actually look at the duration of the events
5 themselves, which is shown on the next slide. In this
6 slide, duration is defined as the time from the onset
7 of the first symptom to the time of resolution of the
8 last symptom.

9 I just showed you that blood pressure
10 tended to be increased by about 60 minutes, but this
11 is a different way of looking at it. With
12 nitroglycerine, most of the symptoms resolved within
13 about 30 minutes. However, there were three patients
14 whose episodes lasted up to two hours.

15 With Natrecor events lasted anywhere from
16 30 minutes to up to five hours and ten minutes in the
17 longest duration of event. Therefore, in some
18 patients, as shown here, the duration of symptomatic
19 hypotension was longer in Natrecor patients than
20 nitroglycerine patients.

21 The next slide will show you the
22 individual characteristics of those seven cases that
23 lasted for longer than two hours. Since there's only
24 seven of these events, I think it's just simplest to
25 show you the actual data.

1. And first, let me state right up front
2 that there were no adverse events in these patients
3 when followed long term, such as MI, stroke, acute
4 renal failure requiring dialysis, or death.

5. All events were mild or moderate.
6 Baseline blood pressures are shown here. There were
7 three patients whose baseline blood pressure was in
8 the 100 millimeter of mercury or less range.

9. The next color here shows you the blood
10 pressure at the time of onset of symptomatic
11 hypotension, and what did the investigators do?

12 Well, in six of these cases, they chose to
13 decrease the dose of Natreacor. In one case Natreacor
14 was discontinued. In one case, an inotrope was added
15 to a lower dose of Natreacor rather than substituting
16 Natreacor for an inotrope.

17 And in the last column, it also helps to
18 put this in perspective that most of these -- all of
19 these patients were receiving at least one vasodilator
20 during this time period. Most were receiving at least
21 two.

22 Well, now let's look at the major events
23 that developed with all patients who developed
24 symptomatic hypotension. The previous slide just
25 showed you the seven events that lasted longer than

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1 two hours.

2 And for all patients, the four percent of
3 Natreacor patients who developed symptomatic
4 hypotension when followed for 30 days, there were
5 no -- none of these events that were observed in those
6 patients.

7 There was death and one myocardial
8 infarction that later occurred in nitroglycerine
9 patients who had developed symptomatic hypotension,
10 but these events were not likely due to the event
11 itself.

12 Theoretically, hypotension may lead to
13 transient increases in creatinine. The next slide,
14 demonstrates that, and I'll walk through this with
15 you, but it demonstrates that compared to
16 nitroglycerine, there is no association of the VMAC
17 dose of Natreacor with increases in creatinine when
18 symptomatic hypotension occurs.

19 So the mean baseline creatinine in these
20 ten and 12 patients here was 1.1 and 1.4. The reason
21 why the n's are different here is that the previous
22 slide, in order to show you all of the data we had, we
23 showed you all events, not just number of patients,
24 whereas this is each -- there's only ten patients who
25 developed symptomatic hypotension and 12 Natreacor

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1 patients.

2 And here's the range of baseline
3 creatinines that occurred in those patients.

4 When creatinine was prospectively measured
5 through these time points, day two, day five, 14, and
6 30, there were no mean increases in creatinine with
7 Natreacor. There were some mild increases in
8 creatinine with nitroglycerine in these patients at
9 developed symptomatic hypotension, but those would not
10 be significantly different.

11 And then when we applied an arbitrary
12 definition of what would be considered clinically
13 meaningful criteria, this was the same definition we
14 used the last time we met two years ago. We defined
15 this as an increase of at least 50 percent of
16 creatinine to a value that was at least two milligrams
17 per deciliter, and you see that this was rare. It
18 only occurred in one Natreacor patient, and that was at
19 day 14, which was not likely due to the initial event
20 on the first day.

21 Okay. This next slide then summarizes the
22 same creatinine information, but now in a group of
23 patients from the integrated safety summary so that I
24 can show you the comparison of the VMAC dose to the
25 two higher doses when Natreacor is administered from

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1 the initiation of the infusion at those doses.

2 This table represents five studies. These
3 are all the symptomatic hypotension events that
4 occurred in all five large Phase III studies.

5 Okay. So to zero in on the two higher
6 doses here, because I just presented to you this data
7 basically, what you see here is that with these higher
8 doses there does appear to be mild increases in mean
9 creatinines in patients who developed symptomatic
10 hypotension, and in addition, there appeared to be
11 more of these patients who met the increased
12 creatinine criteria.

13 So what this suggests is that the Natreacor
14 is an optimum dose, and that the effects on renal
15 function are dose dependent, and that the lack of
16 these events with the VMAC are due to the dose itself.

17 The other thing I'll mention here is even
18 with the higher doses, that there was no increase in
19 the rate of serious renal dysfunction or acute renal
20 failure requiring dialysis, even in these patients
21 from the previous studies.

22 Okay. Finally, this last slide on
23 symptomatic hypotension shows you, again, just to
24 reiterate, that the incidence of symptomatic
25 hypotension was similar with the .01 dose in

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1 nitroglycerine. The adjustable dose itself, there
2 were only two patients that developed symptomatic
3 hypotension. So that was a rate of three percent.

4 One of those occurred at the .01 dose and
5 the other occurred at .015. There was no symptomatic
6 hypotension reported in the few patients that did up-
7 titrate up to .03.

8 And this table clearly shows you that
9 symptomatic hypotension is, indeed, dose dependent,
10 and that the VMAC dose seems to be a safer dose.

11 The next slide then, in summary, there
12 were no different -- I'm sorry. Here's what we
13 actually know then of symptomatic hypotension. First,
14 it is dose dependent. Okay?

15 When we compared the VMAC dose to
16 nitroglycerine, there were no significant differences
17 observed between severity -- most cases were mild or
18 moderate; time of onset -- I showed you that those
19 events were rare during the first three hours. Most
20 actually occurred between six and 24 hours, and that's
21 probably likely due to other concomitant medications,
22 difference in hydration status, et cetera.

23 There was no difference in the impact on
24 dose decrease or discontinuation or on the need for an
25 intervention such as an inotrope or pressor.

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1. And then finally, with the VMAC dose, no
2 difference with nitroglycerine with changes in
3 creatinine associated with these events.

4 As already mentioned, episodes of
5 symptomatic hypotension tended to last longer with
6 Natreacor than nitroglycerine. However, it was
7 extremely important to show that there were no adverse
8 short-term or long-term sequelae associated with that
9 longer offset effect.

10 So far I've only summarized effects on
11 creatinine in patients who developed symptomatic
12 hypotension.

13 Go to the next slide.

14 I'm now going to show you the effects on
15 creatinine overall in the entire VMAC population
16 -- next slide -- which is 489 patients here. So the
17 mean creatinine, as I stated earlier, was 1.6 and not
18 different between the two groups, and the range,
19 because there were no restriction criteria, was up to
20 9.5 in the nitroglycerine group and up to 11.1 in the
21 Natreacor group.

22 Through these time periods, day two, five,
23 14 and 30, there were no significant differences in
24 the changes in creatinine between Natreacor and
25 nitroglycerine at each time point.

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1 And similarly, when you look at the number
2 and percent of patients who met the increased
3 creatinine criteria, there were no significant
4 differences at any time point between these two IV
5 vasodilators.

6 Okay. Next slide.

7 Now, let's review the serious adverse
8 events that occurred in the Natrecor program overall,
9 and then with an emphasis on the VMAC trial. In
10 addition, we'll review the major events that were
11 reviewed by the Data Safety Monitoring Committee,
12 hospitalization data, and long term mortality.

13 Next slide.

14 So before discussing serious adverse
15 events in VMAC, this slide summarizes all serious
16 adverse events occurring within the 14-day period of
17 time in all studies in the Natrecor program. So all
18 941 Natrecor program -- Natrecor subjects in the
19 program are represented by this slide.

20 The control agents here include mainly
21 nitroglycerine from the VMAC trial followed by
22 inotropes from the other Phase III trials, as well as
23 placebo patients from the earlier placebo controlled
24 studies.

25 So overall you can see here that there is

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1 no difference in the reporting of any serious adverse
2 event within 14 days between Natrecor and a variety of
3 control agents, and similarly, when you break that
4 down by body system, there's no difference between
5 Natrecor and control in the incidence of any serious
6 adverse events.

7 Next slide.

8 Now, in the VMAC trial, this slide shows,
9 again, that there were no significant differences in
10 these events between Natrecor and nitroglycerine.
11 There was one stroke in the study. That was in a
12 nitroglycerine patient. There were five myocardial
13 infarctions that occurred at any point up to 30 days.
14 Three of those were nitroglycerine patients and two
15 were Natrecor patients.

16 And the incidence of new onset dialysis
17 was also not significantly different, occurring in two
18 and three percent of nitroglycerine and Natrecor
19 patients, respectively.

20 Given that this was a population with
21 mostly ischemic cardiomyopathy and one with acute
22 coronary syndromes, it's noteworthy that there were no
23 differences in the incidence of myocardial infarction
24 compared to nitroglycerine.

25 Okay. When you look at these same events

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1 in the four larger studies with the next slide, this
2 slide then allows us to break down the incidence of
3 these events by dose groups.

4 This is the VMAC dose, and these are the
5 two higher doses studied in the previous trials, and
6 control represents VMAC, PRECEDENT, and the two Phase
7 III trials in the original NDA.

8 So it's important here to show that even
9 at higher doses there is no dose dependency and no
10 significant difference between Natrecor and control
11 agents in the later incidence of stroke, myocardial
12 infarction, or the new onset dialysis.

13 Okay. Next slide.

14 Now we'll move to hospital readmissions.

15 Next slide.

16 In VMAC overall during the 30-day follow-
17 up period comparing nitroglycerine to Natrecor, there
18 were no significant differences in the rate of
19 hospital readmission between the two groups. There
20 were fewer Natrecor patients readmitted for acute CHF,
21 although these differences were not statistically
22 significant.

23 Next slide.

24 Here's the cumulative readmission
25 information that we have from all of the five larger

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1 long infusion studies just to show that, again, in all
2 of those studies there was no significant differences
3 in the incidence of hospital readmission through the
4 study periods.

5 Okay. The next slide shows length of stay
6 from VMAC, and in all treated subjects Natreacor was
7 associated with the median length of stay that was
8 significantly longer than the nitroglycerine by one
9 day. The VMAC trial did not correct for a variety of
10 factors that might have affected length of stay. So
11 we looked for an explanation for this finding.

12 One imbalance at baseline between the
13 nitroglycerine and Natreacor groups was that
14 significantly more Natreacor patients had study drug
15 added to ongoing therapy with dobutamine or dopamine.
16 Because these patients had to have dyspnea at rest in
17 spite of those therapies, these patients were
18 basically refractory to dobutamine or dopamine, and as
19 a group, they had worse outcomes overall when we look
20 at death, length of stay, and readmissions.

21 And, indeed, this balance does account for
22 the difference in length of stay. The second row
23 here, which excludes those patients, you still see
24 here that this is the majority of patients
25 represented. When you exclude patients where study

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1 drug was added to dobutamine or dopamine, there is no
2 significant difference in the median length of stay
3 between the two groups.

4 Okay. Next slide.

5 So now let's discuss what we know about
6 mortality from the Natreacor program. I'm going to
7 show you a few mortality slides beginning with six-
8 month mortality from the four largest Phase III
9 trials.

10 Next slide.

11 It's important to point out that none of
12 the trials were designed as a mortality trial. This
13 means that the randomization was not stratified by a
14 number of risk factors that might have been known to
15 affect mortality long term, and the studies, of
16 course, were not powered to show an effect on
17 mortality.

18 Six-month mortality was collected in
19 nearly 1,200 patients. Seven hundred and twenty-four
20 Natreacor patients have six-month mortality data versus
21 443 controls. Most of these controls are the 211
22 nitroglycerine patients from VMAC, followed by
23 inotropes from the other studies.

24 Mortality was retrospectively collected in
25 these three trials here, the previous trials, and

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1 prospectively collected in VMAC, and we do have 97
2 percent follow-up on these patients.

3 This next slide is the most comprehensive
4 summary of short-term and long-term mortality data and
5 represents the data from all four trials. The 724
6 Natreacor patients are represented with the yellow
7 dashed line. The 443 control patients are represented
8 by the white solid line.

9 Clearly, these curves are overlapping, and
10 there are no significant differences in mortality
11 between the groups through six months.

12 The point estimates of mortality of six
13 months are 21.5 percent in the control group and 21.7
14 percent in the Natreacor group with a p value of .830.

15 The caveat here is that this total sample
16 size of nearly 1,500 patients is not adequately
17 powered to make conclusions about the total lack of an
18 effect of Natreacor on mortality, even when these
19 differences between the treatment groups are this
20 small.

21 You're being asked today for guidance on
22 what degree of an increase in long-term mortality
23 should be ruled out for a drug that's being studied
24 for this acute treatment of decompensated heart
25 failure, as there is currently on specific guideline

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1 related to this indication.

2 So in order to be comfortable with these
3 data, you might ask what degree of an increase in
4 mortality has been ruled out with 95 percent
5 certainty. The next slide shows that with the
6 observed event rates of 21.5 percent and 21.7 percent
7 at six months with 95 percent certainty, an increase
8 in mortality associated with Natrecor of 20 percent
9 has been ruled out, that is, the right-sided upper
10 confidence bound of a percent increase in mortality.

11 The corresponding upper confidence bound
12 for the hazards ratio is 1.3.

13 These data should also be taken in the
14 context of the totality of the safety profile of a
15 test agent and the severity of the illness of the
16 patient population studied.

17 You've already seen this afternoon that
18 Natrecor is not associated with significant serious
19 adverse events in the short term that could lead to an
20 increase in mortality, such as significant
21 arrhythmias, ischemic events, or severe renal events.

22 Now, as is usually the case when there are
23 no differences overall in integrated summaries, the
24 point estimates in individual studies will vary. This
25 is exactly what we observed with the four largest

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1 trials which are shown on the next slide.

2 So as individual studies, this slide
3 summarizes the point estimates in the 95 percent
4 confidence intervals in six-month mortality for each
5 of the four Phase III studies that were represented by
6 the previous Kaplan-Meier curve.

7 So here you have the 21.5 and 21.7 percent
8 point estimates and the narrow and overlapping
9 confidence intervals, and as the studies get larger
10 and larger, the confidence intervals will increase.
11 Clearly the data bounce around in that the confidence
12 intervals are overlapping.

13 I will point out that the point estimate
14 of six-month mortality in the VMAC trial was higher
15 with Natreacor compared to nitroglycerine, and in the
16 PRECEDENT trial, for example, the point estimates
17 favored Natreacor compared to the test agent.

18 We believe any differences seen here,
19 whether they favor Natreacor or the control agent, are
20 more likely due to chance or to baseline differences
21 in prognosis of patients within the treatment groups
22 rather than to the treatments themselves.

23 Okay. Now let's move on to the adverse
24 event profiles that were observed in two different
25 patient subgroups, starting with patients with

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1 preserved systolic function.

2 Next slide.

3 Sixty-five patients or 13 percent of the
4 trial population had a baseline ejection fraction of
5 greater than 40 percent, and these were equally
6 distributed -- I'm sorry -- these were equally
7 distributed between the two treatment groups.

8 The profile of adverse events that were
9 observed in this patient subgroup is very similar to
10 the overall safety profile that was described in the
11 larger population.

12 For example, headache was more commonly
13 reported with nitroglycerine, and symptomatic
14 hypotension was rare and similarly reported. Again,
15 angina pectoris and ventricular tachycardia were not
16 definitely reported within this group.

17 Now let's look at the adverse events
18 within the first 24 hours of patients with acute
19 coronary syndromes. We've already shown you that most
20 patients had chronic heart failure due to an ischemic
21 cardiomyopathy, and that in the larger population
22 there was no evidence of an increase in ischemic
23 adverse events, such as angina or myocardial
24 infarction.

25 Next slide.

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1 There were 61 patients in the VMAC trial.
2 Thirty-four were randomized to nitroglycerine and 27
3 randomized to Natrecor. This table shows you, again
4 that the pattern of events that were reported were
5 similar to that observed in the overall trial
6 population. Headache was more commonly reported with
7 nitroglycerine and symptomatic hypotension,
8 ventricular tachycardia and angina itself were rare
9 and similarly reported between the two groups.

10 When you look at the major events in this
11 population of patients with acute coronary
12 syndromes -- next slide -- you see, again, that there
13 is no significant difference in the incidence of these
14 major events in this population. There was one
15 myocardial infarction that occurred in each of the
16 treatment groups. There were two new onset dialysis
17 with Natrecor, and one death that occurred in each of
18 the treatment groups.

19 Okay. The last part of the presentation
20 now, moving to the next slide, will cover the results
21 of the PRECEDENT trial. VMAC and all previous studies
22 confirmed that Natrecor does not have a significant
23 effect on arrhythmias or heart rate.

24 Based on data from a safety study that was
25 in the original NDA, a large proportion of patients

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