1 As I read the protocol, it seemed as
2 though it was your intent to show a significant
3 improvement at two years.
4 Do you want to comment on that because
5 that isn't quite met and maybe you could comment on
6 that.
7 DR. ROSE: In earlier incarnations of the
8 protocol, that was indeed the intent. When we
9 formed a DSMB, and actually once we had NHLBI
10 involvement, as well, and a DSMB had been
11 constituted, there was a lot of consideration of
12 what the primary endpoint ought to be and concern
13 that a discrete, single endpoint would pose
14 potential difficulties in monitoring data or the
15 safety of the trial in terms of outcomes, and
16 instead, the area under the curve would be
17 something that would be more easily monitored and
18 monitorable, and for which you could set stopping
19 rules as time went on.
20 So, the statistical plan and the primary
21 analysis then focused on a two-year duration
22 observation, and that indeed became the primary
23 analysis, and the final statistical plan was agreed
24 to by the NHLBI, the Date Safety Monitoring Board,
25 and the FDA.

1 So, I think it is fair to say that that
2 evolved over time.
3 DR. KONSTAM: Personally, I can accept
4 that. That might be some cause of discussion on
5 the part of the panel. I think we are going to
6 circle back on that when we deal with the clinical
7 relevance of the finding more than the statistical
8 significance, but I guess it is worth just
9 mentioning the fact that the timing of the primary
10 endpoint has changed a little bit.
11 I guess the statistics of the log-rank
12 test seem pretty strong. One must ask whether the
13 two groups are similar. They seem similar in most
14 regards. There are a couple of things a little bit
15 different between the two groups. One I noticed is
16 difference in warfarin use between the two groups,
17 and you might want to comment on that.
18 The other thing which is a little bit more
19 troublesome is that there is a discrepancy between
20 the two groups in the number of--as I read it,
21 unless I am misreading it--in the number of
22 patients enrolled within the last year at least by
23 my count.
24 Looking at the FDA document, 34 percent of
25 the LVAD patients were enrolled with less than one

1 year of follow-up, was only 23 percent in the
2 medical management arm, which leads to a couple of
3 issues, but one is, does this suggest some
4 difference between the two groups, and why is that,
5 what would there have been that difference?
6 DR. ROSE: On the warfarin issue, I have
7 no idea. You look at 20 variables on a
8 randomization, and you use a p-value of 0.05, one
9 of them is going to turn out to be that way. How
10 that one ended up being the case, it is not the
11 issue that clinicians have not viewed them as
12 candidates for some kind of anticoagulation because
13 the converse aspirin use was higher in the device
14 patients. If anything, that might have
15 disadvantaged the device patients because going
16 into the surgery, which had to happen within a
17 brief time after randomization on aspirin is
18 something that I think we would find less than
19 desirable, knowing the frequency and severity of
20 the bleeding issues.
21 With regard to that difference over the
22 later part of the trial, as I said, we did block
23 these by center, and the blocks were random. I
24 don't think that this reflects any degree of bias,
25 and just is the way the cards fell out.

1 DR. KONSTAM: Well, I suspect you are
2 right.
3 DR. ROSE: We also still had, in terms of
4 the blocks, you know, the enrollment after the
5 trial was stopped before the 140 that we expected
6 to enroll.
7 DR. KONSTAM: Well, those are the caveats
8 I find regarding the decision that the primary
9 endpoint is met. I think that the statistics are
10 strong that there is an effect on survival. Those
11 are the only holes I can find to pick at, but I am
12 not concerned about those greatly.
13 I think the second issue to discuss, and
14 to me, in fact, I think the whole decision about
15 approvability centers around this, which is the
16 clinical relevance, and then where the clinical
17 relevance comes up for discussion is what is going
18 on at two years. To some extent, this is going to
19 be a very subjective decision about, you know, what
20 does it mean that there is a statistically
21 significant effect at one year, and you lose it at
22 two years, but more than lose it at two years, most
23 of the patients essentially are dead at two years.
24 They are either dead at two years or they are dead
25 within a month or two of two years.

1 Now, there are a number of aspects of
2 this. One is the reliability of the device and to
3 what extent is a less than anticipated reliability
4 of the device contributing to the mortality of two
5 years.
6 The second problem is we don't have that
7 many patients reaching two years, in part because
8 again 34 percent of the patients in the LVAD group
9 were enrolled within less than one year from the
10 time the study ended.
11 Maybe I just can ask you again, Eric,
12 about this two-year thing. When you set up the
13 protocol originally, the primary endpoint was I
14 think you said envisioned at the two-year endpoint,
15 but there is a couple of aspects of that.
16 One is that when you looked at your pair
17 analysis, the pair analysis was constructed saying
18 that you wanted to see, you anticipated 75 percent
19 more mortality at two years in the control group.
20 You hoped to achieve a third reduction. That gives
21 you 50 percent survival at two years.
22 Now, I guess the question I have for you,
23 is that just a numbers game, but you had to put
24 some numbers in to have a pair analysis, or are you
25 implicitly making some kind of value judgment about

1 the survival of 50 percent at two years, are you
2 sort of saying--I guess what I am leading to is
3 does this help us in terms of the overall judgment
4 about the clinical relevance?
5 Were you saying at the beginning that we
6 wanted to have a device that is clinically relevant
7 by virtue of the fact that half of these patients
8 are going to be alive at two years? I don't know
9 whether you can comment on that.
10 DR. ROSE: I think the issue of clinical
11 relevance has been part of the discussion
12 throughout the generation of this trial. We
13 initially did a preliminary randomization where our
14 initial modeling of mortality, we anticipated that
15 it would be worse in the VAD patients and that the
16 two curves would cross late, that that would be the
17 way this would shake out.
18 After pre-match, we actually revised our
19 thinking in that regard, and that is what allowed
20 the more appropriateness of the log-rank as opposed
21 to other types of analysis.
22 With regard to whether or not we wanted to
23 see 50 percent of the patients alive at two years,
24 of course, we would have preferred that, but our
25 thinking also early was that the control group

1 mortality was not going to be as high as indeed we
2 saw.
3 That was a surprise to us even knowing how
4 sick these patients were. We thought that that
5 longer term survival of the control group at a rate
6 higher than 8 percent was likely to result. Now,
7 that clearly was not the case, and I think, you
8 know, would we have preferred to see 50 percent
9 survival at two years?
10 Certainly, but to come up with tripling of
11 survival at two years with a quarter of the
12 patients still alive, and a large number still
13 ongoing, and this field being in its infancy, I
14 would have to say that for patients now, I think
15 this is clinically relevant and important survival
16 benefit that we have documented, and it is time to
17 let this field begin what I believe will be a
18 ascent to better outcomes.
19 With regard to the issue is device
20 reliability accountable for the lower survival rate
21 than I think a lot would have like to have seen at
22 two years, that is only part of it. Don't forget
23 that half of these patients, as well as they did do
24 in the first, half died in that first year, as
25 well, and the overwhelming numbers of death

1 occurred during the initial index hospitalization.
2 About a third of patients with this type of therapy
3 die in hospital with the index hospitalization.
4 I believe that we can cut that down
5 substantially as we learn more over time, but that
6 way you end up with more patient eligible--
7 DR. KONSTAM: Let me ask this then. I
8 mean it seems what happened is the device was
9 exceedingly good at preventing cardiovascular
10 deaths, and the fact that the mortality was so high
11 in the medical management group means that this is
12 an incredibly sick population, and so they were
13 appropriate for consideration of this type of
14 treatment, so that it good.
15 But since the device was so good at
16 preventing cardiovascular deaths, the fact that you
17 have so few people alive at two years, I guess
18 implies there are more other kinds of things
19 happening than you would have anticipated.
20 DR. ROSE: Another way to view it would
21 be, though, to say that half the people that are
22 alive at one year, are alive at two years, and in
23 that regard, the device has a degree of reliability
24 that is still potent. That is not to say that
25 reliability is not a problem, but there are other

1 issues that limit survival in this patient
2 population if we are going to holistically improve
3 it.
4 DR. KONSTAM: Well, part of the problem is
5 we have so few patients at two years. I mean we
6 don't really know what the right number is at two
7 years because there aren't that many patients
8 there. So, I just would comment on that.
9 Just to ask rhetorically, I mean if you
10 are putting in a device that is clearly
11 life-sustaining, what would you like out of that
12 device in terms of its mechanical reliability, and
13 what would you like out of that device in terms of
14 warning signs that it is going to fail?
15 These are I think again questions that are
16 going to come back.
17 The next category I think is the whole
18 issue of Quality of Life assessment. I see some
19 very reassuring things in the data set. I see some
20 confusing things in the data set.
21 The confusion I think stems from the fact
22 that there is such a high dropout rate in large
23 part due to mortality and to some extent due to
24 perhaps patient incapacity that it is extremely
25 difficult to know exactly what the numbers for each

1 of these tests are saying to us.

2 I can, however, accept the fact that

3 things look better in the device group than in the

4 medical therapy group, certainly in terms in your

5 Heart Association class and in some of the Quality

6 of Life parameters.

7 I guess one question that I want to ask

8 you about, though, and the problem then, of course,

9 in any of these, so part of the problem is the

10 dropout rates that we are seeing and what do you do

11 with that, but the other problem is that we don't

12 have a blinded study, and we are going to be stuck

13 with that.

14 The specific thing I wanted to ask about

15 that is if you look at the numbers, let me say a

16 positive thing. I am really reassured by the fact

17 that a lot of the Quality of Life scores,

18 forgetting about the comparisons, but if you just

19 look at the LVAD group, a lot of the Quality of

20 Life scores and a lot of the New York Heart

21 Association class scores are pretty good.

22 What we can glean out of those numbers, it

23 really seems to be, despite all the complications

24 that we do see, there still are a number of

25 patients, a fair number of patients at three

1 months, six months, and 12 months, who seem to be
2 doing pretty well. I get a lot of reassurance from
3 that.
4 The one specific question I was to ask,
5 though, is if you look at the number of patients
6 who are said to be New York Heart Association Class
7 I and II in the LVAD group, it seems that that
8 number is disparate from the number of patients
9 participating, for example, in the 6-minute walk.
10 The number of patients having repeated
11 measures--I don't have it in front of me
12 exactly--but the number of patients having repeated
13 measures in the 6-minute walk is very small, I
14 think, and smaller than the number of patients
15 reported to be in New York Heart Association Class
16 I and II, whom I would have expected could
17 participate in the 6-minute walk as an objective
18 question.
19 Can you comment on that, and why shouldn't
20 we be concerned from that, that there is just some
21 kind of a bias being injected in the New York Heart
22 Association class grade?
23 DR. ROSE: Specifically, with regard to
24 the 6-minute walk and the peak VO_2 measurements, I
25 think it is not unfair to say that a lot of

1 investigators viewed the tests themselves as tests
2 that could impair patients' Quality of Life. They
3 didn't like doing these things.
4 Secondly, I think that we did come to the
5 conclusion that the more subjective measures of
6 Quality of Life were a lot more reasonable and
7 reflected more what is relevant to the patients
8 than anything we would have measured in a 6-minute
9 walk or a peak VO_2 measurement.
10 So, in all those regards, we did not push
11 investigators in the way I wish we had, and the way
12 that the data has turned out to generate those
13 data. That, notwithstanding, also, the correlation
14 between 6-minute walks and peak VO_2's and Quality
15 of Life for any degree of heart failure are not
16 well established, and we certainly did not have a
17 large enough N to do that in this trial, and their
18 correlation with survival is not well established,
19 if at all, as well.
20 So, for all those reasons, I would say we
21 would have to be criticized as remiss in terms of
22 not pushing to get them, but I don't think it
23 reflects any bias on our part towards one group or
24 another in assessing them.
25 Actually, if you look at the data, you

1 don't see much of a difference between the two
2 groups.
3 DR. KONSTAM: Bias is not necessarily a
4 bad thing. It is just a reality. That is why we
5 blind drug trials. You can't escape it. If you
6 know what group of patients it is in, it is a
7 potential bias in how you grade it. That just has
8 to be said.
9 I think, however, I just give you my
10 conclusion again, which is that it certainly does
11 not appear as though everybody alive with the LVAD
12 is alive, you know, miserable in bed, it does not
13 appear that, and I do get that out of the Quality
14 of Life data and the New York Heart Association
15 classes.
16 The next broad category is the adverse
17 events. I think that is really there juxtaposed
18 against the survival benefit, and it was nicely
19 sort of delineated by the statistical reviewer
20 about different ways of looking at this.
21 If you look at all serious adverse events
22 including death as equal, you have got a problem on
23 your hands from the perspective of this trial. I
24 certainly don't look at it that way. I would
25 create a hierarchy where survival is better, and so

1 we are really going to have to face that.

2 I have some specific questions about the

3 adverse events. There seem to be a high number of

4 neurologic adverse events, and there seem to be

5 also a higher number--there are some septic

6 events--but there are a higher number of bleeds

7 than I would have anticipated even remote from the

8 time of the operation.

9 I just wanted to go through your thoughts

10 about a few of those things.

11 DR. ROSE: You mean non-neurologic? There

12 was only one intracranial.

13 DR. KONSTAM: Non-neurologic bleeds, yes,

14 two different things. So, there is strokes, which

15 I guess are predominantly embolic. There are other

16 neurologic events, and then there are some bleeds,

17 non-neurologic bleeds. I guess those are the

18 things that caught my eye.

19 Just to take them in order. Do you want

20 to comment on the strokes? I guess I would have

21 anticipated with the non-thrombogenic surface that

22 we are dealing with, that we wouldn't have seen

23 this many cerebrovascular accidents.

24 DR. ROSE: I think that the disparity in

25 that regard is that many of the strokes occurred in

1 a setting of device infection, so they are septic
2 emboli.
3 DR. KONSTAM: Really?
4 DR. ROSE: Yes.
5 DR. KONSTAM: Is that just your impression
6 or do we have some evidence of that?
7 DR. ROSE: The particular question is with
8 the textured surface and everything else, should we
9 have seen an overall smaller incidence of stroke.
10 DR. KONSTAM: You are saying it in a
11 different light than I was thinking. I thought
12 that these were for embolic events.
13 DR. ROSE: We have a summary slide on
14 neurologic adverse events.
15 [Slide.]
16 The frequency actually of disabling stroke
17 was, at least for the device literature, in this
18 trial remarkably low especially considering the
19 length of time that the patients were on devices.
20 All neurologic events here were not strokes.
21 DR. KONSTAM: I understand that, and I was
22 going to come to that, too, but there are strokes.
23 DR. ROSE: Yes.
24 DR. KONSTAM: And there are more strokes,
25 if you sort through it, you are still left with a

1 certain number of strokes that I am inferring at
2 thromboembolic strokes.
3 DR. ROSE: Yes.
4 DR. KONSTAM: And I guess it would be
5 important to note this, and I would presume, unless
6 we have information otherwise, that the device is
7 somehow contributing to this, because I think if
8 that is the case, then, going forward, we ought to
9 think about ways or preventing that including one
10 question I would have is should anticoagulation be
11 reconsidered with the device.
12 DR. LONG: I am Jim Long. I am the
13 co-director of the surgical arm of this REMATCH
14 trial. I guess for the sake of completeness I
15 ought to also declare that I do not have a conflict
16 of interest financially with Thoratec although they
17 are paying my expenses at this meeting.
18 There are a number of factors that went
19 into the stroke, a couple of which were not
20 specifically device related, but management
21 related. For example, two of those were air emboli
22 that occurred at the time of operation, so included
23 in this are not only device-specific issues, but
24 management issues.
25 Also included in this, and I am sorry I

1 don't have those numbers at my fingertips right
2 now, but also included in this are patient factors,
3 and as Eric alluded to, a fair number of these
4 strokes occurred in the setting of sepsis. That is
5 a fairly well documented occurrence in this field
6 with this technology.
7 DR. ROSE: With regard to the question of
8 anticoagulation, obviously, one of the unique
9 aspects of this device is that we did not routinely
10 use systemic anticoagulation here, and whether or
11 not it would have made a difference in stroke rate,
12 we don't know the answer to that.
13 Certainly, the N that we studied here with
14 68 device patients, even had we randomized them, it
15 was not even close to something that would have
16 allowed us to power this to judge whether or not
17 anticoagulation ought to be part of the management
18 of these patients.
19 DR. KONSTAM: I understand.
20 DR. LONG: Here is a summary of the
21 neurologic events just for frame of reference.
22 [Slide.]
23 Eleven strokes, 10 in the LVAD area. Two
24 of those were, as I indicated, air emboli, two to
25 intracranial hemorrhage, and two presumably due to

1 thromboembolic events, six of those in the LVAD
2 arm, and that is by way of frame of reference,
3 relative comparison to the VE bridge to transplant
4 experience, which you see in the bottom, 0.45
5 events per year in the REMATCH group versus 0.51
6 events per year in the VE bridge, so actually a
7 lower incidence.
8 DR. KONSTAM: I accept that. I am just
9 making note of the fact that there are strokes,
10 that there are events that seem to be
11 thromboembolic strokes, that is far from a zero
12 rate. It's a significant difference between the
13 two treatment groups in this regard.
14 There are other events that are TIAs that
15 I think many of which are likely to have been
16 thromboembolic. So, I think it is worth noting
17 this because I think if that is the case, and if
18 some of the patients are really--if this is a cause
19 of morbidity and perhaps mortality that is
20 contributing to the overall problem, well, then you
21 have to think about that, and perhaps even rethink
22 the whole anticoagulation question in some regard,
23 you know, whether it be antiplatelet or whether it
24 be warfarin anticoagulation. It is worth
25 rethinking in future trials or future experiences.

1 I guess that sort of brings me to the
2 other part, is that there seem to be some bleeds
3 that occurred, that were not limited to the
4 perioperative period, non-intracranial bleeds.
5 Do you want to comment on those? What
6 were they and why were patient bleeding?
7 DR. LONG: The vast amount of the
8 non-neurologic bleeds were associated with
9 operations or reoperations for the device
10 specifically, but there were bleeding episodes in
11 addition to that, that were counted in that, for
12 example, femoral puncture leading to a
13 retroperitoneal hemorrhage got included in that as
14 a bleeding episode.
15 There are a fair number of those, but the
16 vast majority of them are perioperative bleeding
17 episodes either at the time of device implantation
18 or at the time of device replacement.
19 DR. KONSTAM: I couldn't tell that from
20 the data because many of them were temporally
21 removed from the time of the initial implant.
22 DR. ROSE: But some of those were device
23 related, though, too, if we can get the device
24 slide comparing the VE SNAP to the old VE.
25 DR. KONSTAM: The overall bleeding rate

1 looks like about 0.15 per 100 patient days compared
2 to something like 0.01 in the other group. If you
3 look at rate after the first 30 days, it is still
4 about 0.12 or something per 100 patient days.
5 DR. ROSE: One of the mechanisms you see
6 is illustrated in this slide.
7 [Slide.]
8 Without strain relief, you essentially
9 have a kink in the graft, and you then have
10 friction rubbing against it, so that what can and
11 did happen with both this patient population and
12 the bridge patient population is we would see
13 delayed bleeding from erosion of the outflow graft
14 due to this kind of kinking.
15 DR. KONSTAM: I see.
16 DR. ROSE: That is what generates this
17 kind of strain.
18 DR. KONSTAM: If that is the case, you
19 might be able to see a difference in the VE SNAP
20 patients when you analyze them separately. I mean
21 that is something that seems like it would be worth
22 looking at.
23 As I read it, both of those things concern
24 me, the strokes and the bleeds, and I think it is
25 worth some detailed analysis, and I also think

1 that, again, it is worth rethinking the
2 anticoagulation question in my mind in light of
3 those things.
4 If you believe that the bleeding problem
5 is solved technically from this, and if you know
6 that most of the other bleeds are occurring at the
7 time of an operation, then, maybe the patients
8 could benefit from some form of anticoagulation to
9 prevent some of the thromboembolic events that do
10 seem to be occurring.
11 DR. ROSE: That is absolutely fair.
12 DR. LASKEY: Marv, excuse me. Just in
13 fairness to process, we are going to try and
14 finish.
15 DR. KONSTAM: That's fine. I am sorry for
16 going on. I will just skip some of the other
17 things. The only thing else I would say is that if
18 we go forward, if this device is approved for this
19 indication, I guess I would like to see a lot more
20 clearly defined for whom is it indicated.
21 Certainly, the proposed wording by the
22 sponsor--and we can talk about this at more
23 length--doesn't come close to satisfying what I
24 would like to see, and certainly doesn't
25 recapitulate in any way the entry criteria of the

1 study.

2 So, particularly in light of the large

3 number of adverse events and the fact that at this

4 point in time, very few patients are alive at two

5 years, there is going to need to be an awful lot of

6 consideration given to exactly who is a candidate

7 for this and make sure that the genie doesn't get

8 out of the bottle in terms of overusing this

9 device.

10 Sorry for going on.

11 DR. LASKEY: No, no, please don't

12 apologize. This is a terribly important discussion

13 particularly for the lead reviewers, but I will ask

14 subsequent reviewers to just try and limit their

15 time to about 15 minutes if possible to get through

16 the table. We will have a second round.

17 Did you have more questions, Mr. Konstam?

18 DR. KONSTAM: Nothing worth going on

19 about.

20 DR. LASKEY: Well, you never know.

21 Dr. Aziz.

22 DR. AZIZ: Let me also echo the early

23 statements. I think the presentation was extremely

24 well done by Dr. Rose, the company, and I think it

25 is a good model to have industry, academia, and the

1 NIH involved in helping to answer some important
2 questions.
3 I have a lot of questions, but I will try
4 to limit them in the interests of time.
5 Going through the sites, first of all, the
6 Cleveland Clinic was involved and then it withdraw.
7 I wonder if I can ask what the reason behind that
8 was.
9 DR. ROSE: At the time we began the trial,
10 they began their interest in the Batista operation,
11 and accumulated an experience over a couple of
12 years of in excess of 50 patients for the Batista.
13 I think they viewed us potentially
14 competitive with this protocol and withdrew for
15 that reason.
16 DR. AZIZ: In Table 4, it says, "Reasons
17 Patients were not Enrolled, 187 patients refused
18 the device." This is in your selection criteria.
19 Was there any particular sort of events, or were
20 they afraid of an operation? It seems a high
21 number of patients refusing such a therapy.
22 DR. ROSE: You mean from the screening
23 criteria?
24 DR. AZIZ: From the screening criteria,
25 yes.

1 DR. ROSE: I think based on everything we
2 have shown, it is not surprising that there is a
3 considerable degree or range of patient responses
4 to the prospect of this kind of therapy. At the
5 other end, we saw patients who absolutely wanted
6 the device and others who absolutely didn't.
7 Certainly, at least willingness to have a device
8 insertion was essential for the informed consent
9 process in a patient who categorically wouldn't
10 want a device, we excluded from the trial.
11 DR. AZIZ: Going to certain other issues,
12 in the neurological sort of events, in one of the
13 tables they mentioned there were two patients that
14 had seizures. When I was going through the
15 patients who had expired, actually, there were at
16 least sort of four patients who had grand mal
17 seizures.
18 Were there any indications as to the
19 etiology of that?
20 DR. ROSE: They were toxic
21 metabolic-related seizures.
22 DR. AZIZ: Because I mean those were four
23 patients that had actually died.
24 Again, going to the patients who had
25 actually died, I came across at least seven

1 patients who, at autopsy, had evidence of
2 thrombosis either in the graft or on the valves.
3 Now, that again seems like a fairly high incidence.
4 I mean I could understand the value obviously of no
5 anticoagulation and having a textured surface, but
6 do you think that this is, on the other side of the
7 equation, where not being anticoagulated does
8 result in sort of some of these other dramatic
9 events?
10 DR. ROSE: I don't think we can dispute
11 that we don't know the potential value of
12 anticoagulation in these patients, but
13 counterpoised against it also is there is a lot of
14 bleeding morbidity in these patients, as well, so
15 what we would rather see is a better anticoagulant.
16 I think if we had that, that we wouldn't hesitate
17 to use it.
18 DR. AZIZ: Also going to the sort of
19 patient profile, there were two patients that had
20 aortic dissections in the surgical group.
21 DR. ROSE: Yes.
22 DR. AZIZ: I think one of them ended up
23 dying. I think both of them actually died.
24 DR. ROSE: Yes. That is another late
25 bleeding complication from these devices, and there

1 is tension, gravitational force that is delivered
2 to the ascending aorta by the outflow graft that I
3 think was an under-appreciated potential
4 complication, and the way that outflow grafts are
5 sewn to the ascending aorta I think evolved
6 considerably during the course of the trial to a
7 much more meticulous technique with attempts at
8 strain relief at the aortic anastomosis.
9 DR. LONG: Another factor that contributed
10 to that is small patient size seemed to be a
11 predisposing factor, small aorta with a fairly
12 good-sized graft.
13 DR. AZIZ: What was the incidence of
14 hypertension, bad hypertension postoperatively in
15 the majority of these patients?
16 DR. ROSE: Uncontrollable hypertension was
17 not common, but the need for antihypertensive
18 medications in these patients was very common.
19 DR. AZIZ: Was uniform.
20 DR. ROSE: I can't say that it is uniform,
21 but I would say it is fairly typical of a patient
22 on a VAD that they need a lot of the agents, for
23 example, ACE inhibitors and beta blockers they were
24 on preoperatively, they go back on them for other
25 reasons.

1 DR. AZIZ: Let me move on to certain
2 issues related to device dysfunction, either the
3 motor or the valves. The valves are stented
4 valves, I presume, or unstented valves, so they are
5 exposed to a very high pressure particularly
6 because of the pressure generated in the LVAD
7 itself.
8 Now, compared to what the bench testing
9 showed, the longevity was I think about three and a
10 half, four years, but what we actually see in
11 reality clinically, and I am sure there are a
12 number of factors, is that it really isn't that
13 long.
14 What troubles me a little bit is I think
15 this device is clearly good as a bridge to
16 transplantation. I think what we are asking of
17 this device now is to really function for a much
18 longer period of time with the repeated stresses on
19 the valve and other components, and I am not
20 completely convinced that something like this could
21 be, let's say, advocated for a four-year period or
22 a five-year period, the reason being I think again
23 the bench testing values defer from what we find
24 clinically, and particularly there were some
25 patients where the inflow valves I think become

1 dysfunctional fairly quickly.

2 How would you address that, because I mean

3 what we are trying to do is advocate this as a sort

4 of destination therapy.

5 MR. POIRIER: If you look at the valve

6 dysfunction, the primary reason for the valve

7 dysfunction was excessive pump chamber pressure,

8 and that came about from several factors, one,

9 outflow kinks, patient's high arterial pressure,

10 any occlusions in the anastomosis, the anastomosis

11 to the aorta was done with just a simple slit as

12 opposed to removing material, there was a pressure

13 drop across that area.

14 So, unlike the human body, that has only

15 one pressure drop in the ventricle to the aorta,

16 which is the aortic valve, these devices have many,

17 many pressure drops, the anastomosis, the size of

18 the graft, the outflow valve, any kinking, so there

19 were many factors.

20 All of those are additive. The net result

21 is the pump chamber pressure has to increase, which

22 puts stress on the valve. We have taken great

23 pains at improving that. We put the strain relief

24 bond to reduce that pressure drop, we have

25 instructed and written papers on patient management

1 in terms of the anastomosis, how the device should
2 be installed.
3 We have looked at changing, modifying the
4 way the device is controlled to reduce the pump
5 chamber pressure, so we have done many, many things
6 to try to reduce pump chamber pressure, to increase
7 the longevity of the tissue valves.
8 I would like to clarify one point. The
9 in-vitro test does not evaluate the tissue valves.
10 It is impossible to do a long-term test with tissue
11 valves in mock circulatory loop because the valves
12 become contaminated and the tissue deteriorates.
13 So, the valves are never tested. They are
14 tested separately in a separate circulatory loop
15 that can be kept in a sterile environment. So, the
16 results of the in-vitro tests do not include the
17 tissue valve durability, so there is a difference
18 there.
19 I think that should answer some of your
20 questions.
21 DR. LONG: A couple of other thoughts from
22 a clinical point of view. The inflow valve failure
23 problem with the HeartMate device is relatively new
24 within the last couple of years. During its IP
25 era, when it was a pneumatic-driven console with

1 lower pressures, there were virtually no inflow
2 valve failures.
3 It appears that a change in configuration
4 of the inflow conduit to reduce bleeding has been
5 associated with an increased risk that pressures
6 inside the pump will lead to inflow valve failure.
7 It's a new phenomenon. It appears to be
8 correctable by the measures that Vic is
9 introducing.
10 I guess the other issue of relevance is
11 what are the consequences of that inflow valve
12 failure. We don't have a lot of that, the bulk of
13 that data within the REMATCH trial itself per se.
14 From other experiences, we know the natural history
15 of inflow valve failure is slow failure with
16 patients who progressively increase in their heart
17 failure, their pump goes up.
18 It may lead to a decrease in longevity of
19 that pump, as it was alluded to this morning, but
20 in the vast majority of experience, we do not
21 experience catastrophic outcomes with these
22 patients, and they can be managed medically over
23 time, observed, and then finally committed to pump
24 replacement.
25 DR. AZIZ: Obviously, the other issue,

1 which is responsible both from morbidity and
2 mortality, is sepsis. I accept that, I think as
3 most of us, that that is clearly multifactorial.
4 So, there are two questions.
5 One, was there a correlation between the
6 albumin or pre-albumin levels and the incidence of
7 sepsis?
8 DR. ROSE: To show you how ignorant we
9 were of this problem, we didn't even collect
10 prospectively albumins on the patients when we
11 started the trial, obviously, highly relevant data
12 and something we are trying to recreate
13 retrospectively, but I think it is clear serum
14 albumin is the best single predictor in the VA
15 study of operative mortality for all patients
16 having any kind of surgery regardless of what the
17 reason was.
18 I do think that we paid much too little
19 attention to perioperative nutrition in this trial.
20 We had a symposium of investigators to look at just
21 this subject shortly before the trial reached its
22 endpoint, and I think going forward that
23 nutritional management is going to be key in
24 diminishing this frequency of infections.
25 DR. AZIZ: The other, which is probably

1 more than a theoretical suggestion or it may be an
2 etiological factor is the nature of your textured
3 surface.
4 I think people from your own institution
5 have very nicely shown that the new intima,
6 although it actually may prevent thromboembolic
7 events, does cause an elevation of PRAs in a T-cell
8 separation and B-cell hyperactivity.
9 What role do you think that might have
10 played or do you have any evidence that that could
11 have also played a role in the genesis of sepsis?
12 DR. ROSE: I do believe there is firm
13 evidence that these devices do modulate immune
14 function, and, if anything, it seems that they
15 up-regulate humoral responses and perhaps
16 down-regulate cellular responses.
17 I don't think that that is unique to the
18 textured surface. When we have looked at patients
19 with smooth surface devices, we have seen similar
20 perturbations, but I think there is certainly more
21 than the possibility that these devices are, in
22 themselves, immunosuppressant, and can lead to
23 increased susceptibility to infection aside from
24 the issues of access through the transcutaneous
25 ports, and it is a very important set of issues for

1 us.

2 DR. LONG: This is an extremely important

3 part of the future for the field, and if you think

4 about this as an issue-compromising outcome,

5 thinking about it in three categories, one is what

6 might the device do; two, what does the patient

7 bring to bear, and three, how does management

8 affect it, you have already alluded to the

9 possibility that the device may play some role in

10 terms of altering an immune system. Our general

11 consensus is that that is probably a very low role

12 relative to the other two at this point in time.

13 Patient factors, we think are substantial,

14 and there is an analysis ongoing now trying to look

15 at a subset that might predict risk of infection

16 including nutritional factors. These patients in

17 this group were absolutely dramatically different

18 than any we had ever faced in the bridge to

19 transplant group.

20 We thought bridge to transplant patients

21 were sick because they were acutely decompensated

22 with balloon pumps, drips and all sorts of other

23 things. These patients would walk in, but be

24 terribly cachectic, have lost 20, 30, 40 pounds

25 over the last few months, terribly malnourished, as

1 you know, from that, and immune compromised.

2 These are the kinds of patients we were

3 dealing with here, and we believe that to be a very

4 significant factor, patient-host issues that

5 contributed to our infection rate.

6 It goes beyond that, into the third

7 category, though, of management, and let me put a

8 slide up.

9 [Slide.]

10 When we looked at a couple of centers that

11 were responsible or that took on themselves

12 extremely aggressive infection control efforts,

13 which I will try to describe in a minute, we found

14 that infection can be controlled, and we think this

15 infers that management played a significant role in

16 this process.

17 If you look at two centers here that did

18 16 LVADs relative to 52 for the rest, or 24 percent

19 of the total LVADs done, with a median duration of

20 use, even greater than the rest of them, so a

21 longer time of exposure at which they could be more

22 susceptible to infection, we find that in these two

23 centers, we have zero percent of serious infection,

24 0.06 serious drive line or pocket infection, and

25 zero serious pump housing inflow or outflow

1 infection relative to the others that you see
2 there.
3 This is certainly a small and not
4 absolutely demonstrative that management does make
5 a difference, but a strong inference that that is
6 the case. So, out of the three categories of this
7 very, very important topic, device probably plays a
8 small role, patient factors in this patient
9 population played an immense role, and management,
10 we think plays very strong role, as well, and very
11 significant room for the future in both of those
12 latter two categories for improvement.
13 DR. EWING: Excuse me for a moment. I
14 would like to remind the sponsor and the panel
15 members that this is new information to the FDA, we
16 have not reviewed this, and we would like to keep
17 in consideration we are to be discussing material
18 that is presented in the application.
19 DR. AZIZ: One other quick question. How
20 many of the patients at two years had had the
21 original device? In other words, how many patients
22 who went on for a long period of time had had to
23 have the device changed or something done
24 technically?
25 DR. ROSE: A total of eight pump

1 replacements as far as I know. Also, a number of
2 patients who could have had their pumps replaced,
3 who opted not to.
4 DR. LASKEY: Before we move on, Dr. Rose,
5 your comments remind me of a small book I read as a
6 surgical intern, written by Frannie Moore, about
7 the metabolic control of the surgical patient, and
8 I think it still remains true, perhaps more so.
9 It is my understanding that in a
10 randomized trial by the toss of a coin, these
11 predisposing factors should certainly sort
12 themselves out in either arms, so there is
13 something to be said here.
14 Moving on with the other panelists, Dr.
15 Wittes, please.
16 DR. WITTES: First of all, I want to echo
17 everybody's statement that the presentations, both
18 in the panel pack and today, were very clear, and
19 it helps us a lot when there is clarity.
20 I also want to just point out what a good
21 thing it is that you randomized this study, because
22 had you observed 75 percent mortality in your
23 treated group, which is what you expected in the
24 control, I don't think we would be here today.
25 I do see three main themes. One, of

1 course, is the mortality, which has been already
2 brought up in various ways. The other is the issue
3 of device failure. The third is sepsis, which has
4 been brought up, but I only have one extra thing to
5 add.
6 Obviously the question of this very high
7 mortality rate in the control group raises the
8 question of who were these patients, and the device
9 appears to have high risk, raising the concern of
10 this device in a population of healthier patients.
11 I am just stating that, it is not really a
12 question. It's a statement of concern. My own
13 feeling is that death trumps nearly everything, so
14 I am not all that concerned about Quality of Life
15 and things like that. This may not go over so well
16 around here, but it seems to me that when we have a
17 big effect on mortality, that we have to sit up and
18 take notice.
19 But I am troubled by the dearth of data at
20 two years. I understand what happened, that you
21 powered the study in a way that if you have 92
22 deaths, you stop the study at 92 deaths, and
23 because the mortality rate was so high, the deaths
24 occurred before two years, so the follow-up didn't
25 go as long as you planned.

1 I am not looking actually for statistical
2 significance at two years, I am fine with a
3 log-rank test over the period, but I would actually
4 like to see more data at two, and there is 25
5 percent--not 25 percent, more than that--I looked
6 at the data through February, and there is still I
7 think 20 patients in the treated group, in the
8 device group, who are still censored, so there is
9 data in the pipeline that will speak to two years.
10 What are your plans for follow-up of these
11 patients?
12 DR. ROSE: Well, the trial is ongoing. We
13 stopped enrollment and we reached the primary
14 endpoint, and we did an analysis at the time of the
15 enrollment. It is remarkable to me how--it is not
16 well appreciated this is now the largest series of
17 long-term device patients ever as far as I know,
18 and I think that there is a lot of additional
19 useful information that will come to us.
20 We are funded by the NIH to continue to
21 follow these patients, and we intend to follow them
22 all for the duration of their lives. That is our
23 intent, and we intend to keep reporting that as
24 time passes.
25 DR. WITTES: The other thing, I just want

1 to make a note about log-rank. I am very
2 uncomfortable with the language about the log-rank
3 being the area under the curve measure, because it
4 is really not, and I think that it gives a very--I
5 mean the log-rank tests looks at data at the time
6 of deaths, and it is not integrating area at all,
7 and I just want to make sure that that is not the
8 statement that you made, because it gives a very
9 different picture.
10 DR. ROSE: What was the statement I made?
11 DR. WITTES: Well, I don't know who made
12 it.
13 DR. ROSE: It probably was me.
14 DR. WITTES: I heard it several times.
15 The first time I didn't pay any attention to it,
16 but it came up a second time.
17 A question about sepsis. I may have
18 misinterpreted the data in the panel pack, but it
19 looked to me as if the number of cases in the two
20 groups was the same, but the case fatality rate was
21 higher in the device group.
22 So, my first question is, is that true,
23 and the second question, if so, why?
24 DR. ROSE: Do you mean the mortality rate
25 from sepsis?

1 DR. WITTES: Yes. If my first statement
2 is correct, and I am not sure it is, but it was
3 hard for me to find that, that the rate of sepsis
4 is the same in the two groups, and we know that the
5 mortality from sepsis, the split was 17-1 in the
6 device versus the control. That would imply a
7 higher case fatality rate.
8 So, the question is, what is it, why would
9 that have been true?
10 DR. LONG: The overall sepsis rate, total
11 rate was not different between the two groups, but
12 when you look at device-associated sepsis, that led
13 to a significant impact on adverse event that
14 exceeded that in the medical management arm.
15 DR. WITTES: I don't think you are
16 answering my question quite. What it seems to me
17 it is saying is that somehow the sepsis, if you had
18 sepsis in a device, your probability of living
19 through that episode was much lower than if you
20 were in medical management and had sepsis.
21 DR. LONG: That is correct.
22 DR. ROSE: The ratio of the incidence of
23 sepsis in the device patients compared to OMM was
24 2. It was double in the device patients compared
25 to the controls. I don't think that reached

1 statistically significance in isolation, but it
2 still was double.
3 DR. WITTES: But the death was 17 to 1.
4 DR. ROSE: Excuse me?
5 DR. WITTES: Wasn't it 17 to 1?
6 DR. ROSE: As a cause of death, it was
7 significant.
8 DR. WITTES: Well, let me ask in a
9 different way.
10 DR. ROSE: This is hot off the presses
11 March 1st.
12 DR. WITTES: What?
13 DR. ROSE: This is March 1, 2002, data, so
14 that difference was significant.
15 DR. WITTES: I am not interested in
16 significance.
17 DR. ROSE: But another reason for that,
18 though, the medically managed patients died from
19 heart failure.
20 DR. WITTES: But the ones in medical
21 management who got sepsis didn't seem to die of
22 sepsis, is that right?
23 DR. ROSE: It may not have been the exact
24 proximate cause of their death.
25 DR. LONG: One patient died of sepsis.

1 DR. ROSE: That was ascribed to sepsis.

2 DR. LASKEY: Are these not all adjudicated

3 by the DSMB in terms of the cause of death?

4 DR. ROSE: By the M&M Committee, yes.

5 You are correct, there is one death

6 attributed to sepsis. Whether that means that

7 sepsis is worse in the device patients or heart

8 failure is worse in the OMM patients and supersedes

9 it, I don't know.

10 DR. LONG: Your observation is correct,

11 that there are more deaths due to sepsis in the

12 device group than there are in the medical

13 management group.

14 DR. WITTES: Let me say it once more,

15 though, because that is clear, but the other issue

16 is, if the data as reported are correct, and I

17 realize that you could have differential reporting

18 in the classification, and so forth, then, it seems

19 to say that if you are in a septic episode and you

20 have the device, you are at much higher risk for

21 death than if you have a septic episode and you are

22 on medical management.

23 The relevance to me, and I obviously defer

24 to all of you guys, is that that seems like it's a

25 very high risk and maybe some of the discussion

1 that came up before in terms of management of these
2 episodes needs to be addressed.
3 DR. ROSE: I don't think it is surprising
4 that sepsis in the presence of a large
5 intravascular foreign body results in a higher
6 mortality rate than in the other patients. I think
7 that is part of the risk profile.
8 DR. LONG: Plus some of the patients who
9 did get infected, LVADs underwent replacement in
10 the face of sepsis and replacement, ended up with
11 mortality. So, yes, we concur entirely with you.
12 This is an area of extreme concern for the
13 field, as I discussed earlier, out of the three
14 things that you look at in terms of etiology,
15 device patient issues and management issues, we
16 consider the latter two to be very substantial
17 areas for targeting improvement.
18 DR. WITTES: The other issue has to do
19 with patient reported outcomes. I guess I have to
20 confess I find them questionable in an open trial
21 especially with huge differential mortality in the
22 two groups.
23 I am comforted by the people who go from
24 Class IV to Class I and II, but other than that, I
25 think it is really hard to tease out what these

1 mean.

2 DR. LASKEY: Dr. Domanski.

3 DR. DOMANSKI: I would kind of like to

4 back off a little bit to a big picture and make

5 sure that I really understand fully. I think,

6 first of all, on the Quality of Life data, I guess

7 I am taken with the fact--I am sort of coming

8 backwards to things that I think are more

9 important--but I think the small numbers, the

10 unblinded nature of the trial, and so the potential

11 for investigator bias, the potential for placebo

12 effect, the small numbers, from my standpoint, make

13 the Quality of Life data far less than compelling.

14 I share for different reasons Dr. Wittes's

15 lack of interest in it actually, because I don't

16 think it is terribly useful, but I may be wrong,

17 and I am willing to accept an argument relative to

18 that.

19 But I would like to come back to the

20 mortality and also to the serious adverse events.

21 It seems to me that if you look at death, there is

22 a difference, certainly at one year. If you look

23 at death plus serious adverse events as they have

24 been defined, there is no difference, but I guess

25 some of the serious adverse events strike me as not

1 all that tremendously serious.

2 I mean extending hospital stay a bit is

3 unfortunate, but I think that is one of them, and I

4 guess that is not something that you live with long

5 term even being rehospitalized, while it is a

6 significant event, is not I think on a par with,

7 for instance, a cerebrovascular accident.

8 While I don't think, in fact, I know

9 these data weren't tabulated in this way. I guess

10 things that do strike me as being irreparably

11 serious adverse events are things like

12 cerebrovascular accident.

13 So, if one were to look at death plus

14 cerebrovascular accident, I wonder if you have a

15 back-up slide that actually looks at that. If you

16 don't with Kaplan-Meier, can we at least add them

17 up and see what the difference is between the two

18 groups, because that is in the submission, it is

19 just not parsed that way.

20 I think if there weren't a difference,

21 then, I start to wonder. So, that is Question 1

22 and I have a follow-up.

23 DR. ROSE: We don't have such a slide.

24 DR. DOMANSKI: Is it easy to add up? I

25 know you can't get the Kaplan-Meier stuff this

1 easily, but a reasonable approximation to it would
2 be to look at one year at your deaths plus
3 cerebrovascular accident rate. Do you have that
4 for the two groups?
5 DR. ROSE: We have the raw data. Whether
6 or not we can create freedom from death plus CVA at
7 one time--
8 DR. DOMANSKI: Because that is something I
9 would really like to see.
10 DR. LASKEY: You mean death or.
11 DR. DOMANSKI: That's correct. That is
12 what I mean by death plus CVA, that is what I mean,
13 death or cerebrovascular accident. I am just
14 curious because it seems to me that those are the
15 two--
16 DR. ROSE: I assume you mean
17 cerebrovascular accident also with--
18 DR. DOMANSKI: With a bleed, with an
19 ischemic stroke.
20 DR. ROSE: With a permanent deficit.
21 DR. DOMANSKI: That's correct, or with a
22 deficit that lasts beyond 24 hours. I will spot
23 you even the TIAs. I will even spot you the
24 seizures. The reason I am so curious about it is
25 that one is talking about, you know, if one asks

1 whether something should be approved for use, one
2 can reasonably ask whether it is demonstrated to be
3 clinically very useful, and what you are talking
4 about is taking people who are more or less at the
5 end of their lives and saying maybe if I give you
6 this device, I will give you a big operation, I
7 will give you a big, expensive device, and I buy
8 you a year of something, and it is not entirely
9 clear to me what you have bought, all right, so
10 there are a fewer of them dead at one year, but I
11 wonder.
12 You know, if there were no difference
13 between death or CVA, even at one year, then, I
14 guess I would wonder what you have done. I still
15 wonder a little what we have done doing it for one
16 year, but that is the pith of the question.
17 DR. ROSE: I think it's an excellent
18 question. It is something we are going to try to
19 tabulate during the time that we are here. I want
20 to make the point, though, with regard to the
21 analysis of AE's of the two groups, that part of
22 the design and reporting spotted the OMM group,
23 worsening heart failure, as an AE. That was not
24 considered to be an AE in the control group, had
25 hospitalizations for it, you know, getting short of

1 breath, need to be intubated, having to be
2 hospitalized again, I think is a considerable
3 adverse event when you have severe heart failure
4 that was not totalled in the OMM group as adverse
5 events.
6 If we were to do a fair comparison, we
7 need to count everything from a patient perspective
8 as an adverse event, not--
9 DR. DOMANSKI: Why didn't you then?
10 DR. ROSE: Excuse me?
11 DR. DOMANSKI: So, why didn't you count
12 it?
13 DR. ROSE: The sense was that this was
14 tautologic, we knew that these patients had heart
15 failure and they were going to die from it, so that
16 the fact that they had exacerbations even of their
17 severe heart failure was something that there was
18 not much--in retrospect, I wish we had.
19 DR. DOMANSKI: In order for me not to
20 perseverate and hold the committee up, I would just
21 like to, you know, again, just back off. I would
22 like to see that tabulation, and I see the folks
23 doing it over there, and I think the challenge that
24 I would offer to the group that has to sit here and
25 decide whether to approve it is whether or not one

1 has done a clinically significant deed with this.
2 I have some concern about it even if the
3 tabulation is in favor of the device. Certainly,
4 if it's not, my concern would be raised. I think
5 with that, I would pass it to the next person just
6 while they are going ahead with that.
7 DR. LASKEY: Dr. Comerota.
8 DR. COMEROTA: Thank you. Also, I would
9 like to extend my compliments to all the presenters
10 for an excellent job. Many of my questions have
11 already been addressed, so I will funnel them down
12 to a couple comments and perhaps a couple
13 questions.
14 Eric, in the manuscript, I think it was
15 stated that there was no significant learning curve
16 to this or that was a non-issue, but then also it
17 was stated or the observation presented that in the
18 patients enrolled in the last year, there was a 25
19 percent decline in mortality relative risk per year
20 when survival was adjusted for date of entry.
21 Are those contradictory statements, so is
22 there truly a learning curve or perhaps is there a
23 change in patient care that resulted in this
24 observation?
25 DR. ROSE: I do believe that there is a

1 learning curve. I don't think REMATCH is a large
2 enough trial powered to assess it. It was that
3 difference of survival, adding a year to the date
4 of enrollment we found did occur was not
5 statistically significant.
6 When we tried to remeasure it again, it
7 still does not reach statistical significance, but
8 I think for anyone who gets involved in this field
9 and starts doing it, the collective wisdom of the
10 investigators I think is increased considerably
11 during the course of this trial.
12 Also, I want to point out that before
13 this, there was no experience of any large number
14 with destination therapy. PREMATCH was a total of
15 21 patients. That was essentially the American
16 experience, and it was only 11 patients that got
17 devices, so the entire American surgical experience
18 with destination therapy is now 79 patients.
19 I do think that there is a lot more to be
20 learned at this point.
21 DR. LONG: Also, this is the first trial
22 ever to look at a patient population of this age,
23 which gives us a new learning insight, as well.
24 DR. COMEROTA: Correct, and that age issue
25 obviously is unique to this trial.

1 DR. ROSE: Encouragingly, in patients that
2 were younger than 60 years old in this trial, the
3 one-year survival was 74 percent, which approaches
4 outcomes at least at one year for the process of
5 transplantation.
6 That is not to say that this is up to
7 that, but that observation in that subgroup is a
8 very encouraging observation.
9 DR. COMEROTA: That is a good segue to my
10 next question. It was stated this morning that the
11 mean time in your bridge to transplant group was
12 about 29 days.
13 DR. ROSE: Right.
14 DR. COMEROTA: In those patients in the
15 bridge to transplant group that exceeded the 29
16 days, that may have gone out to two months, have
17 you looked at the survival curve in those patients
18 and compared them to the survival curve in the
19 REMATCH patients?
20 DR. ROSE: Meaning bridge to transplant
21 patients with a longer hospital stay than--
22 DR. COMEROTA: Well, the bridge to
23 transplant patients that had their heart
24 transplants delayed, so had the device implanted
25 for a much longer period of time, and how did those

1 early curves fit with the early curves for a
2 similar time frame in the patients in the REMATCH
3 study who were randomized to the device?
4 DR. EWING: I was just going to say that
5 he could answer, I would recommend that he could
6 answer the question, but you need to remember that
7 we have not read the transplant the data. So, we
8 can't tell you our opinion on that data.
9 DR. COMEROTA: Perhaps it is not an
10 appropriate question for the purpose of the
11 deliberation of this panel.
12 DR. ROSE: We have published on the
13 subject of the long-term results of bridge to
14 transplant patients, and there is an incidence of
15 adverse events that I think is analogous to what we
16 saw in the REMATCH data.
17 With regard to N's, though, that are out
18 more than a year as a bridge, that N is pretty
19 small as I remember.
20 [Slide.]
21 DR. ROSE: There it is. It is 104
22 patients.
23 DR. LASKEY: It is of interest, but not
24 germane.
25 DR. COMEROTA: I would just echo my

1 concern as to who this is indicated for. That
2 question was raised, so obviously, it need not be
3 addressed.
4 The concern in terms of the potential
5 patient bias and the Quality of Life was also
6 raised, and I think there is an enormous potential
7 bias because those patients who were randomized to
8 the device are going to get a great deal more
9 attention than those that are randomized to ongoing
10 medical care, feel, well, perhaps I am abandoned
11 and I don't want to live like this, so I will just
12 die.
13 Well, obviously, that bias is there, and
14 my final comment was since most--this is infection
15 related--since most of the infections were in the
16 drive line tract, are there any specific
17 recommendations coming from the manufacturers
18 regarding how to manage this drive line infection?
19 DR. LONG: There are several issues that
20 are very critical. The drive line does play an
21 important part of that. One is the location of the
22 drive line as it exits allowing for immobilization
23 at the exit site.
24 One of the keys to success when we have
25 looked at subsets within the REMATCH group, and

1 again this is outside the data you have access to,
2 but it will answer your question, is those who paid
3 a great deal of attention to immobilization and
4 proper exteriorization of the drive line had a very
5 much lower rate of infection.
6 We also believe that the stiffness of the
7 percutaneous lead has been a factor, and that is
8 being addressed with a lead that is now being
9 introduced that is more flexible and less prone to
10 trauma at the exit site itself.
11 There are also measures being looked at in
12 terms of antimicrobial impregnation. So, this is
13 an area clearly that is very, very important for
14 the future, that has to be considered strongly when
15 you look at attempts to correct infection in this
16 patient population.
17 DR. STEVENSON: If I can just interject,
18 with regard to the issue about attention, we agree
19 completely that we cannot eliminate the patient
20 bias in terms of how they feel about having a
21 device or not.
22 On the other hand, we controlled what we
23 could, the frequency of clinic visits, the
24 frequency of telephone contact was virtually
25 exactly the same per patient month of follow-up in

1 the two groups. We were very careful to try to
2 achieve that.
3 DR. HEITJAN: I am Daniel Heitjan, the
4 REMATCH statistician from Columbia University. I
5 have no financial interest in Thoratec although
6 they are paying my expenses to attend the meeting.
7 Dr. Domanski had a question about the
8 stroke and death. Everyone who had a stroke died,
9 so if you consider stroke or death an event, it
10 doesn't change the event rates compared to the
11 death rate. So, the death fractions are exactly
12 the same.
13 DR. DOMANSKI: So, you had no non-fatal
14 strokes.
15 DR. HEITJAN: I believe that is not the
16 case, but they all eventually died. Some of them
17 died from other causes, they may have died from
18 sepsis or heart failure
19 DR. DOMANSKI: That is interesting. Okay.
20 Got it.
21 DR. LASKEY: I mean we have to live by
22 what they are adjudicated as. Isn't that the key
23 question here, you had an independent committee
24 that assessed etiology and causation, and so forth,
25 so if I understand you correctly, every stroke was

1 fatal--

2 DR. HEITJAN: No. I believe the question

3 was, Dr. Domanski's question was instead of

4 considering an event death, let's say death or

5 stroke as an event, does that change the picture at

6 all, and the fact is that everyone who had a stroke

7 in either arm died, although they didn't necessary

8 die of stroke, they may have died of sepsis or

9 other causes.

10 DR. DOMANSKI: Yes, but it might well

11 change the time to event analyses.

12 DR. HEITJAN: That is correct. I have

13 never computer the Kaplan-Meier curve death or

14 stroke, and I don't think TCI or Thoratec has done

15 that either. In principle, it could change it.

16 DR. DOMANSKI: What I was trying to get at

17 with that question is I don't buy into the Quality

18 of Life data in this study. Frankly, I don't think

19 it is useful. But I also don't buy into the death

20 plus serious adverse event rate as it is defined.

21 I think that attacks the machine inappropriately

22 because I don't think some of the serious adverse

23 events are so serious.

24 So, what I was trying to do is pick out

25 something that I knew was serious and look at it at

1 that point, and I guess you have answered the
2 question. The bottom line is that if we approve
3 this device, and you can go to somebody and say at
4 one year, if you are willing to pay for this, I can
5 buy you less death at one year.
6 I don't think you can say that for any
7 other time. I don't think you can say that for two
8 years really, I don't think, but certainly at one
9 year you can.
10 DR. KONSTAM: He hasn't really said that,
11 because he hasn't told you when they died.
12 DR. LASKEY: We are getting out of
13 sequence here, so we will have a chance to
14 reapproach this again after everyone has had their
15 first round. I think this is very, very fruitful,
16 but we need to at least complete round one.
17 Have you at least delivered the totality--
18 DR. HEITJAN: Yes.
19 DR. LASKEY: Thank you.
20 DR. COMEROTA: I have finished my
21 comments, thank you.
22 DR. LASKEY: Dr. Nissen.
23 DR. NISSEN: I will try to keep us on
24 time.
25 DR. LASKEY: Well, after you, we will take

1 a break.

2 DR. NISSEN: Lynne, you characterized the

3 medical treatment of these patients very well, but

4 there is one thing I didn't see, and I may just

5 have missed it in here, but AICD use. I would like

6 to know about AICD use in this trial. What can you

7 tell me about that?

8 DR. STEVENSON: If you want to wait a

9 couple minutes, I can give you slightly more

10 thorough, but as I recall, there were 15 ICDs in

11 the medical management arm at the time of

12 randomization. There were several put in after

13 that. I would have to look up the data.

14 Of interest, though, I think we have got

15 to get back to how sick this population is. In

16 fact, five of the people who had ICDs and requested

17 that they be turned off, so they would be allowed

18 to die without any further ICD firings. So, I

19 think this is not a population in which sudden

20 death, in fact, is our major concern. We are more

21 concerned with kind of the slow, miserable dying

22 from heart failure.

23 DR. NISSEN: Let me just take issue with

24 you on that. During the course of this trial,

25 there was a lot of evolution of data on the

1 benefits of implantable defibrillators, and
2 remember now we are talking about very small
3 numbers. We had seven patients alive at the end of
4 two years in the LVAD group, and we had three
5 patients alive in the medical group.
6 All it would have taken was survival of
7 four additional patients in the medical group to
8 have equalized the actual two-year mortality. I
9 would argue that 15 patients, only 15 patients in
10 implantable defibrillators represents a shockingly
11 under-utilization of a therapy that has been shown
12 to prolong life in these patients.
13 DR. STEVENSON: I actually have the
14 correct number here. Fifteen had it at baseline,
15 an additional 10 had it inserted, so that would be
16 25 patients in that arm.
17 DR. NISSEN: It's a little closer.
18 DR. STEVENSON: Again, I would emphasize
19 that none of the ICD trials have addressed Class IV
20 heart failure at all. They have been specifically
21 excluded from every ICD trial done. So, we, in
22 fact, have no data that ICD would prolong survival
23 in Class IV heart failure, and certainly even less
24 concept that it would prolong meaningful survival
25 in Class IV heart failure.

1 DR. NISSEN: Let me move on for the
2 moment, but I do think that currently, patients
3 with low ejection fractions are getting a lot of
4 ICDs put in. Wouldn't you agree that today, more
5 of these patients would arrive into the trial with
6 an ICD in place?
7 DR. STEVENSON: They would arrive into it,
8 but wouldn't necessarily get it if they didn't
9 arrive with one.
10 DR. NISSEN: But I am just saying it is a
11 low utilization for this type of population by
12 contemporary standards.
13 DR. STEVENSON: I don't know. In fact,
14 the patients referred to us for transplantation,
15 approximately 15 to 20 percent have ICDs in, which
16 would be very comparable with what you see here.
17 DR. NISSEN: I am also interested in
18 understanding how New York Heart Association
19 classification was determined and who assessed it.
20 Let me tell you why I want to try to understand
21 this. There is a divergence in the data with the
22 best data being the NYHA classification for the
23 device.
24 So, in the medical patients and in the
25 surgical patients, who determine what their New

1 York Heart Association classification was, how was
2 that done?
3 DR. STEVENSON: At baseline, that was done
4 by the cardiologists at the time of enrollment, and
5 certainly I think all the baseline qualifications
6 indicate that Class IV was appropriate at baseline.
7 DR. NISSEN: No, no, no, I am talking
8 about during the course of the trial. There was an
9 improvement in classification in the group that got
10 the LVAD, and what I want to know is how was NYHA
11 classification determined during the course of the
12 trial.
13 MS. TIERNEY: I am Anita Tierney from the
14 Data Coordinating Center. I have no conflict of
15 interest with Thoratec.
16 We credentialed both the surgeons and the
17 cardiologists at the beginning of the trial. The
18 patients were seen on follow-up generally by both
19 the surgeon and the cardiologist. It was one of
20 the two who determined the Class IV heart failure
21 or the class of heart failure during the duration
22 of the trial.
23 DR. NISSEN: You understand why I am
24 asking the question, and that is, that if I am a
25 surgeon and I put an LVAD in a patient, and I am

1 asked to assess whether their NYHA classification
2 has improved, my answer may be very different
3 from--I mean I think I would have been much more
4 comforted if you told me you had an independent
5 person not involved in the trial, and I think it is
6 how you should have done the trial, is someone not
7 involved in the direct care of the patient should
8 have interviewed them about their symptoms and
9 determined their classification.
10 So, to me, this process really doesn't
11 validate that aspect of the results.
12 DR. ROSE: But the Quality of Life aside
13 from NYHA classification, which was not made by the
14 patient, but is done by the clinician seeing them
15 or the nurse clinician seeing the patient, the
16 Quality of Life questionnaires themselves were not
17 administered by the investigators themselves.
18 DR. NISSEN: No, but you see the data
19 there is very limited and much weaker. The
20 strongest data you presented on Quality of Life was
21 New York Heart Association classification, and when
22 I saw that, and I saw this big divergence between
23 the Quality of Life questionnaires and the 6-minute
24 walk, and all the things that might be
25 quasi-objective, I said to myself I wonder if the

1 surgeons weren't determining the Quality of Life,
2 you know, the NYHA classification for surgical
3 patients, and the medical people determining of
4 medical patients, and didn't that, in fact, bias
5 the assessment. So far, nothing is addressed.
6 DR. ROSE: Your point is well taken, and
7 it very well may have.
8 DR. NISSEN: I think we really have to not
9 consider that data to be valid for purposes of this
10 study.
11 I guess the other question I had was, were
12 any patients deemed Functional Class I if they were
13 in the hospital, could you be Functional Class I
14 and be hospitalized?
15 DR. ROSE: I would think not, but I don't
16 feel like I can assert for sure.
17 DR. NISSEN: I guess at some point, if
18 there is an answer to that, I would like to know
19 that.
20 DR. PINA: You can have an infection and
21 still be a Class I, you can still walk around and
22 have an infection.
23 DR. NISSEN: Again, I think it would be
24 just helpful to me to understand that.
25 The final question that I had was what was

1 the mean time to internal device failure and what
2 was the mean time to any device failure for this
3 device in this trial. I saw the 3.4-year figure,
4 but I would like to know what the mean time to
5 internal device failure was for the use of the
6 device in this trial.
7 DR. ROSE: Well, something is still
8 changing because there are devices in place.
9 DR. NISSEN: Yes, but I mean all the other
10 data you have given us, have given us as of a
11 specific time.
12 MR. POIRIER: We have not calculated that.
13 DR. NISSEN: If it would be possible to
14 determine that, it seems to me it would be useful
15 to know, because if we are going to label the
16 device, I mean if you are going to use a device,
17 say, for an indication for a two-year period of
18 time, it would be nice to know what the actual mean
19 time to device failure is in actual clinical use as
20 opposed to the data we heard from bench lab
21 testing.
22 I mean you have that data now for a
23 significant number of patients.
24 MR. POIRIER: We are going to try to do
25 that calculation at break.

1 DR. LASKEY: Your timing is propitious.
2 I would suggest we break. I have 2:30.
3 May we reconvene at 2:45. Thank you.
4 [Break.]
5 DR. LASKEY: Congratulations to all for
6 keeping us on schedule.
7 We would like to continue on with Dr.
8 Pina.
9 DR. PINA: I add my congratulations since
10 I know how very difficult this is to do, and I
11 think that for once we have data on probably the
12 sickest group of heart failure patients that have
13 ever been looked at or studied. I am amazed, as
14 many of you are, at the incredible mortality rate
15 of this population.
16 A lot of my questions have already sort of
17 been answered, but I want to come back to the
18 Quality of Life for a few minutes. Another recent
19 trial of a lot less sick group of heart failure
20 patients has equated their lack of worsening of
21 Quality of Life, and there is a difference
22 obviously between improvement in Quality of Life
23 and lack of worsening to being out of the hospital.
24 So, my question is, in the patients whose
25 Quality of Life was able to be assessed at multiple

1 times, were those most likely to be the patients
2 who were out of the hospital when those Quality of
3 Life assessments were done?
4 DR. ROSE: The completeness of the
5 patients surveyed Quality of Life data actually was
6 much greater in the VAD patients compared to the
7 OMM, and they also were the ones that spent more
8 time in the hospital, so I don't think it is the
9 issue of whether or not you are hospitalized that
10 determines whether or not we had completeness of
11 data.
12 We do have some data as to the reasons
13 that we didn't have responses to the Quality of
14 Life data. Those we have in a back-up slide, and
15 we can show. Before, as they bring up the slide,
16 most of that data that is missing is in the OMM
17 group, and a typical reason was that they were too
18 sick to want to respond to the questionnaire or to
19 come in for a visit.
20 DR. PINA: You also wonder how much the
21 depression of not having been chosen to get the
22 device counted in it, because I also noticed that
23 there were 12 patients who withdrew care in the
24 medical treatment group or asked for withdrawal of
25 care, and at least five of those were within 30

1 days of randomization, so you wonder how much the
2 Beck would pick up the depression of not being
3 chosen since I think there is the perception from
4 patients that you are doing something to them
5 rather than just sticking in an IV and sending them
6 home.
7 DR. ROSE: I don't know if we have Beck
8 data at 30 days, do we? I think the earliest that
9 we had the follow-up was at three months, but your
10 point is very well taken. I think there was in
11 some patients a sense of letdown, but I would say
12 also in some, there was probably a sense of relief.
13 DR. PINA: It depends upon how you look at
14 it.
15 DR. ROSE: That's right, and patients have
16 a range of subjective views, you know, going
17 forward. Some are going to want to do this, and
18 some are not, and the way it is perceived is either
19 as a victory or a loss.
20 There is some element we found of
21 cognitive dissonance in patients, you know, who
22 would I got randomized to the better limb. That
23 was their own perception. That was keeping them
24 going with the sense that the process worked for
25 me, and I got the better limb, and that could be

1 either.

2 DR. PINA: Just in concept.

3 DR. ROSE: Yes.

4 DR. PINA: My other question relates to

5 the implant element replacement of which there was

6 really one patient alive, so it seems that that

7 complication of the device failure seems to be the

8 greatest.

9 How many of those were in the SNAP version

10 versus the previous version?

11 [Slide.]

12 DR. ROSE: Apparently, there is 30-day

13 data on Beck depression.

14 DR. STEVENSON: [Off mike.]

15 DR. EWING: I am sorry. Could you repeat

16 that into the mike, so we can get it into the

17 transcription.

18 DR. STEVENSON: Looking at the one-month

19 score, in fact, the OMM arm was less depressed at

20 one month than baseline, which suggests that the

21 randomization outcome did not significantly

22 increase their depression.

23 DR. ROSE: Going from 16 to 13 on the Beck

24 compared to 16 to 10.

25 DR. PINA: It's a small change on the

1 Beck, but nonetheless.

2 Do you have that data about the SNAP, how

3 many of the device failures, the implant element

4 failures were?

5 DR. ROSE: I don't believe we have that

6 data immediately at hand, if it's obtainable. I

7 think your point, though, about reoperation

8 regardless of whether it was the VE SNAP or the

9 other device is a highly risky procedure at this

10 point, but again, the world experience now is 8 in

11 REMATCH plus a small N, as well, in the bridge to

12 transplant experience, it's a major reoperation.

13 DR. LONG: And that is an area that is

14 subject to evolution in the management of that.

15 While there were 7 out of 8 in the REMATCH trial

16 that died with device replacement, there has been

17 experience outside that now that suggests by doing

18 it entirely extra-thoracic approach to device

19 replacement, not doing a median sternotomy, you can

20 see much better results. In fact, in one series, 6

21 out of 6 patients survived to do well with

22 hospitalizations half of the length of their

23 initial implant experience.

24 DR. PINA: I think two items that I know

25 that we don't have the data for the submission, but

1 the issue of malnutrition in this population, being
2 unable to handle another invasive procedure added
3 to whatever the immune response is.
4 I wonder if you looked at the women
5 separate from the men, did the women have more
6 septic complications? You have a very small number
7 of women. My sense is that the women's immune
8 response is very different particularly if they
9 have had children.
10 DR. ROSE: We are in the midst of a
11 multivariate analysis of all of the potential
12 demographic factors, procedural factors, process
13 issues for death and adverse events. My suspicion
14 is that few of them will shake out as significant
15 determinants just simply because the N is too small
16 to make that judgment.
17 DR. PINA: That would be an interesting
18 point to look at.
19 DR. ROSE: We are in the midst of the
20 analysis. We do not have that data here.
21 DR. OSSORIO: First of all, I would also
22 like to add my congratulations to those who
23 sponsored and conducted this trial. It is really
24 clear that you are certainly adding to the
25 knowledge base that we have in this very important

1 and under-studied area.

2 My first question has to do with DNR

3 orders, particularly in the Medical Management

4 population. It seems to me in looking through the

5 case reports that a number of those people had

6 DNRs, and that could certainly influence the time

7 to death in the sense that those people, on their

8 first event in which they had a DNR, and since most

9 of them died of heart failure, this is going to

10 influence the results.

11 So, I am wondering how many of those

12 people had DNRs and in how many of the instances

13 that was really relevant and how many of the people

14 with the device had DNRs.

15 DR. STEVENSON: In terms of the medical

16 arm, there were five patients during the index

17 hospitalization who had DNR at some time during

18 that hospitalization. I don't remember exactly, I

19 believe two or three of them died, the other two

20 went on to hospice, but this, in fact, is I think

21 indicative of the overall feeling of patients with

22 heart failure, which is that frequently, at some

23 point, during a hospitalization, they decide there

24 are certain things they don't want done again,

25 whether that is intubation or defibrillation.

1 In many instances, however, DNR doesn't
2 necessarily mean do not treat, it just means they
3 don't want to be resuscitated, and the efficacy of
4 resuscitation in this group when something happens
5 in hospital, is in general the outcome is pretty
6 poor.
7 DR. OSSORIO: I think that is right, but I
8 think that could just add to a particular bias,
9 which is that for those patients who are on medical
10 management, they are not perhaps so interesting to
11 medical staff, and there already is I think good
12 evidence to suggest that resuscitation is not very
13 effective in these patients, and physicians often
14 just don't want to do it, right? So, the effort
15 might be pretty slender on those who are just on
16 medical management, whereas, those who have the
17 device are much more interesting to the physicians
18 around them, and the sort of effort put in to
19 keeping them alive may be much greater, and also
20 because the patients on the medical management arm
21 were dying particularly of heart failure, where the
22 DNR really is relevant as opposed to the ones who
23 are dying of other things, like sepsis, where that
24 is a little different issue because it is not a do
25 not resuscitate, so that is why I was thinking that

1 could have actually contributed to--I guess I am
2 wondering with respect to efficacy, whether the
3 difference in time to death really can be
4 attributed to the device as opposed to these other
5 things that might be related to have the device in
6 you or not.
7 DR. STEVENSON: First of all, it is only 5
8 of the 61 who requested DNR, so it is a small
9 number during that hospitalization. With regard to
10 the intensity of their therapy, certainly when a
11 patient finally comes to a DNR decision, we begin
12 focusing more on comfort issues than a prolongation
13 of life.
14 In fact, however, that is what we are
15 treating all the way along are comfort issues.
16 With regard to the intensity of therapy in this
17 population, I think all of the cardiologists
18 involved felt extremely committed to provide the
19 patients who got randomized to medical therapy with
20 the optimal medical management that, in fact, we
21 had promised them in that arm.
22 All I can say is that one has to at some
23 level have some faith in the integrity of the
24 investigators.
25 DR. OSSORIO: Oh, I am not actually

1 questioning anybody's integrity. I think it is
2 just a cognitive bias that ends up coming into
3 play.
4 I would also like to sort of second, I
5 guess, Dr. Domanski's interest in knowing the time
6 to stroke, as well as the time to death, and in
7 part because I do think that to assess efficacy, we
8 have to decide, okay, whether the device, if used
9 as intended, really produces clinically significant
10 results.
11 That must mean something more than just
12 keeping a warm body around, and so from my point of
13 view, the Quality of Life measures really have a
14 lot to do with understanding whether or not we have
15 achieved something clinically significant and the
16 sense of whether those adverse events were
17 really--how many of them were so adverse that they
18 could really have quite a negative impact on
19 somebody's Quality of Life.
20 I won't belabor the issue of the weakness
21 of the Quality of Life data that we have, and I
22 commend you for doing what you did because I know
23 it is very hard to do, and there aren't baselines
24 aren't out there, and so forth. I guess for me, I
25 have a hard time really assessing whether we have

1 achieved something clinically significant without
2 those data.
3 That was just a comment.
4 Also, this is perhaps also a sort of
5 seconding of something that has already been said,
6 is that it seems to me that the indications, if
7 this were approved, there would have to be
8 something much more clearly stated about the
9 indications for which it would be used and in which
10 patients it would be indicated, because it seems
11 that the reasonableness of the risks in a situation
12 like this, where you have got patients who are very
13 sick, the reasonableness of the risk depends on the
14 situation the patient is facing.
15 Nobody is going to say that having this
16 implanted in you is not very risky because it is.
17 It is just that it may be worth it if your other
18 alternative is even a more likely death. But if it
19 were approved with very sort of slender guidance as
20 to which patients were appropriate for this, it may
21 be used in a much wider variety of patients than it
22 was in this trial, people who are much less ill and
23 perhaps have other alternatives, or in people for
24 whom the reasonableness of the risks might not be
25 as compelling as it might be in a case where

1 somebody has no other alternatives.

2 Certainly, I would want to see more about

3 that.

4 Also, in terms of sort of labeling and

5 guidance, both the physicians and patients, I think

6 particularly for patients, the manual was very

7 technical for one thing, and it wasn't clear to me

8 whether you did anything to assess patients'

9 understanding or whether they even read this

10 manual, whether you did anything to assess their

11 understanding of that, whether you did anything to

12 assess their understanding of the training that

13 they received, and, in particular, with respect I

14 think to infection control, that might be very

15 important.

16 Did you do anything to assess that?

17 DR. ROSE: I think one of the lessons that

18 we learned in PREMATCH is that these patients are

19 so sick, that the original Quality of Life battery

20 that we had for them, they couldn't endure even

21 those levels of measurement.

22 So, to say that we were in a position to

23 test their cognitive function and say how much of

24 the manual did you read and how did you score on a

25 test, I hope the investigators would have done

1 better on such a test than the patients would have,
2 but it is not something that we added as a test to
3 this.
4 I don't think there is any question that
5 the labeling on this and beyond the labeling, the
6 interaction between clinicians and patients, it is
7 going to have to happen, and it does happen over
8 this kind of therapy, is intense, very individual,
9 and has to happen before a decision like this is
10 made. If it is not, I don't think that a standard
11 of care in general for a terminal patient is being
12 met if those types of options are not being
13 discussed.
14 Whether or not that is an issue that can
15 be addressed in labeling, I personally doubt it. I
16 don't think that is going to have the impact. I
17 think the major issue is really whether or not the
18 panel has faith enough in the community of
19 physicians doing this that this type of discussion
20 will indeed happen.
21 I am certain that this happens in heart
22 failure programs and in transplant programs, which
23 is the kind of group that we had doing this kind of
24 study, I think it is reasonable to say, will that
25 continue if it becomes more generalized to other

1 types of institutions, for bridging, for example,
2 centers had to be trained in the use of the device.
3 I think it is perfectly reasonable to say that part
4 of the training ought to be a patient education
5 piece around what patients, you know, ought to be
6 told in this context.
7 I think those are issues for going
8 forward. We don't have data on the issue of how
9 much they grasp. Unfortunately, I think they are
10 not in a position to grasp as much, and there are
11 profound ethical issues that that raises in people
12 that are so helpless that often they are going by
13 instinct rather than by analysis.
14 DR. STEVENSON: I would just like to
15 address briefly your previous point, which I think
16 is the most pertinent one in front of us, which is
17 who are the best patients to benefit from this
18 therapy, and there is no easy answer to this.
19 For this trial, in addition to the
20 criteria we had here, which were really very
21 general, there were gatekeepers, there were three
22 of us, one of whom reviewed every single case and
23 often made recommendations for further therapy
24 before randomization, particularly early in the
25 trial.

1 Our best precedent may be looking at what
2 happened with cardiac transplantation. Over the
3 experience, we gradually assembled a set of
4 contraindications and indications for cardiac
5 transplantation. Regardless of how rigorous these
6 were, however, they really could not employed
7 except in the context of people with extensive
8 experience.
9 I don't think one can come up with a
10 labeling set of indications that could be delivered
11 divorced from the concept of expertise in the
12 clinical hands of the physicians advising the
13 patient. So, this is clearly a major issue, there
14 are no easy answers, but we certainly can rely on
15 some of the lessons that we learned from
16 transplantation.
17 DR. OSSORIO: I also had just one other
18 question, which has to do with recruitment of
19 people into this study. I noticed that 90 percent
20 of the patients in the study were white. It seems
21 to me that if this goes out onto the market, well,
22 at the very least we know that there is a higher
23 rate of diabetes and serious complications from
24 diabetes in people of color, and there may be other
25 reasons why people of color are less likely to get

1 transplants in general, at least with kidneys.

2 So, it may be that there would be a

3 disproportionate number of people of color who

4 might actually be at least potential patients for

5 this kind of a device supposing they could get it

6 paid for.

7 Do you think that there is a problem? Do

8 you think that if is widely used among people of

9 color that there would be any differences?

10 DR. STEVENSON: I think at this point,

11 based on at least in the medical management, you

12 know, 61 patients, and 68 in the VAD arm, we

13 clearly have tremendous amounts to learn about all

14 the different subgroups.

15 Minority enrollment in this trial, in

16 fact, is very comparable to what happens in most

17 NIH trials in which minorities are

18 under-represented, a specific focus of the NHLBI at

19 this point, but we all recognize that there is a

20 lot of information that will come in the future as

21 well get more experience with this.

22 DR. OSSORIO: I am finished.

23 DR. DeWEESE: Thank you for the excellent

24 presentation. One quick question. Of the patients

25 who did not receive the implant, how many of them

1 had DNRs before they had their procedure?

2 DR. STEVENSON: That was five during the

3 initial hospitalization.

4 DR. DeWEESE: No, the five were for those

5 who did not get the implant.

6 DR. ROSE: I think I misunderstood the

7 question. The people who did have the device?

8 DR. DeWEESE: Yes. Did any of them have

9 DNRs prior to the procedure?

10 DR. ROSE: Prior to procedure, I don't

11 believe any of them had--the procedure itself in

12 many respects, you could consider a resuscitation.

13 DR. DeWEESE: That is what I wondered.

14 DR. ROSE: But late in the course of the

15 trial, there were patients on device with

16 complications that made that conclusion. We

17 certainly were committed to them enough to want to

18 resuscitate them, though, perioperatively.

19 DR. DeWEESE: Infection is a real problem

20 obviously, 17 out of 65, about 25 percent. How

21 about in the studies to bridge, how many of those

22 developed infections?

23 DR. ROSE: Those rates are comparable in

24 the bridging experience with this type of

25 implantable VAD.

1 DR. DeWEESE: That would argue against
2 what you said, that the cause of death might be due
3 to malnutrition.
4 DR. ROSE: Well, the rescue from infection
5 in the bridge patients, though, is transplantation,
6 where if you can suppress the infection and get a
7 donor heart, you can take the infected device out
8 and put a biologic replacement in instead, which is
9 a definitive solution in general to the problem of
10 infection. That is not an option for patients
11 here.
12 DR. DeWEESE: Device failure was listed as
13 a cause of death was only two patients, I think, or
14 none in one of your slide, two patients in Table
15 14, a summary of the cause of death. There were
16 only two who were attributed to device failure?
17 DR. ROSE: Two devices which could not
18 generate a cardiac output. That was the strict
19 definition of device failure. Can you bring up
20 that slide, my causes of death slide?
21 [Slide.]
22 Three deaths in patients perioperatively
23 at the time of device replacement for a component
24 failure of the device. For example, if these there
25 are a bearing failure and the patient were being

1 pumped pneumatically, which this device allows, as
2 opposed to using the electric pump, you can see
3 those.
4 There were three patients who died at the
5 time of operation or a VAD replacement, where using
6 a strict definition of the pump is not pumping was
7 not the case because the device in which a
8 component had failed was still working well enough
9 to sustain the patient to get to the point of being
10 able to replace it in the operating room.
11 But these are devices in which we knew it
12 did not pump and that the pump was explanted and it
13 was found to have failed. That was the strictest
14 definition of VAD failure.
15 We showed you before there were device
16 malfunctions.
17 DR. DeWEESE: I know there were a high
18 percentage of that.
19 DR. ROSE: One definition, you could say
20 that inflow valve insufficiency is device
21 malfunction, that generally allowed time enough to
22 replace it. By some constructs, you might say that
23 is a device failure because you need to replace the
24 device, but these are the malfunctions, 70 were
25 confirmed, as we said, 50 external components, 20

1 internal, the controller most commonly followed by
2 the inflow valve.
3 Actually, the mechanism of failure in the
4 in-vitro studies was something that we saw rarely
5 in the trial.
6 DR. DeWEESE: But the cause of death was 6
7 device failures, is that correct?
8 DR. ROSE: The nomenclature that the M&M
9 committee has used is root cause of death, and,
10 yes, it is more than you two patients, I think you
11 could say it is probably in the range of 6 or 7,
12 the root cause of death was pump failure and the
13 need to replace it.
14 DR. DeWEESE: How about the patient who
15 refused another procedure where it had failed?
16 Where was his death put?
17 DR. ROSE: How did we adjudicate that?
18 This is a patient who is a candidate for device
19 replacement because of an inflow valve, for
20 example, failure, and then elects not to have the
21 reoperation. How was that death classified? The
22 cause of death would be, what? That is what Dr.
23 DeWeese is asking.
24 DR. DeWEESE: That's all right. There
25 could be an additional. We are getting more. How

1 about the patient who went ahead and had the
2 implant and died postoperatively within three or
3 four days?
4 DR. ROSE: Those are these three here. We
5 are looking to see what that death was classified
6 as ultimately. Actually, those may be the LVAD
7 dysfunctions. One of these is a pump that is
8 turned off. There are two deaths from heart
9 failure in the VAD group, and that is where those
10 are.
11 DR. DeWEESE: I just wanted to clarify. I
12 had the impression that there were none, there are
13 6 or 7.
14 DR. ROSE: Yes, in that range.
15 DR. DeWEESE: The other is a question
16 about the air venting. Did that cause any
17 infection problems? I know it is not touching the
18 blood, but did the passageway for the air venting
19 get infected or not?
20 DR. ROSE: Well, to know whether or not
21 the channel for infection was either through the
22 air vent or around the periphery of the drive line,
23 I don't know that we could discern. One of the air
24 embolism events, though, was in a lining rupture
25 that resulted in air embolization with

1 communication with the outside world.

2 The hypothetical you raised, that specific

3 patient was classified as LAD dysfunction.

4 DR. DeWEESE: Thank you.

5 DR. KLOCKE: Eric, like everyone else, I

6 recognize this is a landmark study, and I do want

7 to express my admiration for the people who

8 conducted the study and the way in which it was

9 conducted.

10 In the discussion, I still find myself

11 most focused on the infection issue. I sense and

12 realize that you are also. Frankly, you have

13 demonstrated a temporary survival benefit that

14 clearly, by 30 months or something, has essentially

15 closed.

16 My concern is, I am trying to assess and

17 would appreciate your comment on whether the

18 continuing infection is perhaps the dominant role

19 in that. That is, you have made so many advances

20 with the pump and everything else, but it seems to

21 me that that is perhaps the biggest unsolved issue,

22 and that at least gives me the most pause in trying

23 to decide how far are we ready to go forward.

24 I think the slide you had up there, in the

25 first 40 deaths, there were 17. That is 40

1 percent, and actually, as I read through the
2 individual patient summaries, and obviously, the
3 care is remarkable, but I have the impression and
4 realize how adjudication of deaths goes on, but it
5 seems to me that infection, continued serious
6 infection played a prominent role in many of the
7 cases where it was not a primary cause of death,
8 for instance, if a VAD had to be removed because of
9 infection and the died of perioperative bleeding, I
10 have no quarrel with the classification.
11 So, I am troubled by that, and I presume
12 from the course that the infection business wasn't
13 just in the first 30 days. In terms of the
14 Kaplan-Meier curves, that had to be a continuing
15 problem over time, and I don't know if you have any
16 data. Those are the first 40 deaths. I realize
17 you have more. I am not sure if things have been
18 adjudicated, but there are now 65 deaths, if I
19 understand correctly, in the LVAD group.
20 DR. ROSE: No, there are still 18 ongoing.
21 DR. KLOCKE: Good. So, there are 50
22 deaths.
23 DR. ROSE: Right.
24 DR. KLOCKE: So, in the first 40, it was
25 40 percent, and I guess the infection rate is

1 continuing on.

2 DR. ROSE: Right.

3 DR. KLOCKE: Jim asked you about the

4 bridge to transplant. I guess I would have liked

5 to hope that with the benefit in LV function, which

6 I am sure the LVAD patients got, that apparently,

7 that benefit in overall, even those these were

8 terribly sick patients, but that benefit apparently

9 is not sufficient to reduce the infection problems.

10 So, that is the one that I am sort of left

11 struggling with the most, and I sense that you are.

12 DR. ROSE: I think we are struggling, but

13 I don't think we are in the dark at this point as

14 to what it is that we need to deal with.

15 DR. KLOCKE: Okay.

16 DR. ROSE: As I said, malnutrition was not

17 something that was even on the investigator's radar

18 screen when we began this, because our assumption

19 was that if you fix the cardiac output, the

20 nutritional depletion of these patients would

21 reverse itself.

22 I think it is clear to us at this point

23 that that is not the case, that simply restoring an

24 adequate cardiac output in a nutritionally depleted

25 patient may not be enough, and there was no

1 particular attention paid to preoperative
2 nutrition, as well.
3 DR. KLOCKE: I hear you, and I guess in
4 the bridge to transplant patients, the same
5 nutrition issue occurs?
6 DR. ROSE: Except for the sense that the
7 entry criteria here was initially that you had to
8 be sick with heart failure for three months, which
9 actually I hope in the labeling will not be there
10 because that allows an awful long interval for
11 people to really waste away.
12 DR. KLOCKE: I hear you. I guess the
13 question I am sort of left with is how strong is
14 the information we have at the moment to think that
15 the current infection rate, which I see at this
16 stage as the dominant limiting factor, and we have
17 ideas how to address it, but we have limited
18 experience in addressing it successfully.
19 DR. ROSE: I want to sing Jim Long's
20 praises. There are two centers in the trial that
21 have taken that on as a very specific area of
22 interest, and they have offered a lot of guidance
23 to us, and now with a small, but very encouraging
24 experience with us, I think will become a model for
25 the rest of those of us involved in the field.

1 As well, I think the drive line in the VE
2 was too rigid, and is a source of contamination
3 because the inflexibility of the drive line would
4 crack the junction between the device and the skin,
5 which a softer drive line, which the newer
6 iterations have, we believe will also help deal
7 with this.
8 DR. KLOCKE: I am confident that you will
9 and we will go out and we will solve it. I guess
10 the problem that we have is at this point in time,
11 where do we stand in terms of having satisfactory
12 evidence to approve the request that has been made
13 to us. That is really what I am struggling with.
14 DR. ROSE: The issue there is that even in
15 spite of all the infections and all the other
16 adverse events, there is still a highly significant
17 statistically valid survival benefit to the device,
18 so in spite of all these troubles, these people are
19 still living longer, and for those of us who do
20 believe the Quality of Life, they are feeling
21 better, as well.
22 That, I think is the overwhelming
23 evidence, and I think the very reasonable
24 expectation that these results are the floor of
25 what we are going to be able to achieve going

1 forward.

2 DR. LONG: Some evidence of that is a

3 shift in infection rates between the precursor to

4 this trial, which is called the PREMATCH trial, and

5 the REMATCH trial, and there was a very significant

6 reduction in infection between those two with

7 efforts to try to improve management.

8 Now, that is limited in its data, but is

9 one more inference that management plays a

10 significant role in helping control this. In

11 essence, in considering the etiologies of this, it

12 is device related, patient related, or management

13 related, and our sense is that it would be unfair

14 for us to place the burden of this entirely on the

15 device.

16 There is a very substantial portion of

17 this that is related, in fact, to management and to

18 the patient especially in that early upfront period

19 while we have so many comorbid factors ongoing. A

20 very important topic, though.

21 DR. LASKEY: Mr. Dacey.

22 MR. DACEY: I want to salute everybody

23 involved with this because I don't think, at least

24 when you get out in the general population, that

25 people will fully capture in their daily lives how

1 much the landscape is changing and how much work
2 that you are doing is contributing to that change.
3 When I first read over this material, the
4 first thing that occurred to me was is this a heart
5 prosthesis, because if it is, this also is a change
6 in landscape and understanding.
7 If my prosthetic leg malfunctions, I can
8 still hop around, I can use crutches. If a heart
9 prosthesis malfunctions, then, it is a much more
10 serious problem. I know you understand that, but
11 speaking as a consumer, as a representative of the
12 consumer, trying to capture these ideas in ways
13 that are very understandable to them is part of my
14 mission.
15 Also, I see this remarkable change, both
16 quantitatively and the velocity of change in the
17 body of knowledge especially around something like
18 CHF. There is a few of us in this room who
19 remember this, which was the ACPR guideline for
20 heart failure, which is only eight years old. This
21 is just eight years. That is not a long time
22 really, yet, in some people's eyes, it is an
23 eternity.
24 But at the end of the algorithm for end
25 stage, refer for evaluation for heart transplant,

1 and now you have got to add a couple more steps.
2 There is no reference there to bridge to
3 transplant.
4 Then, also, on the patient handbook, and I
5 know this is a work in progress, there was a time
6 in patient education and information where the pass
7 of distribution of information, words on paper, was
8 enough to satisfy legal requirements, informed
9 consent requirements, and I have heard very
10 reassuring words today from the professional
11 perspective there is a great deal of intensity at
12 trying to work with patients, because these are
13 very, very sick patients. I have known some of
14 them.
15 But as we know, if you are going to get
16 people to the point where they understand, and it
17 is not just the patient, it's the family, it's the
18 caregivers, it's the people around them who have to
19 take care of them, they have to have skill
20 training.
21 When this was published, 24 pages of fifth
22 grade text, now we are seeing 50- and 100-page
23 technical documents that are being given out to
24 satisfy this requirement. There is no substitute
25 for that one on one, and I know you know that.

1 I hope if this should be approved and
2 moves out across the country, that all the
3 colleagues involved understand it, as well.
4 Finally, as I end my four years on this
5 panel, there is just one editorial comment I would
6 like to make. Having been an advocate for the
7 subject of Quality of Life for such a long time,
8 going back a very long time, and maybe my age is
9 showing, but I sure wish we could find another
10 term.
11 I know you have to test and measure it,
12 but it has become a marketing term also, and I sure
13 would hope to see it convert to a marketing term
14 within the context of this subject. I understand
15 all the methodology involved, SF-36, and the well
16 life expectancy model and the general health policy
17 model, and I have worked with them, and it's a
18 daunting task, and it's horribly subjective.
19 You are at the cutting edge of some new
20 work here also, and for this I salute you. So, in
21 summary, my perspective says you have got a heart
22 prosthesis, and it is part of a process that is
23 going somewhere, and I don't know fully yet where
24 that "where" is, but I salute your effort.
25 DR. ROSE: Thank you very much, appreciate

1 it.

2 DR. LASKEY: Mr. Morton.

3 MR. MORTON: Thank you. Thank you, Bob.

4 Thank you, Dr. Laskey.

5 Just to follow up, Mr. Dacey, on your

6 comments about this being a heart prosthesis, I

7 would like to bring up something that was discussed

8 during the break, and something that is of interest

9 to me, and that is, we have heard several comments

10 that the device, as presented to us, does not have

11 an end of pump life indicator on it.

12 I would respectfully like to remind the

13 panel that many other heart prostheses and critical

14 devices also do not have an end of device life

15 indicator, and I would ask us not to view that lack

16 of such an indicator for this device as a negative,

17 but review it as tested, designed, and presented to

18 us today.

19 That ends my comments.

20 DR. KNAPKA: I am supposed to be

21 representing the patients, and as a heart patient

22 myself, I do have a defibrillator, a pacemaker like

23 Vice President Cheney, you know, both waiting for

24 them to go off.

25 I just have to make several comments. I

1 think from a patient's standpoint, strictly not so
2 much as a scientist, just as a patient, I would
3 probably be scared.
4 We talked a lot about first effects and
5 then Quality of Life, and to me this was kind of
6 contradictory because it was saying with this
7 implant or with this device, there is all these
8 adverse effects, and then we say, well, this is
9 improved Quality of Life, and to me, that is a
10 little contradictory.
11 I mean maybe when you first start, and as
12 you said, you are very sick, and you are glad to
13 have something, but you go through all these
14 adverse effects, and then maybe that last year,
15 maybe the Quality of Life is good, maybe there is a
16 balance there.
17 Now, that being said, I think it is good
18 that many, many of us patients would be very glad
19 to have another two years, praying that there is a
20 new development that is going to help us. So, from
21 that standpoint, I think again this becomes a very,
22 very individual decision.
23 I know I was very sick, and quite frankly,
24 I didn't care if I lived or not, so maybe in that
25 case, those people, they don't want to live, and

1 that is their choice, but I think it is good that
2 people have a choice to maybe have two more years,
3 and, gee, maybe NIH is going to come to something
4 that is really going to be top-notch, and I will
5 live the next hundred years, which may or may not,
6 probably not, because even some of the people that
7 Jesus saved died, too, you know.
8 [Laughter.]
9 DR. KNAPKA: I would like to just make one
10 other comment about the patient handbook, and I
11 would agree it is very technical, but I think if I
12 were a patient reading it the first time, every
13 other page there is warning, caution, that would
14 just make me more scared, and I think if you redo
15 it, and I think it is very honest, don't get me
16 wrong, I think it is very honest, but I think some
17 of these maybe could be tuned down, and I would
18 agree that probably there should be a training
19 session with the physician and the patient rather
20 than just hand it, you know, here is your handbook.
21 It is really highly technical, and I don't think
22 most people would know.
23 I got a lot out of it. The other one
24 thing that surprised me, and again I am going to
25 talk a little bit as a scientist, and not as a

1 patient, but this issue came up that there wasn't
2 much until now, much concern about the management,
3 the 20 different centers that were involved, they
4 all seemed to have different management this and
5 this, and to me, that is Statistics 101. You
6 identify all your variables and measure. I am a
7 little disappointed in that because to me,
8 management of any disease, any experiment is very
9 important, and I would think that would be, as I
10 say, that is Stat 101. You identify your variables
11 and start considering it.
12 Thank you very much.
13 DR. LASKEY: Thank you, sir.
14 I think before we get on with the
15 nitty-gritty, I think there has been additional
16 food for thought and some people have some
17 follow-up questions, so I would like to limit that
18 to perhaps five minutes per person, also, with the
19 hope that maybe some of the information that was
20 requested before the break is available.
21 Janet.
22 DR. WITTES: I actually have one other
23 thing that I think we haven't really addressed very
24 much, and that is the distribution of time to
25 critical failure. What we have is information

1 about estimated mean and estimated median time to
2 failure, but not a distribution of time.
3 I wonder if you have that both in vivo,
4 especially in vivo, but also in vitro, so not just
5 the point estimates of failure.
6 MR. POIRIER: We don't have all our data
7 here. We will be looking at it, and we can
8 certainly get that information back to you, but we
9 don't have the data that we can come up with any
10 mean time to failures in the clinical environment.
11 Also, I think FDA frowns upon look at
12 clinical data for reliability because it is
13 uncontrolled. Every patient is different. If you
14 look at reliability, you really want to look at a
15 controlled environment where you control the
16 parameters, and you can compare one device to
17 another. You cannot do that clinically.
18 So, that is why we have not made those
19 calculations because FDA frowns on that.
20 DR. LASKEY: Mike.
21 DR. DOMANSKI: No.
22 DR. LASKEY: Dr. Konstam.
23 DR. KONSTAM: I have just a few things
24 that I want to touch on that I don't think we have
25 gone into at any length. One is some help about

1 indications for use, what patients are we talking
2 about is one topic, and the other topic is, Eric,
3 you mentioned training, and I am going to want to
4 pick your brain about what ideas you had for that.
5 With regard to indications, I guess I have
6 got some deep concerns on both sides of utilizing
7 this device in patients who are not as sick as you
8 have in this study given the mortality that you see
9 with the device at two years, we had better be
10 reserving the use for patients who are really sick,
11 really have a very, very limited life expectancy.
12 I am worried about the other side, too,
13 but, first, let me ask you about that one. How
14 would you propose this indication be written, so
15 that we are sure that patients who get it have a
16 very limited life expectancy?
17 DR. STEVENSON: Well, as I said before,
18 this is probably the most pertinent question that I
19 think some of us are focused on at the moment. I
20 would suggest that we perhaps add language that
21 says "refractory to all current standard therapy,"
22 and in addition, including the proviso that
23 patients be ineligible for cardiac transplantation
24 implies, in fact, that they will be evaluated for
25 cardiac transplantation by people who are