

1 device.

2           At the same time, Marv Konstam's group,  
3 Dr. Wong was looking at a meta-analysis of the  
4 literature and came up with a performance goal or  
5 an average of survival to 30 days post-transplant  
6 of 74 percent.

7           [Slide.]

8           Well, then, I looked at the literature on  
9 BiVAD survival to transplant, and you can see on  
10 the left is our goal of 65 to 70 percent.

11           On the right, the CardioWest survival to  
12 transplant at 79 percent for the core group, and  
13 the higher bar, the success, which is defined as  
14 survival to 30 days post-transplant, NY Class I or  
15 II, ambulatory, which I have a question about the  
16 hemiplegic patient, of the definition of  
17 ambulatory, also not on a ventilator and not on  
18 dialysis.

19           You can see that even with the high bar of  
20 success, it was comparable to our performance goal.  
21 When you look at four papers I chose for the  
22 literature that looked at biventricular assist  
23 devices, you can see the results of survival in  
24 those four studies, and again, the CardioWest  
25 device is certainly comparable or better in those

1 studies.

2 It is important to note that the papers  
3 that I could find that both looked at LVAD devices  
4 and BiVAD, BiVADs were always less good results,  
5 and clinically, it is our opinion that BiVAD  
6 patients are certainly sicker. So, we can see that  
7 when you look in relation to the literature, the  
8 CardioWest device compares favorably.

9 [Slide.]

10 Well, what happens with left ventricular  
11 implantation with right ventricular failure? It is  
12 a diagnostic dilemma, first of all, to define who  
13 on the operating table at the time of implantation  
14 needs a biventricular device.

15 We know that when left ventricular devices  
16 are put in, the right ventricular failure rate is  
17 about 10 to 30 percent. In fact, an article in the  
18 Wong literature, 24 percent of the patients  
19 required RVADs.

20 A very interesting article just came out  
21 of Mehmet Oz's group, with their large experience,  
22 saying that they had a 7 percent right ventricular  
23 failure rate requiring biventricular assist.

24 What is usually done? Well, these days,  
25 medical therapy, inotropes, volume load, and, in

1 particular now, off-label use of nitric oxide is  
2 the treatment of choice for right ventricular  
3 failure with left ventricular assist device in  
4 place.

5           Then, there are short-term pumps that can  
6 be used, and then one approved percutaneous  
7 external biventricular device. So, that is the  
8 current treatment, and the diagnostic dilemma for  
9 the panel to consider is who needs a biventricular  
10 device at the time of bridge.

11           [Slide.]

12           Let's look now at the data for CardioWest,  
13 and the study was approved in 1993, and the agency  
14 agreed at that time that there was not clinical  
15 equipoise for a randomized study, and FDA approved  
16 the use of the control group that was subsequently  
17 utilized for these patients.

18           [Slide.]

19           As you can see, we are mainly considering  
20 the 81 core patients who met all the inclusion and  
21 exclusion criteria for the device.

22           [Slide.]

23           These are the data that you have seen.  
24 For the core patients, 79 percent survival, all  
25 device patients, which is 75 percent survival. The

1 out-of-U.S. patients, 59 percent survival.  
2 Success, again the bar is higher, 69 percent, again  
3 looking at our performance goal of 65 to 70 percent  
4 on the righthand side.

5           So, this device really appears to again  
6 look reasonably equivalent or better to the other  
7 devices.

8           [Slide.]

9           What about adverse events? Well, it is  
10 really difficult in the literature to develop a  
11 performance goal for adverse events, because mainly  
12 the definitions are completely different among the  
13 studies, and some of the studies don't even list  
14 definitions.

15           The rates differ for devices, and the  
16 rates for the same device changes over time, so we  
17 think that this clearly has to rely on clinical  
18 judgment.

19           [Slide.]

20           When you look at the adverse event rates  
21 that have been presented for the CardioWest device,  
22 they are really comparable especially to the  
23 meta-analysis by Wong in Konstam's group, where  
24 they found a bleeding incidence at 28 percent, and  
25 I have to second the idea that right ventricular

1 assist patients are certainly sicker.

2 Even if they have a normal PT and a PTT,  
3 they really can't recruit the coagulation agents,  
4 and they have a higher incidence of bleeding no  
5 matter what you are doing, be it liver transplant  
6 or any other operation.

7 So, Wong found a 28 percent incidence of  
8 bleeding with lots of definitions of that,  
9 infection of 22 percent, which compares favorably  
10 here, and a thromboembolism rate of 8 percent,  
11 which again compares favorably to this device.

12 [Slide.]

13 There are two areas of discussion that we  
14 would like the panel to look at in particular. One  
15 is the distribution of implants among study  
16 centers, and the second is the indications for a  
17 biventricular device versus a left ventricular  
18 device.

19 [Slide.]

20 Our first concern is whether these results  
21 are generalizable across studies, and when we see  
22 that 72 percent of the patients were implanted at  
23 one study set, that is somewhat of a concern. It  
24 is not optimal trial design.

25 We have five clinical centers in this

1 study, and the majority of devices were done at one  
2 center, essentially, a single center design, and we  
3 are also concerned about the appearance of conflict  
4 of interest, and the primary investigators at UMC  
5 have equity interest in the device.

6 [Slide.]

7 So, can we compare the results at this one  
8 center with the other centers? We asked the  
9 sponsor to attempt this comparison, and what we  
10 have is that when you look at success, it was  
11 identical success between UMC and the other four  
12 centers combined, essentially, the other two  
13 centers, so that we think, based on this, it is  
14 reassuring that the results are comparable.

15 [Slide.]

16 What about evidence of right heart failure  
17 as Dr. Yancy was asking about? These are the  
18 indications based on why a biventricular device was  
19 chosen. Again, is the incidence of biventricular  
20 use, especially at one center, equivalent to the  
21 use at other centers?

22 When you look at Mehmet Oz's paper that  
23 came out, 7 percent of the LVAD patients needed  
24 biventricular assist. So, what we would like to  
25 understand is what are the true indications.

1 I noticed Dr. Slepian's slide, that I  
2 hadn't seen before, listed approximately 10  
3 indications for use for this device, only a couple  
4 of which really have any patients in the study that  
5 met those diagnostic criteria, so we would like you  
6 to also be concerned about the indications for use  
7 of this device.

8 [Slide.]

9 This device is irreversible in that the  
10 ventricles are resected, so one patient group that  
11 you won't see is bridge to recovery, and we now see  
12 some literature appearing, although we have no  
13 ability to predict really ahead of time who is a  
14 bridge to recovery patient, but clearly, these  
15 patients will not be bridged to recovery.

16 It is clear in the literature that RV  
17 failure may become evident only after LVAD  
18 implantation. In the Oz paper, approximately half  
19 the patients had an RVAD placed later than 24 hours  
20 after the procedure.

21 So, when should this device be used and  
22 should this be addressed in a post-market study,  
23 and how can the label reflect this problem of  
24 deciding who needs a biventricular device.

25 [Slide.]

1           The clinical summary or conclusions of Dr.  
2 Pina and I is that for efficacy, this device has  
3 really shown that survival to transplant is similar  
4 or better than other devices reported in the  
5 literature, and for safety, even though we have a  
6 hard time comparing adverse events, it appears to  
7 be a reasonable safety profile for this device.

8           I also want to take this opportunity to  
9 thank the sponsor. It has been a pleasure to work  
10 with them. They have been very responsive to our  
11 requests for additional data.

12           Thank you.

13                           **Questions and Answers**

14           DR. TRACY: Now, if the panel members have  
15 any questions for the FDA? Dr. Maisel.

16           DR. MAISEL: It was mentioned that the  
17 initial study design called for about 32 patients  
18 to be implanted with the device, and obviously,  
19 many more ended up being implanted. From one of  
20 the graphs, it looked like that goal was reached in  
21 about 1997 or 1998.

22           Can you discuss what conversations were  
23 had with the sponsor at that time, whether any data  
24 was reviewed at that time, and what led to more  
25 devices being implanted than were initially

1 planned?

2 MR. CHEN: Well, according to  
3 conversations with the sponsor that I have looked  
4 at, through previous memos and stuff, I wasn't the  
5 primary reviewer during the IDE stage, so I had to  
6 go back to look at previous memos, but according to  
7 what was discussed with the FDA, the sponsor had  
8 requested on three occasions to have 25 more  
9 patients on three occasion, thus giving them 75  
10 more than the original 32 that were planned.

11 Their concern was that they wanted to be  
12 more assured about the safety of the device,  
13 therefore, FDA granted them additional more  
14 patients, thus came up with the 95 total patients  
15 that they have implanted, which actually increases  
16 our confidence in the safety of the device.

17 DR. MAISEL: So, I guess the question is  
18 were there initial safety concerns with the first  
19 patients that were implanted, and, if so, what were  
20 those concerns?

21 MR. CHEN: I would like to defer that  
22 question to Bram Zuckerman. He would probably know  
23 more about the history of the device than I would.

24 DR. ZUCKERMAN: To our knowledge, there  
25 weren't any red flags, the history as summarized by

1 Mr. Chen.

2 DR. SWAIN: Also, I guess I can comment in  
3 that we asked the sponsor to divide the data  
4 analysis up into three periods during this, and  
5 when you look at the etiology of the patients'  
6 failure and all that, it appeared that the results  
7 are comparable in all three periods during this 10  
8 years.

9 DR. BLUMENSTEIN: First of all, I really  
10 appreciate your presentation, Dr. Yue. That was  
11 right on the money. I should also point out for  
12 the benefit of others that if you look at the  
13 briefing document provided by the sponsor, that  
14 there were a lot of instances where p-values were  
15 used to compare the "control group" to the  
16 intervention group.

17 In fact, one of my comments is that we  
18 really shouldn't be calling this a control group at  
19 all, and we should actually be calling it a lack of  
20 control group, but I wouldn't really say that  
21 seriously. I think reference cohort would be a  
22 better term for this than control group.

23 The reason this is important is because,  
24 as this study is represented to the public or to  
25 future users, and so forth, to call it a control

1 group gives it a perfume of legitimacy that just  
2 doesn't exist.

3 I am going to be making a recommendation  
4 at the end of all of this that the term "control  
5 group" be struck from the literature on this thing.

6 There is an additional element of concern  
7 of non-comparability between what I call the  
8 reference cohort and the intervention group and it  
9 especially concerns the presentation of  
10 Kaplan-Meier curves, and that is, that I am  
11 concerned that the baseline date that is assigned  
12 to each of the reference cohort patients and the  
13 intervention patients may not be comparable.

14 Can anyone comment on that, please?

15 DR. YUE: With data, there is a concern.  
16 We raised this question to sponsor.

17 DR. TRACY: Are we expecting a response  
18 from the sponsor or are we just accepting that  
19 these are not direct control groups. I think the  
20 FDA did a nice job at providing an alternate  
21 comparison.

22 I think that is going to be an issue for  
23 discussion, but we have the group that was decided  
24 by the FDA and the sponsor at the onset of the  
25 study, which we all agree it is not directly

1 comparable to the treatment group, and we have the  
2 largely literature-based review that the FDA has  
3 provided to provide some comparison.

4 I think everybody in the room is in  
5 agreement that these are not directly comparable  
6 groups, and this is just we are wrestling with a  
7 single treatment arm here basically.

8 DR. BLUMENSTEIN: The question that I am  
9 asking, though, pertains to the presentation of  
10 Kaplan-Meier plots, which there is a great  
11 temptation to do that because you are talking about  
12 survival, but if you are putting a Kaplan-Meier  
13 plot up in this kind of a situation where you don't  
14 have randomization to assure that the baseline date  
15 has been assigned in a way that is comparable  
16 between the groups, the Kaplan-Meier plots can be  
17 quite misleading.

18 What I am interested in is how it was,  
19 well, the issue is whether these Kaplan-Meiers have  
20 any meaning at all even without p-values, and one  
21 of the issues there is how the baseline date is  
22 assigned to each of the patients that appear in a  
23 Kaplan-Meier.

24 DR. YUE: I completely agree with you, it  
25 is a very good comment.

1 DR. ZUCKERMAN: I think our summary FDA  
2 slides point that out, but with regards to the  
3 sponsor saying this particular problem, it can be  
4 done in the afternoon per our usual protocol.

5 DR. TRACY: Thank you.

6 Dr. Krucoff.

7 DR. KRUCOFF: Dr. Yue, your ability to  
8 make complex statistical situations clearer to  
9 people who are morons like me is really helpful, so  
10 thank you.

11 DR. YUE: Thank you.

12 DR. KRUCOFF: Julie, let me ask you first.  
13 Is your sense that there are no randomized studies  
14 in this area because it just takes too long, or are  
15 there other reasons for steering away from  
16 randomization?

17 DR. SWAIN: Well, I think that after one  
18 has one device approved, that randomized against an  
19 approved device might be a reasonable way to go,  
20 and when you look at the relatively limited number  
21 of patients in this field, estimated at perhaps 500  
22 per year, and then how many of those would be  
23 eligible for a study, that is a big question.

24 I think that scientifically, my personal  
25 opinion is that it could have been done in the

1 past, and I would hope that it would be done in the  
2 future as a scientist.

3 DR. KRUCOFF: Well, once one device is  
4 approved, maybe you can start thinking about  
5 equivalence, but certainly, unless there was a  
6 time-prohibitive rate-limiting step in enrolling  
7 these patients, and I guess we can't go back 10  
8 years and reinvent this, but why you don't do a  
9 superiority design relative to standard care, since  
10 these patients already exist escapes me a little  
11 bit, but even more so, it escapes me why you guys,  
12 you know, you have got a half a dozen medical  
13 centers and 10 years of medical records, why don't  
14 we have a better matched control set.

15 I mean why not go get the data rather than  
16 sit here and mosh around what is basically, as  
17 everybody has said, a one-arm data set, and why  
18 wouldn't that be more informative particularly over  
19 10 years as was indicated this morning, a lot of  
20 those patients now do have a device that would give  
21 us some indication about some real comparisons  
22 rather than working in a total vacuum which leaves  
23 all of us, I think, in a very hamstrung position  
24 including the sponsor, who I think is going to be  
25 subject to a great vicissitude of this body and you

1 guys, why not get the data, you know, if a  
2 historical group of real patients from the medical  
3 centers is accessible.

4 I am not exactly sure why we are wrestling  
5 with quite the vacuum we are.

6 DR. SWAIN: I sort of view this as almost  
7 a grandfather device. Mr. Chen probably wasn't  
8 born when the study started, and the rest of us,  
9 you know, we are looking at this device and we have  
10 what we have right now to decide on, and we certain  
11 would appreciate the panel's input on future trial  
12 designs.

13 Having been I guess the primary reviewer  
14 for a previously approved LVAD when I sat on the  
15 panel, and then as chair of the panel approving  
16 another, this has been a constant problem, and I am  
17 sure the FDA would appreciate guidance as to what  
18 future clinical designs could be for devices that  
19 will be being developed.

20 DR. KRUCOFF: I have another question for  
21 you, Doctor. The unique element here to me is that  
22 this is a total artificial heart styled as a bridge  
23 device, where obviously, other work with total  
24 artificial heart designs have been done, and on the  
25 safety side, is there not something that we could

1 learn from comparisons there rather than again,  
2 particularly for some of these endpoint  
3 definitions, on a time course that is definable.

4           Again, I guess that is somebody really  
5 looking at, not just the LVAD and the articles that  
6 you picked, but where is the other artificial heart  
7 data relative to at least the initial phase, say,  
8 first 60-day behavior of other artificial hearts,  
9 would that teach us anything.

10           The other key question I have for you guys  
11 is there is this ongoing sort of put in the middle  
12 of the pack assumption of equivalences kind of okay  
13 in the background of a lot of what is being  
14 discussed here, and yet the list I saw from the  
15 sponsors, which emphasizes the down side of leaving  
16 the heart in place, the arrhythmias, the embolic  
17 events, et cetera, would suggest to me that we  
18 shouldn't be thinking so much about equivalent if  
19 it is really that much of a difference, shouldn't  
20 we be seeing something superior, shouldn't we be  
21 seeing something that actually looks different.

22           Again, I would have particularly expected  
23 you guys to help us be clear on what is being asked  
24 and what is being answered in some of these  
25 questions.

1 DR. SWAIN: Well, superiority, I won't  
2 give my opinion as a scientist, but I will let Dr.  
3 Zuckerman talk about the regulatory requirements  
4 for a PMA, where the bar is.

5 DR. ZUCKERMAN: Your task is to give us  
6 advice as to whether this device has a reasonable  
7 assurance of safety and effectiveness. Reasonable  
8 assurance of safety and effectiveness does not  
9 necessarily apply that this device needs to be  
10 better than a comparable device on the market.

11 DR. KRUCOFF: Well, I guess when we think  
12 about safety and efficacy, I mean the other missing  
13 factor here to me is there is a percentage of  
14 patients, as you indicated, you and Eleana, Julie,  
15 that there are some patients who really are the  
16 sick, who actually ultimately, if they are  
17 supported, successfully recover.

18 It would seem to me that if part of this  
19 device is to cut the heart out, that in those  
20 individuals, that would be a detrimental effect,  
21 and yet I see no statistic anywhere that even  
22 begins to incorporate the loss of the heart and the  
23 removal of a recovery option in a patient  
24 population, about two-thirds of whom don't make it  
25 to transplant.

1           So, again, I really wonder where is our  
2 ability to grasp safety and efficacy with the data  
3 that is in this panel pack.

4           DR. SWAIN: Well, when you look at what  
5 literature was available on bridge to recovery  
6 during the course of the study, 1993 to 2003, you  
7 know, Bud Frazier and a few folks were coming up  
8 with a few of these reports in the mid-1990s, but  
9 very few reports.

10           I think that the whole bridge to recovery  
11 question is one that can't be answered by the  
12 literature currently, and it represents probably  
13 one of the greatest challenges we have as  
14 clinicians of figuring out who is going to have a  
15 heart that recovers, and obviously, if you knew  
16 that ahead of time, you might make a different  
17 decision whether to use this device or another.

18           So, right now there is really no  
19 literature that helps us whatsoever telling us who  
20 those patients are, and it's a small number.

21           DR. KRUCOFF: I agree with you clinically.  
22 I am talking about statistically. There is a  
23 range. This is not zero, and you guys are treating  
24 it like it's zero, and I think it's wrong.

25           DR. TRACY: Dr. Bridges, did you have a

1 question?

2 DR. BRIDGES: I had just a statistical  
3 question for Dr. Yue. The propensity scores you  
4 outlined essentially is the probability that a  
5 given patient would be in the total artificial  
6 heart group.

7 What statistical method is used to  
8 calculate that propensity score? You didn't really  
9 tell us how you get to that number.

10 DR. YUE: Multiple propensity regression.

11 DR. TRACY: Dr. Yancy.

12 DR. YANCY: One question that Dr. Swain  
13 touched on that I would like to go back and  
14 revisit. The agency determined that the data  
15 needed to be separated into three time periods, and  
16 those three time periods have differential numbers  
17 of success, 84 percent, 62 percent, 61 percent.

18 The first question is the rationale for  
19 the separation. I think there was an attempt to  
20 address that comment earlier, but I would like to  
21 hear that developed more.

22 The second would be particularly by your  
23 review, Dr. Swain, are we to expect that the 84,  
24 62, and 61 are different, or are they the same  
25 outcome, but just with some variation?

1 DR. SWAIN: Well, we didn't look at it  
2 really statistical comparison, because I asked that  
3 that data be divided, to see if we could see any  
4 big treatment period effect. You know, surgeons,  
5 we assume we are getting better at what we do.

6 The other thing is that the percentage of  
7 ischemics were different in those three eras, a lot  
8 more ischemics later, and ischemics are the group I  
9 think that does worse in general, comorbidities and  
10 things of that sort. So, we have a problem with  
11 that.

12 It is kind of like Mitch's question that  
13 he just had about recovery. You know, we don't  
14 count it as a zero incidence, but in order to know  
15 an incidence, you have to know a numerator and  
16 denominator, and there is tons of case reports that  
17 give us the numerators, but how in the world one  
18 can find a denominator, I can't find it in my  
19 review of the literature.

20 So, the short answer to your question is  
21 different patients, different treatment period, you  
22 can't say they are different results.

23 DR. YANCY: Well, the specific thing that  
24 I wanted to be certain on--and I think you have  
25 spoken to this, but I would like to have this

1 completely clear for my decision--I wanted to be  
2 confident that the difference in outcomes does not  
3 reflect the technology going from the primary  
4 center to the other two centers, because that would  
5 be a concern that the effectiveness was achieved in  
6 the center with the most expertise, but there was a  
7 lower threshold in centers that were attempting to  
8 duplicate the same technology.

9 I don't think that is the case based on  
10 the bar graph you showed, but I think that needs to  
11 be specifically addressed.

12 DR. SWAIN: The sponsor may be able to get  
13 that data for you after lunch. The dividing of  
14 treatment success per three-year period in each  
15 center, that is what you want? I do not know the  
16 answer to that.

17 DR. BLUMENSTEIN: In point of fact, one  
18 could do the same kind of analysis about  
19 comparability between the reference cohort and the  
20 intervention group, that is, between treatments, to  
21 find out if the patients going into the procedure  
22 were comparable between centers.

23 DR. YUE: That's right.

24 DR. TRACY: Dr. Weinberger.

25 DR. WEINBERGER: The FDA has focused its

1 analysis on the bridge to transplant time and on  
2 comparisons historically with other devices. Based  
3 on that analysis, it appears that this device might  
4 be comparable.

5           The patient, however, is interested in the  
6 clinical endpoint, and that is what the company  
7 studied, a 30-day survival post-transplant. If you  
8 look at the company's data, there is a 10 percent  
9 mortality in that first 30-day period in the  
10 patients who got the device.

11           I was wondering whether or not in the  
12 analysis of that initial 30-day mortality  
13 post-transplant has been done comparing this device  
14 to any other groups of patients, so we can get some  
15 feel whether or not the device itself predisposes  
16 to some problems immediately post-transplant.

17           DR. SWAIN: When you look at the  
18 literature, which I guarantee you we have reviewed  
19 virtually everything published in the area, there  
20 is a certain dropoff in survival to transplant  
21 between survival to 30 days or survival to hospital  
22 discharge, and everybody defines this differently.

23           It is also a difference in the literature  
24 when you define as when does survival to transplant  
25 start, is it induction of anesthesia for the

1 transplant procedure, what is it, and when you look  
2 at all the literature, you really can't make good  
3 comparisons.

4 All groups with all devices studied show a  
5 dropoff, a 10 percent dropoff is pretty much  
6 consistent, if you can measure it, of what the  
7 other studies are reporting. Again, it reflects my  
8 disappointment with us, as surgeons as a group, in  
9 studying this group of patients rigorously and  
10 comparably.

11 MR. CHEN: I would like to make one  
12 comment, that the panel recognize that FDA was not  
13 trying to use the literature search as a comparable  
14 comparison for the success rate of the device. In  
15 no way is FDA trying to say that 65 percent is  
16 comparable to what is in the literature.

17 It should be noted that FDA discovered  
18 that the control patients were not comparable to  
19 the device patients, so we tried to do some  
20 analysis, therefore, and then after the analysis,  
21 we found out that through propensity scores that  
22 once again there was no way to compare control  
23 patients to device patients.

24 So, the last thing we did was we went  
25 through a literature search and found previously

1 approved devices with actual success rates in the  
2 literature, and we used those data and not in a way  
3 compared it to the CardioWest device, but we wanted  
4 to show that the CardioWest device has the same  
5 trends as what is in the literature.

6           So, in no way are we trying to say that we  
7 are comparing the success rate of the device to  
8 what is in the literature.

9           DR. TRACY: I think the other issue, just  
10 to clarify, that nobody is comparing this with a  
11 bridge to recovery. This is not an issue with this  
12 device.

13           This device is standing alone here as a  
14 bridge to transplant in a group of patients with an  
15 extraordinarily difficult patient population to  
16 come up with any type of control either by  
17 literature or by comparison even with exhaustive  
18 review of a very small overall patient population.

19           I think these are critical things that the  
20 panel has to recognize. It took 10 years to accrue  
21 this very modest number of patients to this study.

22           DR. YUE: From a statistical point of  
23 view, I would strongly recommend randomized trials  
24 whenever possible.

25           DR. TRACY: Dr. Hirshfeld.

1 DR. HIRSHFELD: I think this question is  
2 mainly for Dr. Zuckerman, but you mentioned before  
3 that the burden is that we need to determine  
4 whether the device is safe and whether it's  
5 effective.

6 I guess as I am sitting here listening to  
7 this, I am having difficulty deciding what in my  
8 mind is the appropriate threshold for calling a  
9 device safe, and I wonder if you can enlighten us a  
10 little bit more as to what the definition of safe  
11 is.

12 DR. ZUCKERMAN: We can bring up the  
13 regulatory definition, but from a clinician's  
14 perspective, it is when in the indicated patient  
15 population, there is a reasonable risk-benefit  
16 profile such that one would want to utilize the  
17 device, i.e., it is safe.

18 Does that help you?

19 DR. HIRSHFELD: To a degree, however, you  
20 also instructed us that we shouldn't be comparing  
21 it to other existing devices in terms of making  
22 this judgment, but here, when we have a device that  
23 has a large number of device-related complications  
24 associated with its use in a patient population  
25 that is terribly critically ill and has a dismal

1 prognosis left to its own devices, I am finding  
2 difficulty deciding that we can determine safety  
3 without comparing it to other potential treatments  
4 that are out there.

5 DR. ZUCKERMAN: I think there is a need to  
6 clarify the situation as you have pointed it out.  
7 Certainly, in the best of all possible worlds, one  
8 would like to see a controlled clinical trial here  
9 where the internal controls could provide that  
10 comparison, such that your safety determinations  
11 could be made more easily.

12 The agency has indicated that there are  
13 problems with the internal controls in this trial,  
14 and you will have to grapple with that this  
15 afternoon. You may disagree. As a result, the  
16 agency has looked for other ways to compare this  
17 device to other appropriate literature.

18 There are some pluses and there are some  
19 minuses to doing that, but by the same token, it  
20 does provide an avenue for the advisory panel to  
21 discuss the safety issue. We don't bring the easy  
22 applications to the advisory panel, as you are  
23 pointing out, Dr. Hirshfeld.

24 DR. TRACY: Dr. Aziz.

25 DR. AZIZ: Bram, I guess I could ask you

1 this question and maybe you could ask the sponsor  
2 later on. This device or a similar device has been  
3 run for a number of years, since the early  
4 eighties.

5 In the early generation, there were a lot  
6 of issues in terms of I guess safety complications,  
7 but a number of changes have taken place that have  
8 now, if you compare the complications to the early  
9 time period, in the eighties, to what the data  
10 shows here, there has clearly been a marked  
11 improvement.

12 Could you address that, because the device  
13 could be compared to itself in sense?

14 DR. ZUCKERMAN: Right. I think perhaps,  
15 Dr. Aziz, what you are pointing out is that given  
16 perhaps some of the problems with the internal  
17 controls in this trial, you would like to utilize  
18 external data, your clinical expertise, to evaluate  
19 safety. That is exactly why this application is  
20 brought to an advisory panel.

21 The agency is here to listen to your  
22 expert clinical opinion, as well as others, and  
23 that is one valid way to help advise the agency by  
24 using that approach.

25 DR. SWAIN: I will comment on that also.

1 As surgeons, we would like to think we are getting  
2 a lot better and that our complications rate are a  
3 lot lower especially in this area, but when you  
4 look at the literature, there doesn't appear in  
5 many of these complications to be a time-dependent  
6 decrease in the number of complications.

7           It may be because there is unknown  
8 covariates and the patients are getting a whole lot  
9 sicker and that is who we are doing, but the  
10 literature doesn't support that we are a lot better  
11 today than we were five years ago at treating these  
12 patients with mechanical assist devices.

13           DR. AZIZ: I think this device, comparing  
14 it to the early generation, where there were a lot  
15 of thromboembolic events, I think when the sponsors  
16 come up later on, the change in the antithrombotic  
17 or antiembolic sort of regimen that they use now, I  
18 mean making a more tailored therapy rather than  
19 just blunderbuss therapy.

20           I think we will get an answer from the  
21 sponsor I think later on to satisfy some of those  
22 questions, because this device, in a sense, could  
23 be tested to itself from the early generation  
24 rather than comparing it to an LVAD or a BiVAD.

25           DR. TRACY: Any other questions for the

1 FDA?

2 MR. MORTON: Dr. Tracy, this is actually a  
3 point that I would like to make as the industry  
4 representative. I had an earlier conversation with  
5 the sponsor, and they expressed to me that they  
6 were prepared to give fuller financial disclosures,  
7 and I said no, I don't think that will be  
8 necessary, but since the question of conflict of  
9 interest has come up, I would like to give the  
10 sponsor the opportunity now or at your direction to  
11 respond to that.

12 DR. TRACY: Can we hold that and ask  
13 somebody to be prepared? I am not sure that, in my  
14 mind, it has raised an enormously relevant issue,  
15 but we can certainly have them address that after  
16 the lunch break.

17 Anything else before we break?

18 If not, let's try to regroup here at 1:05.

19 [Whereupon, at 12:05 p.m., the proceedings  
20 were recessed, to be resumed at 1:05 p.m.]



1 the early eighties, and in the early eighties, at  
2 least from what one heard, there was a lot of  
3 thromboembolic problems associated with it.

4 Looking at what you showed us today, and  
5 reviewing the literature, there has clearly been a  
6 marked improvement in the thromboembolic potential  
7 of the device.

8 Can you, before going on to the other  
9 questions, give us an overview as to what are the  
10 landmarks, what have you guys done that have made  
11 it look so good compared to what we were used to  
12 hearing about this device?

13 DR. COPELAND: Thank you for your  
14 question. I think you refer back to the early  
15 eighties when this device, and this is nearly the  
16 same device that was used by Bill DeVries for  
17 permanent implants, was associated with a lot of  
18 strokes. In fact, almost every patient had a  
19 stroke.

20 What we have learned I think over the last  
21 20 some-odd years about devices in general, not  
22 just this device, but all of the others, as well,  
23 is to treat coagulation as coagulation,  
24 procoagulants, and platelets, and to treat them  
25 separately and to look carefully at both of those

1 elements in deciding how much anticoagulation to  
2 give, to use thromboelastography along with this,  
3 to look at platelet function by platelet  
4 stimulation testing and also by bleeding times--or  
5 platelet aggregation studies, I am sorry--and  
6 bleeding times.

7 By doing all of those things, I think we  
8 have reduced the rate considerably.

9 The other thing, that if you read  
10 carefully the history of Dr. DeVries' experience,  
11 you will see that his patients began having strokes  
12 when they began having fevers. The devices or some  
13 parts of the patients got infected, the patients  
14 became hypercoagulable, and then they went on to  
15 develop endocarditis of the device.

16 I think that we have all in this field  
17 become much more alert and aggressive about  
18 preventing and treating infections, and I think the  
19 combination of those two things has resulted in an  
20 improvement in care for these patients and a  
21 reduction in the thromboembolic rates.

22 DR. AZIZ: So, there would be no change in  
23 the lining of the device, the valve sizes, have  
24 there been any changes made in that?

25 DR. COPELAND: There has been no change in

1 the physical device, no.

2 DR. AZIZ: So, basically, the patients'  
3 environment is really what you have changed by the  
4 antiembolic regimens that you have.

5 DR. COPELAND: Yes, there has been one  
6 other modification, and that is in the philosophy  
7 of running the device. Our tendency is to run the  
8 device at fairly high outputs, and that can be done  
9 by managing the patient's fluid and by managing the  
10 initial settings on the pump.

11 If we run the device at 7 or 8 liters a  
12 minute, this discourages clot formation on any  
13 surface. It washes the inside of the device and  
14 allows the patient to go without thromboembolism.

15 DR. AZIZ: Looking at the graft material  
16 that connects to the aorta and the pulmonary artery  
17 in the samples that you have passed around here, is  
18 that dacron?

19 DR. COPELAND: Yes.

20 DR. AZIZ: Obviously, people are using  
21 Hemashield, has that been a source of a lot of  
22 bleeding problems?

23 DR. COPELAND: It has not been a source of  
24 bleeding problems because those dacron cuffs are  
25 pre-clotted, but I will have to hasten to admit

1 that you are absolutely right, and one of the first  
2 changes we would love to make with that device once  
3 approved is to put outflow conduits that have no  
4 interstices, that have a pre-treatment with some  
5 sort of gel, as the modern conduits do.

6           You may know that there are BiVADs out  
7 there that are approved, that have the same dacron  
8 as this, that have to be pre-clotted before they  
9 are used, that are commercially approved now, but  
10 our hope would be to change this in our device very  
11 soon.

12           DR. AZIZ: When you use this device, I saw  
13 that there were two patients that had severe  
14 pulmonary edema, and all the ones that had sepsis,  
15 also had multiple organ failure, really had a lot  
16 of pulmonary edema.

17           Is there a chance or does it happen that  
18 you get hyperperfusion of the right side, are you  
19 actually pushing a lot of blood into the pulmonary  
20 tree, do you think that is an etiological factor in  
21 some of these few cases that you have had, or is  
22 that just a theoretical concern?

23           DR. COPELAND: Before I answer that  
24 question, I forget when I first approached the  
25 rostrum to mention something that I wanted to

1 mention, and that is the conflict of interest  
2 issue.

3           This device was initially owned by a  
4 private company and then was given to the  
5 University Medical Center. It was owned by  
6 University Medical Center in Tucson for  
7 approximately 10 years. The complete study was  
8 done under that ownership. None of the presenters  
9 or sponsors were financially attached to this  
10 device until the study was completed and gone on  
11 for one year.

12           Then, because the Medical Center, like  
13 many academic institutions, found that they could  
14 no longer support this, as they no longer supported  
15 many other things, dropped out from the support.  
16 We founded a company to keep the technology going  
17 and to seek FDA approval.

18           So, from the point of view of financial  
19 interest, there was no known bias from that point  
20 of view while the study was being conducted.

21           Now, on to your question. I apologize for  
22 inserting that, but I meant to, and it was brought  
23 up before, and I just wanted to cover that early  
24 on.

25           The concern about pulmonary edema from

1 high flow. As far as we are concerned, there is no  
2 such thing. We have never seen it, we have never  
3 experienced it. The only way you get pulmonary  
4 edema in these patients is they come to the  
5 operating room with pulmonary edema because they  
6 are very sick, and these are very sick patients who  
7 are dying.

8 I hope the panel will recognize that and  
9 realize that these people have no alternative. So,  
10 they either come with pulmonary edema or they  
11 develop pulmonary edema because of pulmonary venous  
12 compression from the device, such as we saw in two  
13 cases in this experience, and that can happen, but  
14 then adjustments can be made to prevent the  
15 compression in most cases.

16 DR. AZIZ: How do you measure the  
17 pulmonary artery pressures once this device is in  
18 place? Do you have any idea what the PA pressures  
19 are?

20 DR. COPELAND: We can measure it probably  
21 to plus or minus 5 millimeters of mercury. The way  
22 you do it, if you recall the slide that Mr. Smith  
23 showed, of the pressure curve with the caret [ph].  
24 You just simply turn down the pressure until you  
25 lose the caret. That means that the diaphragm is

1 then being pushed with the same amount of pressure  
2 that is pushing against the diaphragm, and it is an  
3 indirect measurement of pulmonary artery pressure.

4           You can also measure the systemic pressure  
5 the same way.

6           DR. AZIZ: I would assume that most of  
7 these patients that have received this device have  
8 had to have blood transfusions at some time or the  
9 other, I mean following implantation of the device.

10           DR. COPELAND: I believe that is a safe  
11 assumption.

12           DR. AZIZ: Looking at the cytotoxic  
13 antibodies screen, in one of the tables, it seemed  
14 that the control group had a higher incidence--I  
15 don't know if it is significant--of cytotoxic  
16 antibodies--than the group that received the total  
17 artificial heart.

18           DR. COPELAND: To the best of my  
19 knowledge, it wasn't statistically greater number  
20 of cytotoxic antibodies, but you might expect it  
21 based on the history of the control group having  
22 had more previous operations, therefore, more  
23 exposure to transfusions.

24           DR. AZIZ: This device is obviously  
25 coming before the panel as a bridge to

1 transplantation. If you had a patient who had  
2 received a lot of blood transfusions and did  
3 develop very high PRAs, in a sense, that would sort  
4 of negate or interfere with the patient getting a  
5 transplant.

6 How would you handle patients of that  
7 nature, because I am sure we will be seeing those.

8 DR. COPELAND: We have run across that a  
9 number of times, not just with this device, but  
10 with other devices, and our policy has been not to  
11 delay transplant on the basis of the PRA, to  
12 plasmapheresis the patient in the operating room and  
13 then prospectively for five more treatments after  
14 the transplant operation, and we have not noticed  
15 any significant dip in our survival in those  
16 patients.

17 DR. AZIZ: Let me go to some of the  
18 device malfunction sort of issues, and I will go  
19 over some of the adverse events that have occurred.

20 You mentioned that about 19 percent of  
21 patients had device malfunction, I think 15  
22 patients, and most of them were related to kinking  
23 of the tubes due to patient positioning.

24 Has anything been done to sort of prevent  
25 that happening? In a sense, some of those could be

1 catastrophic if nobody was in the room or if they  
2 were in a sort of halfway house.

3 DR. COPELAND: I am going to ask Mr. Smith  
4 to comment on that, if he would, please.

5 MR. SMITH: Let me address two factors  
6 related to that. One was a number of the device  
7 malfunctions were called air leak. What that was,  
8 was where the drivelines actually go into this, if  
9 you push so hard that you actually cause this wire  
10 spring to have tension on it, and what was done was  
11 we put a larger distance here.

12 The end result is you can't push it in as  
13 far, so the air leak issue at least we feel has  
14 been resolved associated with that. That was I  
15 think five situations there.

16 The driveline kink, which is a lot of  
17 force that has to be applied to this pneumatic  
18 system, you have 7 feet between the device exiting  
19 the body and the external console.

20 Many things can happen in that period of  
21 time, and we teach the patients to be aware of  
22 that, but to answer your question, when that is  
23 kinked, the system is monitoring it all the time,  
24 and there is an alarm that goes off within seconds  
25 of that to alert, not only the patient, but

1 obviously the caregivers.

2           This device, at this point in time, we are  
3 only asking for in-hospital use, so that is the way  
4 we approach this. Along the same lines of what Dr.  
5 Copeland mentioned is that during the study, we  
6 were hesitant to make any changes as technology  
7 changed, because it may impact the device that we  
8 were studying.

9           Hopefully, at a time, if approval is  
10 granted, those are the kinds of things that we will  
11 try to look at and do the due diligence and  
12 engineering, and possibly with the driveline,  
13 basically get a driveline that is less kinkable or  
14 less possible for that to happen.

15           DR. AZIZ: Does the right heart output  
16 have to equal the left heart output on a  
17 minute-to-minute basis?

18           MR. SMITH: That is a good question. The  
19 pneumatic system is a very forgiving system and  
20 whatever gets pumped over from the right side,  
21 let's say you pump 6 liters over, as long as you  
22 are pumping that out on the--I mean whatever is  
23 pumped over from the right to left side, as long as  
24 you are pumping that on the left side, we have not  
25 seen any issue at all related to that, and we

1 always set this with a little bit of room for  
2 errors, so that if, let's say, for an example, the  
3 patient's blood pressure went up, you could still  
4 overcome that pressure.

5 Like I said, we have now done this for 20  
6 years, and there is probably 50 years of patient  
7 years associated with this, and I have not seen  
8 that.

9 DR. AZIZ: Let me go to the question of  
10 neurological events. Clearly, I think there has  
11 been an improvement, marked reduction compared to  
12 the early generation of this system, but I think  
13 these strokes or neurological events still occur,  
14 and I think Dr. Copeland just highlighted that  
15 obviously using tailored therapy guided by TEG and  
16 platelet aggregation studies.

17 Are there any other ways you could pick up  
18 patients who would have a propensity like doing TCD  
19 monitoring, to see that the number of hits that you  
20 are seeing in some of these patients correlate with  
21 events happening, and that they could allow you to  
22 maybe add more antiplatelet agents or things of  
23 that nature?

24 DR. COPELAND: Yes, I believe there are,  
25 and I think transcranial doppler is a technology

1 that may offer a great deal, not only in terms of  
2 monitoring this device, but other devices as well.  
3 To the best of my knowledge, that really hasn't  
4 been adequately studied, neither have the brain  
5 breakdown proteins, which might be helpful in this  
6 setting.

7           Certainly for many years we have always  
8 said that if you did a head CT every day on every  
9 patient with a device, then, you would diagnose  
10 these things as they occurred, but obviously we, as  
11 clinicians--and this is a very clinical type of  
12 subject that we are dealing with today--as  
13 clinicians, we have to work within the realm of  
14 practicality, and that's not possible.

15           But I think the transcranial doppler idea  
16 is an excellent suggestion and I would like to see  
17 that done.

18           DR. AZIZ: Let me just sidetrack a little  
19 bit. I think most of us now obviously view the  
20 heart more than just a pump, but also a  
21 neuroendocrine organ, and I think the gist of this  
22 system compared to BiVADs is that you are actually  
23 taking out the organ's pumping function, but the  
24 brain peptide and the other peptides that the heart  
25 produces, do you have any indication, not

1 necessarily from this panel pack, what happens to  
2 the B&P levels and the like in these patients when  
3 you remove the whole heart?

4 DR. COPELAND: We have not looked at this  
5 in an extensive group of patients, but in a small  
6 group of patients it returns toward normal.

7 DR. AZIZ: So, you could use that as a way  
8 of monitoring the recovery, I guess.

9 DR. COPELAND: Yes, you could.

10 DR. AZIZ: Do you have problems with  
11 patients with high blood pressures on this pump? I  
12 see you have a number of patients who have reduced  
13 blood pressures and you sort of suggested that in a  
14 number of cases, this is related to volume  
15 depletion, but do you see the other end of the  
16 scale where the patients are hypertensive?

17 DR. COPELAND: That can happen and  
18 occasionally we have treated patients with oral  
19 antihypertensive agents who have been on this  
20 device. The reason we have treated them is not  
21 related to the device itself, it is simply based on  
22 the idea that people who are hypertensive should be  
23 treated for other reasons, such as brain aneurysms  
24 and the morbidity and mortality related to  
25 hypertension.

1 DR. AZIZ: Looking at the data, they said  
2 there were 20 to 25 percent of patients who did  
3 need a BiVAD at the time they come to end-stage  
4 heart failure. Obviously, you have a lot of  
5 experience in this area having done a lot of  
6 devices, and I think you bring a different focus  
7 because most people obviously don't have the  
8 experience at using the total artificial heart for  
9 patients who have biventricular failure.

10 But even in this study, it seems that very  
11 few centers, you did most of the total artificial  
12 hearts, how do you think that the community out  
13 there at large views removing the organ rather than  
14 using biventricular therapy, what do you think are  
15 the points that would convince people to focus more  
16 on using a total artificial heart versus using a  
17 biventricular system apart from the ones that have  
18 had, let's say, a tumor or a ruptured heart?

19 DR. COPELAND: I would like to answer that  
20 question, because I think that may be one of the  
21 most important questions facing us today, in a  
22 stepwise fashion.

23 First, if I may, I would like to call Dr.  
24 Walter Dembitsky up to comment on that question.

25 DR. TRACY: Can I just remind people who

1 are coming up to the microphone for the first time,  
2 just to state your financial relation and other  
3 association with the industry.

4 DR. DEMBITSKY: My name is Walter  
5 Dembitsky. I am a cardiovascular surgeon in San  
6 Diego. I have no financial interest in the company  
7 other than the interest that they may reimburse me  
8 for my airplane ticket here, which has not yet  
9 occurred.

10 But I also stand here as an advocate, not  
11 only for the field in general, but for specifically  
12 this technology, and to address Dr. Aziz's  
13 question.

14 We think this is an important technology  
15 to have, because there are certain patients where  
16 biventricular support simply does not work, and we  
17 have used it in those niches. We have used it in  
18 patients with massive myocardial destruction from  
19 infarct BSDs or biventricular infarcts.

20 We have used it in situations where we  
21 have had rejection of grafts on the table, and it  
22 is especially appropriate in that arena because you  
23 can stop immunosuppression, and not continue to  
24 injure the patient in that regard, allow them full  
25 recovery and then retransplant them, and I think it

1 is essential technology to have on hand for that  
2 population. There is no other technology that  
3 supports that particular kind of patient.

4 In addition to that, I think patients with  
5 arrhythmias, ventricular arrhythmias, where the  
6 retained heart again remains a specific liability  
7 to the patient and needs to be removed. Those  
8 patients can only be served with this technology.

9 DR. AZIZ: If you had a patient in whom  
10 you had put a total artificial heart, and they were  
11 really getting into respiratory failure, how would  
12 you handle that then?

13 DR. DEMBITSKY: Well, I would handle it  
14 like I would any other patient with a respiratory  
15 failure, because the one nice thing about this  
16 technology, unlike a univentricular or left  
17 ventricular assist device, is if you have pulmonary  
18 failure, you are not faced with the liability of an  
19 unperforming right ventricle to work against high  
20 pulmonary artery pressures, so it is just not an  
21 issue.

22 In addition to that, since you now can  
23 control the central venous pressure and keep it  
24 low, the peripheral organ recovery is much better  
25 with this biventricular device as opposed to a

1 univentricular one.

2 DR. AZIZ: I am sort of looking a little  
3 ahead. If you wanted to use a membrane oxygenator,  
4 have you done that, or could you use it in  
5 conjunction with this?

6 DR. DEMBITSKY: Well, I haven't done that  
7 in this arena, but, yes, you can do that. You  
8 would use it in venovenous capacity without a  
9 problem.

10 DR. AZIZ: Has anybody done that as far as  
11 you know?

12 DR. DEMBITSKY: I haven't done it, I am  
13 not aware if it has been done, but it would be  
14 easily done.

15 DR. AZIZ: I am trying to sort of  
16 understand. I think there are certain indications  
17 clearly where the total artificial heart I think  
18 has a role to play, I think as you mentioned, but  
19 in terms of once you take the heart out, you know,  
20 the concept of reversibility and the chance that  
21 the other heart would recover, you have obviously  
22 negated that, not to say that this would have a  
23 role to play anyway.

24 It seems that one has to be sort of be  
25 convinced to find some clear indications to guide

1 other people as to when to use the system versus  
2 using a biventricular system. It may not be an easy  
3 answer, but I think I would like to hear a little  
4 bit more on that.

5 DR. DEMBITSKY: With regard to  
6 irreversibility, I think we are all hoping for that  
7 in the future, just like we are hoping for antibody  
8 therapy for cancer, and that may occur in the  
9 distant future, but right now it is not a reality,  
10 and with these patients, we are interested in  
11 survival just so they can live for a brief period  
12 of time.

13 DR. COPELAND: The ultimate aim of what we  
14 are doing in bridge to transplant is to take the  
15 patient's heart out. I think the panel needs to  
16 continue to focus on that. We are going to a  
17 transplant. We are going to take the patient's  
18 heart out and put in someone else's heart at  
19 transplantation.

20 So, that is a fairly definitive act, as  
21 well, and I would remind the panel that heterotopic  
22 transplantation, which is a natural way of putting  
23 in an LVAD, it's a natural LVAD, has never caught  
24 on because it has a higher morbidity and higher  
25 mortality, and a lot of that is associated to the

1 pathology of the native heart.

2 I think this focusing on taking an  
3 irreversible action is perhaps not looking far  
4 enough down the road, because down the road, we  
5 want to transplant this patient. That is our goal.

6 One other thing on that question, if I  
7 may. Could you pull up RVF1, please.

8 [Slide.]

9 This is taken from the literature and as  
10 has been explained by a number of the speakers  
11 today, there is a scatter of opinion within the  
12 literature and scatter of data within the  
13 literature.

14 These are opinions from various authors  
15 including some who are present here today about  
16 what constitutes right heart failure - insufficient  
17 flow from the right ventricle to the left  
18 ventricle, elevated CVP, transesophageal echo, and  
19 so forth, and so on.

20 On the bottom, you see the definition  
21 essentially that was used in this study, which was  
22 the patient is on cardiopulmonary bypass with  
23 global dysfunction of his heart, has a high central  
24 venous pressure or a very low right ventricular  
25 ejection fraction.

1           There is probably going to be no final  
2 answer on what constitutes right heart failure, but  
3 basically, if you look at the people that have done  
4 the most work on this, at the University of  
5 Pittsburgh, Dr. Kormos and his colleagues, and ask  
6 them what it is, you can see right here.

7           Dependent on patient's clinical status,  
8 greater inotropic need, lower right ventricular  
9 ejection fraction, larger right ventricular  
10 volumes, fixed elevated pulmonary vascular  
11 resistance, and liver dysfunction, and I would  
12 submit that the patients that we included in this  
13 group, in this study, fulfill every one of those  
14 criteria.

15           So, in getting back to your question,  
16 then, how do you define this group of patients, how  
17 do you focus on this group of patients? Well,  
18 there are a number of authors that have taken a  
19 number of different directions, but there are a lot  
20 of similarities, and I think that most of them are  
21 contained in this slide.

22           DR. AZIZ: Just another technical  
23 question. At the time of transplantation, is it  
24 easier to do a heart transplant in somebody who has  
25 had a total artificial heart or somebody that has

1 had a BiVAD?

2 DR. COPELAND: From my point of view, it  
3 is about the same. It is not easy in either case.  
4 It requires a skilled, experienced transplant  
5 surgeon, but it can be done, and there are plenty  
6 of evidence to prove that in this study and in  
7 other documentation in the literature.

8 DR. AZIZ: In patients in whom you are  
9 going to be putting one of these in, who either had  
10 an AICD, one of the recent generation, or the early  
11 generation where the patches are stuck on, what do  
12 you do about that?

13 DR. COPELAND: Well, if the patches are  
14 external to the pericardium, we generally try to  
15 cut away as much of the left pericardium down to  
16 the phrenic nerve as we can to make room for the  
17 device.

18 If there is a big enough space, we don't  
19 do anything and we just leave the patches in place  
20 and put the device in. So, yes, and if they are on  
21 the heart, of course, we just take them out with  
22 the ventricles.

23 DR. TRACY: Dr. Yancy.

24 DR. YANCY: Thank you.

25 I will start with just a brief review. It

1 will not be a summary of what we have seen, but  
2 just my own perspective on the data that we have  
3 seen, and then raise a few questions.

4           Obviously, the investigators and inventors  
5 of this technology should be acknowledged for what  
6 I think is an effort and persistence with a 10-year  
7 clinical trial looking at a very, very ill patient  
8 population.

9           I feel obliged to specifically comment on  
10 trial design even though it is tangential to our  
11 discussions today, because as a clinician involved  
12 in the care and management of patients who have  
13 end-stage heart disease, I recognize the difficulty  
14 with having strict control groups and having  
15 randomization because there is a sense of clinical  
16 urgency given the severity of illness here, so  
17 other than comparing similar technologies in a  
18 superiority design, I think we are left with these  
19 more experiential study designs for this kind of  
20 technology.

21           So, in that regard, I am comfortable with  
22 it, and that is from the perspective of the FDA, as  
23 well, where our obligation is to demonstrate safety  
24 and efficacy, and not really to have it meet the  
25 same standard as a traditional clinical trial

1 particularly from a cardiology standpoint.

2 I think that the advantage of this  
3 technology, as I view it, is in the biventricular  
4 support and the unique applications, which frankly  
5 were not looked at in this trial. I think one of  
6 the last graphics that was demonstrated suggested a  
7 menu of clinical scenarios where, in fact, it would  
8 be reasonable to not only replace the ventricles  
9 and the valves, and that appears to be a future  
10 application.

11 I don't think we can quibble with the  
12 outcome, statistics notwithstanding. The  
13 improvement in functional capacity, the survival to  
14 transplantation, the 30-day survival, as well as  
15 the more chronic survival parameters, particularly  
16 in the context of the anticipated survival based on  
17 the UNOS data points are actually quite  
18 satisfactory from a clinical standpoint, and I find  
19 that to be reasonable.

20 The concerns I have are really in two or  
21 three big buckets. One has to do with morbidity  
22 and then one has to do with indication yet again,  
23 and I recognize this will continue to haunt and/or  
24 trouble this technology.

25 I would agree that the notion of meeting

1 the community standard vis-a-vis morbidity probably  
2 is one that needs to be altered. Having been  
3 involved in the management of patients that have  
4 had perioperative neurological events after  
5 mechanical device support, it really is a tragic  
6 complication that is terribly difficult to deal  
7 with.

8           So, I think we need to think in global  
9 terms of how we can drive that down. Frankly,  
10 after reviewing the data before getting here and  
11 seeing the data, I really am at a loss regarding  
12 the infection issue, because the infection issue  
13 seems to be as low as 15 to 20 percent, or as high  
14 as 70 to 75 percent, and what strikes me oddly is  
15 that the majority of the infections appear to be  
16 not device related per se, but rather procedural as  
17 in perioperative care, so I wonder if there are  
18 some opportunities to modify proven strategies in  
19 that regard.

20           Neuro events are compelling and I think we  
21 need to drive this entire field to a lower  
22 threshold because of the unfortunate consequences  
23 of those events.

24           The bleeding rates also are problematic in  
25 my mind. They appear to be high looking at the

1 published data for other platforms of mechanical  
2 support.

3           Even though they may not be out of  
4 arrears, they are at least on the high side with  
5 numbers as high as 37 to 42 percent, and at least  
6 in our clinical experience in Dallas, the more we  
7 use blood products, the more likely we are to have  
8 sensitization, and we perhaps have a somewhat more  
9 conservative approach in our sensitized patients  
10 and moving promptly forward with transplantation,  
11 and this can unfortunately create a significant  
12 delay in our ability to transplant. It would be  
13 nice to know the specific data referable to  
14 antibiotic sensitization.

15           Now, as for my questions, if you will,  
16 again we go back to which patient is really ideal  
17 for this, and I am more inclined to accept the  
18 indication for multi-system organ dysfunction.

19           I think one of the points that was not  
20 emphasized in the early presentations were the data  
21 that showed the dramatic decrease in the hepatic  
22 function going from bilirubins of 2 or greater to  
23 normalization and transaminases that were  
24 significantly above the normal, that appeared to  
25 normalize, as well.

1           It would seem to me that going beyond  
2 trying to define this relatively abstract  
3 phenomenon of RV dysfunction, what is not so  
4 abstract is hepatic insufficiency, renal  
5 insufficiency in the context of advanced heart  
6 failure, and maybe that is the more helpful arena.

7           I have to press Dr. Copeland once again on  
8 the RV dysfunction question, however, because even  
9 in the graphic that we just saw, the specific  
10 definition of RV dysfunction by SynCardia is  
11 referable to the RVF and the CVP greater than 18,  
12 and it would be nice to see the data for that group  
13 of 50 or so patients.

14           I think that one also has to put this into  
15 a more global context. From the time the study was  
16 put together, especially looking at the reference  
17 control population from '91 to '93, there are a  
18 number of clinical iterations that have come about  
19 both in chronic management and in acute management  
20 for which that reference group was not exposed, and  
21 thus, they may represent, beyond just the  
22 statistical issues, clinically, they may be an  
23 inappropriate group for comparison.

24           They clearly were not exposed to beta  
25 blockers or aldo antagonists, they clearly were not

1 exposed to device therapy, and in the acute care  
2 model, with all the things that Dr. Swain and  
3 others have commented upon with regard to  
4 vasodilators, inotropes, naturated peptides, PD5  
5 inhibitors, et cetera, a number of treatment  
6 strategies, albeit none of which are strikingly  
7 beneficial, there are treatment algorithms that can  
8 be designed to deal with the medical issues of RV  
9 dysfunction.

10           So, I think that that question of whether  
11 we are dealing with RV dysfunction or multi-system  
12 organ failure probably merits a bit more thought  
13 and clarity, and from my judgment, as I have looked  
14 at the information, I think this is a clear  
15 indication for advanced heart failure with  
16 multi-system organ disease, and less so for the RV  
17 issues, because they are so difficult to address.

18           There are several specific questions that  
19 I think have not yet been fully addressed. There  
20 is a comment that there were a number of episodes  
21 of hemodynamic insufficiency identified, which is a  
22 somewhat awkward phraseology, but there is a  
23 comment that it was referable to episodes of  
24 hypovolemia, but these were not device related.

25           I am assuming that that means that there

1 was a significant diuresis when the device was in  
2 place, and it would be interesting to know,  
3 particularly since you are precluded from putting  
4 in monitoring lines, how one follows this and  
5 avoids it.

6           It is more than just an academic concern  
7 because if they were hemodynamic insufficient  
8 episodes, that might further compromise neurologic  
9 function.

10           A second question has to do again with the  
11 antibody sensitization, the incidence and any  
12 treatment modality specifically for that.

13           Yet another question is that as the  
14 testimony started the day off, this is a fairly  
15 bulky and heavy console. I am curious as to how it  
16 impedes the rehabilitation potential for these  
17 patients and whether there are iterations on the  
18 drawing books at least for tighter, smaller  
19 consoles that would give the patient more mobility  
20 and would give them a sense of not being connected  
21 to this fairly large instrument.

22           And we didn't hear anything today about  
23 the cost profile for this device, and I would like  
24 to know what that is particularly in the context of  
25 other platforms that are currently available.

1 Overall, I would say that by my review, I  
2 think there is a reasonable place for this  
3 technology, but I think the indication is fairly  
4 narrow, and it would be people with advanced  
5 disease that have evidence at least of multi-system  
6 organ dysfunction, but there are some nagging  
7 questions that I would like to have resolved  
8 referable to the RV issues and referable to some of  
9 the technology per se.

10 DR. TRACY: Do you have specific questions  
11 you want or does the sponsor feel that they have  
12 got their directive as to the comments that they  
13 are going to make at this point?

14 DR. COPELAND: If I may, I would like to  
15 take a stab at a few, and I would apologize if I  
16 have missed some of the questions because there  
17 were quite a few. I would like to call up Slide  
18 S1, please.

19 [Slide.]

20 The first answer is in response to your  
21 question about adverse events. This shows adverse  
22 event rate by time period, and we are looking at  
23 days zero to 2, after implantation days 3 to 21,  
24 day 22 to transplant. This constituted 77 percent  
25 of the days, and there were 19 years worth of days

1 for the whole group, and there were 17 1/2 patient  
2 years in this study. Then, there is transplant to  
3 30 days.

4 You can see that almost all of the adverse  
5 events occurred early on, in the first 3 weeks  
6 certainly, the rate being 0.51 events per day in  
7 the first 2 days, and 0.02 events per day in the  
8 days 22 to transplantation.

9 Now, if I could have S2, please.

10 [Slide.]

11 There was a clustering phenomenon of the  
12 adverse events and the reason I show this slide is  
13 to show that clustering phenomenon. The number of  
14 adverse events is shown on the x axis, and the  
15 number of patients on the y axis.

16 For instance, for the first bar, there  
17 were 4 patients who had no adverse events. For the  
18 second bar, there would be 6 patients who had 1  
19 adverse event, and so forth.

20 If you look at the green, the patients are  
21 alive, and the orange are the patients that died.  
22 There is definitely a relationship between the  
23 number of adverse events and the deaths.

24 If we use a cutoff of 6 adverse events, we  
25 see that the mortality in this group out here on

1 the right side is 46 percent, and the mortality  
2 rate for the ones with less than 6 is 9 percent.

3           These occurred early on and multiple  
4 adverse events tended to occur in the same  
5 patients, so there was a clustering, and basically,  
6 the way it works is if you have one bad thing  
7 happen, like pneumonia or renal failure, the  
8 likelihood is that you are going to have bleeding  
9 or an infection or something else of that sort.

10           If you don't have many adverse events, and  
11 they are only mild, chances are you are going to  
12 get through with a 9 percent mortality rate.

13           I would like to go on S3, if we could.

14           [Slide.]

15           You asked about the hemodynamic  
16 insufficiency, and the FDA asked us to divide that  
17 into two groups, because it does sound sort of  
18 strange, what does it mean, and we divided it into  
19 reduced systolic blood pressure, less than 90 mm of  
20 mercury for a period of at least 4 hours.

21           This is the number of patients. The total  
22 number of patients with that event were 12, in 6  
23 there was sepsis, in 4 volume depletion, in 1 it  
24 seemed to be a medication, and in another it was  
25 gross hematuria from over-anticoagulation.

1 We will go on to S4, please.

2 [Slide.]

3 This is the same type of definition,  
4 reduced cardiac index in the patients to less than  
5 or equal to 2 L/min/M<sup>2</sup> for a period of 4 hours or  
6 more . There were 7 events here, 1 from device  
7 malfunction, 1 from a fit complication, and the  
8 rest seemed to be patient related - volume  
9 depletion, pneumothorax, tamponade, and PIC line  
10 going across the tricuspid valve.

11 You asked about rehabilitation and the  
12 console size. The console size is fairly large.  
13 The tether is about 7 to 7 1/2 feet.

14 As a routine in our center, patients are  
15 sent daily to what is called the wellness center,  
16 which is a big exercise room, and put on a  
17 treadmill or a bicycle, and pretty much every  
18 patient that is capable of doing that, and most  
19 were by the data that we showed, presented earlier,  
20 did that at least 3 days a week.

21 So, there was rehabilitation and we did in  
22 a number of cases look at peak oxygen consumption  
23 studies in these patients with total artificial  
24 hearts, and it tended to run around 14  
25 cc/kilo/minute maximal consumption, so certainly

1 not normal, but enough to keep the patient alive  
2 and getting better while he waited for his  
3 transplant.

4           With respect to the smaller consoles, if I  
5 may, I would like to call Dr. Aly El-Banayosy from  
6 Bad Oeyenhausen to speak on that since he has  
7 experience with big consoles and small consoles  
8 with this device.

9           Would that be okay?

10           DR. TRACY: That's fine, thank you.

11           DR. EL-BANAYOSY: Good afternoon. My name  
12 is Dr. Aly El-Banayosy from Bad Oeyenhausen,  
13 Germany. I am the medical director of the  
14 Mechanical Circulatory Support Program in the heart  
15 center in Bad Oeyenhausen, Germany.

16           I don't have any consulting agreement with  
17 SynCardia, however, my trip to Washington, D.C. was  
18 financially supported by CardioWest.

19           Regarding our clinical experience with  
20 small driver, we started last year with animal  
21 trials with the Bell and Hart X-Core system, which  
22 is a portable driver.

23           We did an animal trial and we did a  
24 laboratory test to drive the CardioWest system with  
25 this portable driver, and after successful animal

1 trials and bench data, we started with the clinical  
2 trial in Germany to support patients with  
3 CardioWest system with X-Core driver.

4 DR. ZUCKERMAN: Can I interrupt a moment,  
5 Dr. Tracy. It is my understanding that none of  
6 these data are in the PMA application, and as such,  
7 our need to look at safety and effectiveness of the  
8 device under consideration should not take into  
9 account the interesting data that this speaker is  
10 going to talk about.

11 Hence, other than saying that there are  
12 upcoming interesting modifications of the device, I  
13 don't know what else we want to get from this  
14 speaker here, Dr. Tracy.

15 DR. EL-BANAYOSY: Am I allowed to show one  
16 slide?

17 DR. TRACY: If you could just be very  
18 brief, that would be fine.

19 [Slide.]

20 DR. EL-BANAYOSY: I would like to show you  
21 the slide with the patient living with this  
22 portable driver, and he is now at home. We have 7  
23 patients with this device; 3 are still in the  
24 hospital and 4 at home.

25 DR. TRACY: Thank you.

1 MR. SMITH: Can you restate your question  
2 relating to financial--

3 DR. TRACY: I don't think that that is a  
4 comment that we can accept. Financial interest in  
5 not part of the purview of this review, the  
6 reimbursement side of it.

7 MS. WOOD: Yes, that is correct. I want  
8 to reiterate that, that the cost of the device is  
9 not within the directives of the FDA.

10 DR. YANCY: My apology.

11 I would like to go back because obviously,  
12 the sponsor has quite a bit of data, and I would  
13 find it odd if they didn't have the data stratified  
14 as a function of hemodynamics, and if they do have  
15 the data stratified as a function of hemodynamics,  
16 I think it would be worth our time from a safety  
17 and efficacy standpoint to see that information.

18 DR. COPELAND: Could I ask you to be a  
19 little more specific about that? I am not exactly  
20 sure what you are asking for.

21 DR. YANCY: CVP greater than or less than  
22 18 RVF, less than or greater than 20 LVF, et  
23 cetera. We have a full profile in our manual for a  
24 description, very careful description. The  
25 hemodynamics just shows an average normal PVR, a

1 mean CVP of 16, a peak systolic PA pressure of 55  
2 with some variations in the ranges.

3 My specific question, again just trying to  
4 drill down on this question of RV dysfunction, is  
5 whether or not we have a data cut for what was  
6 prespecified as an RV concern, a CVP greater than  
7 18, an RVF less than 20.

8 The direction, of course, is how we, as  
9 cardiologists, would feel about referring for this  
10 device implantation, would we make our decision  
11 based on impending multi-system organ dysfunction,  
12 would we make our decision based on hemodynamic  
13 measure of right-sided hemodynamics, would we make  
14 our decision based on an absence of a risk factor  
15 for that 46 percent mortality in a group that had a  
16 number of adverse events.

17 I think that we need to consider what kind  
18 of patient profile in the clinical arena we would  
19 look for, or maybe it's a combination of all the  
20 above, but the data we haven't yet seen or that I  
21 have overlooked are data that are stratified  
22 according to those hemodynamic parameters.

23 DR. COPELAND: Can we have BD8, please.

24 [Slide.]

25 I hope this at least partially answers

1 your question. This is baseline hemodynamics,  
2 looking at some of the hemodynamics. We don't have  
3 everything here, but we do have central venous  
4 pressure, we do have arterial pressures, we do have  
5 SVR, PVR, cardiac output index, and organ perfusion  
6 pressure for the core group.

7 This is an old slide. We hadn't yet taken  
8 out the control and the p-values, and I apologize  
9 for that, but we have, as you might have noticed in  
10 our presentation today, taken all that out.

11 DR. YANCY: Is this the extent of the  
12 hemodynamic data?

13 DR. COPELAND: Is there something  
14 specifically you are looking for? I don't know how  
15 many more parameters we looked at, but this is sort  
16 of a summary of most of the hemodynamic data at  
17 baseline.

18 DR. YANCY: I fully understand the  
19 baseline data, but my concern--and I apologize if I  
20 am not clear--but referable to outcomes, do we have  
21 data that are stratified as hemodynamics upon entry  
22 and how that relates to outcomes?

23 DR. COPELAND: No, we don't, I am sorry.  
24 The only thing we do have is that we know for this  
25 and other devices, that if the immediate cardiac

1 index after implantation is 2.5 or greater, there  
2 is a very good success rate, and if it is not,  
3 there is about a 3- to 4-fold drop in success  
4 rates, so there seems to be a cutoff in the amount  
5 of blood that is pumped, and if it is 2.5 L/min/M<sup>2</sup>,  
6 the patient seemed to do well.

7 DR. YANCY: The only corollary I would  
8 suggest just for the purposes of having this  
9 component brought to some closure and being clear,  
10 if I look at the BiV literature, then, we can look  
11 at the pre-intervention QRS duration and identify  
12 outcomes that may vary as a function of what that  
13 baseline QRS prolongation was with regards to the  
14 responsiveness to BiV. That is kind of the way  
15 that I am trained to look at data that are based on  
16 objective parameters at start.

17 So, we have a whole family of objective  
18 indicators here, and my concern is, or my question,  
19 not even a concern, is whether or not we can have a  
20 similar model where we look at a description of  
21 right-sided or right ventricular pathology, and  
22 then identify how this platform specifically  
23 benefits that model. But it seems as if we need to  
24 move forward.

25 DR. TRACY: Yes. I think the answer is

1 that the data has not been looked at in that way.  
2 It is a composite picture, and there is not QRS  
3 duration--correct me if I am wrong--but there is  
4 not a specific hemodynamic or profile parameter  
5 that identifies those who will do well versus those  
6 who will not do well with the device.

7 DR. COPELAND: Not from this study. If  
8 one looks in the literature, and I can provide this  
9 information if you would like, at experiences with  
10 LVADs, for instance, there is a fair amount of  
11 literature on prognostic factors that relate to  
12 baseline characteristics.

13 I can show you an example of that if you  
14 would like to see it.

15 DR. TRACY: I am not sure that the LVAD  
16 would be particularly relevant to the total  
17 artificial heart anyway.

18 DR. COPELAND: The only reason I brought  
19 it up is that we use that kind of information in  
20 making our decisions about using a total artificial  
21 heart. In other words--may I show this? Pull up  
22 LVAD1, please.

23 [Slide.]

24 This is taken from the data at Columbia  
25 University, Dr. Oz and colleagues published this.

1           These are the factors that increase the  
2 risk for using an LVAD, and obviously, if you are  
3 making a choice to put in a total artificial heart,  
4 you are going to be thinking about these kinds of  
5 things when you are looking at the patient - a low  
6 urine output, a high CVP, and mechanical  
7 ventilation all increase the risk of that patient  
8 dying to about, well, I am not exactly sure what  
9 the mortality rate is in the program, but by 3-fold  
10 or more.

11           Prothrombin time of greater than 16  
12 perhaps indicating again right ventricular failure  
13 and hepatic dysfunction increases the risk by 2.4,  
14 and reoperation by 1.8.

15           The other thing I might do in answering  
16 that question, if it's approved by the chairman, is  
17 to ask Dr. Jim Long to comment on that. He is one  
18 of our investigators from the LDS Hospital in Salt  
19 Lake City.

20           DR. TRACY: That's fine.

21           DR. LONG: I am Jim Long. I am a  
22 cardiothoracic surgeon at LDS Hospital. I was a  
23 principal investigator during the CardioWest trial.  
24 I have no financial incentive or disincentive with  
25 this corporation.

1 I have been involved in the field of  
2 advanced mechanical circulatory support for 15  
3 years now, and I had an opportunity to participate  
4 with most of the clinical trials, with a number of  
5 the technologies including the HeartMate LVAD. Our  
6 center was the leading enroller in the rematch  
7 trial.

8 We have had considerable experience with  
9 that, and that is my device of choice in this day  
10 and age, but regrettably so, because I am not able  
11 to use with the frequency I would like  
12 biventricular support of specifically this device  
13 even though I am an investigator because my  
14 durations of support are averaging in the four to  
15 five month range, and nowadays with electric  
16 technology that allows discharge of patients, it is  
17 hard for me to justify using a technology that  
18 doesn't get them out of the hospital, so we are  
19 eagerly looking forward to that.

20 Now, having said that, and having told you  
21 that I have been essentially put into this position  
22 of having to use LVADs in excess of what I consider  
23 appropriate, I can tell you that I am looking  
24 forward to being able to use a technology that I  
25 can get reimbursement for and eventually get

1 patients out of the hospital, that will allow me to  
2 support some that I think clearly have  
3 biventricular failure potential or potential for a  
4 serious compromise because I didn't support them  
5 with biventricular technology.

6           This last week I spent two nights putting  
7 an LVAD into a patient and then a temporary RVAD in  
8 a patient whose right heart failed after an LVAD,  
9 and had a very complicated time doing it, and would  
10 have been much better served had I been able to  
11 remove the ventricles and put in a CardioWest  
12 artificial heart.

13           This was a patient who had severe  
14 dysrhythmias, a very large myocardial infarction.  
15 Rebuilding the apex for a left ventricular  
16 cannulation was a massive undertaking, that took a  
17 large amount of teflon felt patched on the heart  
18 and actually led to breakdown the next night, that  
19 caused me to bring him back for bleeding. I had to  
20 replace a valve.

21           All of that would have been better served  
22 if I had been able to remove this heart and put in  
23 a biventricular support device. I now face the  
24 situation where I have got recurrent arrhythmias  
25 ongoing, and I have got biventricular support in

1 with a temporary RVAD.

2           The whole concept of predicting who is  
3 going to fail with left ventricular support only is  
4 really in its infancy, if you will. It has been  
5 studied for a long time. I think at this stage, it  
6 is fair to say that the answer is we just simply  
7 don't know.

8           We focus on a number of things including  
9 the right ventricle itself and look at hemodynamic  
10 parameters, such as CVP, but not only CVP, can that  
11 right ventricle generate pressure, can it do work,  
12 can it push pressure into the lungs, does it have  
13 enough capacity to do that.

14           So, the right ventricle itself is  
15 important from a hemodynamic point of view, as well  
16 as from a visual point of view both in the  
17 operating room, as well as echocardiography.

18           It goes way beyond that, however, not just  
19 right ventricular contractile performance, but the  
20 overall state of the heart in terms of arrhythmias  
21 or anatomic abnormalities that you have heard  
22 about, and it goes beyond that, because systemic  
23 factors play a major role, probably at least  
24 according to Bob Kormos, the most important factor  
25 to predict who is going to suffer right heart

1 failure after implantation and LVAD.

2 Today, we don't know the answer to that,  
3 and as much as I would like to be able to come up  
4 with a formula to predict that, it is not possible.

5 I think we are going to have to end up  
6 creating some guidelines that suggest that when it  
7 appears that right ventricular failure is going to  
8 threaten the patient, that we be entitled to be  
9 able to move to technologies like this.

10 I think this is going to be a niche  
11 technology. I can't ever imagine using this  
12 technology when I have any inclination whatsoever  
13 of recovery.

14 This is a technology that is clearly  
15 destined for those who you would not want to ever  
16 recover, and personally, I doubt that we are going  
17 to see, at least in my center, more than probably  
18 two to three, four applications of this a year at  
19 its very most. It is going to be very narrow and  
20 very limited.

21 I am not sure, as excellent as the  
22 question is, that I know today, having participated  
23 in this study, having looked at this data, how to  
24 be able to create some specific criteria that tell  
25 me when I can use this technology as opposed to a

1 Thoratec biventricular support except for specific  
2 things like arrhythmias, anatomic issues, and some  
3 very discrete things that we know from the  
4 literature are more likely to be of concern.

5 DR. COPELAND: Just a couple of follow-up  
6 points for your questions, Dr. Yancy. One was  
7 about the CVP. We quickly reviewed our database  
8 and found that 38 percent of patients had CVPs  
9 higher than 18 at baseline, and 25 of those went on  
10 to transplantation, for 65.8 percent.

11 So, it would appear that the ones that had  
12 chronically high CVPs were sicker and had a less  
13 satisfactory outcome than the other ones.

14 The other question was about cytotoxic  
15 antibodies. There were 9 patients who were  
16 implanted who developed cytotoxic antibodies, who  
17 then went on to transplant. They all survived.

18 DR. TRACY: Any other questions, Dr.  
19 Yancy?

20 DR. YANCY: No.

21 DR. TRACY: Then, I will ask the other  
22 panel members, and we will start with Dr.  
23 Weinberger to address any questions they may have  
24 to the sponsor.

25 DR. WEINBERGER: My concern again focuses

1 around the same issues that seem to be troubling  
2 Dr. Yancy. I think if I am going to have a patient  
3 with end-stage heart failure, and if I look at the  
4 inclusion criteria in the study, one could get in  
5 there with relatively low CVP pressures, in other  
6 words, if you take a low cardiac index and a low  
7 systolic blood pressure, you could get into the  
8 study, and you didn't have to have demonstrable  
9 right heart failure, at least according to the  
10 formal inclusion/exclusion criteria.

11 I am wondering, since we are totally  
12 disregarding the control patient population, and  
13 was just thinking of these patients as very sick  
14 people who are going to die, if, as a surgeon,  
15 patients come to you with very poor cardiac outputs  
16 and very high filling pressures, when are those  
17 patients going to get LVADs and when are those  
18 patients going to get BiVADS.

19 At least in our center, we use that CVP as  
20 a pretty strong predictor of who is going to be  
21 able to fly with or without a BiVAD.

22 Is that not what you are finding?

23 DR. COPELAND: I would like to first  
24 explain that in our center, contemporary with the  
25 total artificial heart experience, was an

1 experience with approximately 150 BiVADs and VADs  
2 sort of equally divided between the two, so each  
3 time a patient came to us, we had to make that  
4 decision, does he get a BiVAD, does he get an LVAD,  
5 or does he get a total artificial heart.

6 Our way of addressing this was to wait  
7 until the last minute, more or less, in other  
8 words, to try to support the patient with inotropes  
9 and any other medical means that we could until  
10 there was no other possibility to keep him alive.

11 At that moment, we made the decision as to  
12 whether to go ahead. What we found was quite  
13 simply that if we waited that long with LVADs, we  
14 had much less survival to transplant than we did  
15 with total artificial heart, if we waited that long  
16 with BiVADs, we were even more disappointed than we  
17 were with LVADs.

18 Could I have Slide FU1, please.

19 We were asked earlier in the session this  
20 morning to look at what happened to the controls in  
21 this study who received VADs and BiVADs, and we  
22 looked up that data. We did have a number, and  
23 that was 48 percent survival to transplant of that  
24 group, from the controls, who were eliminated  
25 because they had received a VAD.

1 [Slide.]

2 This is the rest of the data. There were  
3 36 BiVAD patients that were eliminated from being  
4 controls because they received a BiVAD. Fourteen  
5 of these made it to transplant or about 39  
6 percent. There were 123 LVAD patients, 60 made it  
7 to transplant, 48 percent, and then the 30-day  
8 survivals are shown here.

9 This is very similar to the experience  
10 that we have had in our own center, having a  
11 philosophy of waiting until the last minute. The  
12 reason we wait until the last minute is very  
13 simple. This is a big operation. It exposes the  
14 patient to a lot of risk. He had better be very  
15 sick and nearly dead in order for us to justify  
16 such an operation.

17 But in that group of patients, we find  
18 that the total artificial heart seems to be the  
19 best solution.

20 DR. WEINBERGER: One other question is  
21 given today's practice of VAD use, if you were to  
22 design a trial today to randomize patients between  
23 LVAD, BiVAD, or cardiac replacement, would it be  
24 harder to enroll?

25 I mean it seems to me like you had a devil

1 of a time enrolling in this study, and I think that  
2 what I see happening is the device gets approved  
3 and people will then say do I take a chance on  
4 putting an LVAD in and getting away with it, or do  
5 I just go to complete cardiac replacement.

6 I would like to know whether or not, in  
7 real world use of what you expect, in other words,  
8 the sponsor, when you got up to list the kind of  
9 people that you would like to have the device used  
10 for, was a whole set of anatomical criteria that  
11 were very acute, that weren't sort of  
12 representative of the patient population specified.

13 I get the picture I had in my mind of the  
14 patient population was more of a chronic heart  
15 failure population, that it was sort of slowly  
16 spiraling towards transplant rather than some  
17 person who fell apart either from an acute anterior  
18 infarction or during cardiac surgery and couldn't  
19 come off bypass.

20 So, if we take the large group of  
21 patients, 2,000 or so patients who are transplanted  
22 and look at the people who get devices, which are a  
23 lot more people now than there were 10 years ago,  
24 at least in our center, VAD use has gone up  
25 dramatically.

1           So, a population of patients who are  
2 eligible for VADs is now much larger than it was  
3 over the earlier years. So, if you had your  
4 druthers, would you randomize patients between LVAD  
5 and complete cardiac replacement prospectively for  
6 all comers? Would that be a study that would be  
7 doable?

8           DR. COPELAND: I guess it would depend on  
9 the entry criteria because I am convinced by the  
10 experience that we have already had that once a  
11 patient--see, there is another set of indications  
12 besides the anatomic indications and the pressure  
13 indications and the right ventricular ejection  
14 indications, it is the gestalt of the entire  
15 patient, it is how sick this person is.

16           He is terribly sick, he is on lots of  
17 inotropes, he is on vasoconstrictors, his kidneys  
18 and liver are failing, he is going into multiple  
19 organ failure.

20           If it's that kind of patient, and he is  
21 big enough, I would want to put in a total  
22 artificial heart because I think that is the only  
23 way to salvage a significant number of those  
24 patients, and I do not believe that an LVAD can do  
25 it.

1           You would have to have a cutoff or entry  
2 criteria that preceded that point in the natural  
3 history of the disease. If you were to want to go  
4 prospectively one way or the other, so that you  
5 would really not know whether the LVAD or the total  
6 artificial heart were going to do the better job,  
7 and I am not sure I would be willing to put in  
8 either one of those devices at that point in time.

9           Do you see what I am saying?

10          DR. WEINBERGER: It is troubling.

11          DR. COPELAND: In other words, I don't  
12 know.

13          DR. LONG: I will offer my opinion. I  
14 think the field considers LVAD therapy in this day  
15 and age so far superior to any biventricular  
16 therapy that exists, whether it be paracorporeal or  
17 whether it be the total artificial heart, that it  
18 would never be able to randomize them, LVAD versus  
19 BiVAD versus total artificial heart.

20                 It may be possible to do a BiVAD versus  
21 total artificial heart trial, but not LVAD in that  
22 mix given the current technology and current  
23 outcomes with those technologies.

24          DR. PAE: Just to reinforce that a bit, I  
25 think that people have to understand that one of

1 the reasons it would be very difficult to do what  
2 you are talking about, an LVAD versus total  
3 artificial heart, is that in many respects, if  
4 properly applied, and this is why there is such a  
5 huge range in the reported incidence of right  
6 ventricular failure, if you do the right patients  
7 at the right time, which we always don't have the  
8 luxury of, you have a very low incidence of right  
9 ventricular failure.

10 So, if you were to set up a trial, it is  
11 much like Dr. Long said, it would have to be  
12 biventricular support versus a total artificial  
13 heart.

14 DR. WHITE: I would like to congratulate  
15 the sponsor, Dr. Copeland specifically, for  
16 conducting this trial. Ten years is a long time to  
17 birth this baby, and I appreciate your  
18 presentation, I think you have been very  
19 straightforward.

20 Could I ask you some questions, actually,  
21 a very questions, though. On P30, on the study  
22 presentation, you mentioned that you had two  
23 indications for implanting hemodynamically this  
24 device, the criteria A and the criteria B.

25 Could you give me a feeling or an actual

1 number of the patients that were enrolled by each  
2 of those indications? I mean there were a majority  
3 of A's or B's? Could you tell us that number?

4 DR. COPELAND: My gut feeling is that the  
5 majority fulfilled both criteria A and B. These  
6 criteria were set up in 1991, before we ever did  
7 the study, but, in fact, in point of fact, it  
8 wasn't either A or B. I mean they were on the  
9 whole thing, the full monte.

10 They were on all the inotropes. They had  
11 a low output, they had low blood pressures, and  
12 they had high CVPs. We never put in this device in  
13 anybody that wasn't completely full unless they  
14 were on an ECMO system or a CPS system.

15 You have to remember that when you look at  
16 these data points and you see a low CVP, that might  
17 have been a patient that was on a Biomedicus pump  
18 or something, because anybody that wasn't on a  
19 Biomedicus pump had to have a CVP of at least 18 or  
20 20 before we would even look at them.

21 DR. WHITE: When we talked about the  
22 training program for institutions and physicians,  
23 is it your intention to have this device placed in  
24 institutions that don't currently do heart  
25 transplantation? Would you limit this device to

1 only centers that are currently doing heart  
2 transplantation?

3 DR. COPELAND: My feeling is it should be  
4 limited to centers that do heart transplants and  
5 have some experience with devices. I would like to  
6 ask Dr. Slepian to comment on that, as well.

7 DR. SLEPIAN: It is our intent to only  
8 place this type of system in experienced hands as  
9 this comes forward. We have a very detailed  
10 training program, and if I could put up Slide P90  
11 to just again reemphasize this for you.

12 [Slide.]

13 There would be multiple elements to  
14 training, and this would be in the hands of  
15 experienced surgeons that are transplant surgeons.  
16 Not to skirt around the question, but it is our  
17 intent to only do this in a very slow, careful  
18 fashion. We don't expect, if we were to receive  
19 approval, that every center is going to be able to  
20 come on board with this type of thing.

21 I mean clearly, this is a sophisticated  
22 technology where you require experience, technical  
23 skill to be able to do that, and the sponsor is  
24 cognizant of that, would not just allow this to  
25 roll out.

1 I think the other point, not to create  
2 controversy, but if there is a medical center which  
3 has multiple hospitals, and it happens to be across  
4 the street, for instance, imagine a center like  
5 Texas, that system would be made available if the  
6 patient could be easily transported, but in large  
7 part and extent, this is for transplant centers.  
8 This is a device to support a patient for an  
9 ultimate goal of transplant, so it is within that  
10 guise that this will be rolled out and developed.

11 I can expand on this if you have any  
12 additional questions about the training, we have a  
13 little bit more detail here.

14 DR. WHITE: I don't do this work, but it  
15 seems to me that if you restrict this device to  
16 active or approved transplant centers, you not only  
17 get complex surgery issues solved, but you get the  
18 support staff and the institutions used to other  
19 devices, and you get a whole bunch of other things  
20 as opposed to trying to put this in an outlying  
21 center where perhaps you are going to handle  
22 cardiogenic shock patients and try to run a program  
23 that way.

24 DR. SLEPIAN: Sure. It is intended to be  
25 in transplant centers, that is the concept.

1 DR. TRACY: Dr. Hirshfeld.

2 DR. HIRSHFELD: I would like to ask Dr.  
3 Copeland to help with some of the aspects of  
4 indication for this. A lot of the previous  
5 questioners have brought up that the indications  
6 right now are not precisely defined, and a lot of  
7 the choice to use the device in the trial was based  
8 on the investigator's intuition that the patient  
9 would do better with a total artificial heart than  
10 with an LVAD or a BiVAD.

11 In looking through the data, I am  
12 harboring a concern that there is a price in terms  
13 of post-procedure risk that the patient who gets  
14 the total artificial heart pays over what the  
15 patient who gets an LVAD pays. I think this is  
16 related to the thromboembolic risk and related to  
17 the bleeding risk.

18 It is hard to be certain about this  
19 because of the nature of the trial design, and one  
20 has to look at published literature, and so forth,  
21 but looking at the published literature, it appears  
22 that the thromboembolic event rate in the  
23 population that was reported here appears to be  
24 higher than, say, those that are reported with some  
25 of the LVAD devices, at least in the literature.

1           Similarly, the implant bleeding and also  
2 the post-transplant bleeding frequency also seems  
3 to be higher. I think this is all plausible since  
4 this is a device with mechanical valves rather than  
5 biological valves, and because of the requirement  
6 for aggressive both antiplatelet and anticoagulant  
7 therapy that these patients require.

8           What I would like to ask from the people  
9 who have the experience with this device is, is the  
10 patient paying a certain price in terms of  
11 thromboembolic and bleeding risk to receive this  
12 device compared to the risk that the patient would  
13 be exposed to if they received a conventional LVAD.

14           DR. COPELAND: Why don't we start first  
15 with the stroke part of your question. As I  
16 understand it, it's a two-phase question. One is  
17 directed at stroke and the other is at bleeding.

18           DR. HIRSHFELD: But stroke, when I use the  
19 term "thromboembolic," I was summing the events  
20 that were reported as frank strokes, which I  
21 believe were 11, but there were also 9 events that  
22 were reported as thromboembolic events, so all  
23 together there are 20 systemic embolic events that  
24 occurred in the patient population.

25           DR. COPELAND: At any rate, we will start

1 with stroke. Admittedly, that doesn't cover the  
2 peripheral thromboembolism, but we do have the data  
3 from the literature on stroke from some fairly  
4 notable authors.

5           Go back to the last slide, please, S6,  
6 please.

7           [Slide.]

8           These are comparative stroke rates with  
9 other devices reported in the literature. You  
10 recognize the names, I am sure. Dr. DiBella is an  
11 Italian surgeon. Manami is from Bad Oeyenhausen.  
12 Aly El-Banayosy is from Bad Oeyenhausen, is here  
13 today.

14           These are the various LVADs and BiVADs  
15 that are out there. I would just point out that  
16 your assertion that our rate is higher is  
17 incorrect. For instance, this is one of the more  
18 commonly used left ventricular assist systems, the  
19 stroke rate reported at 59 percent, and these are  
20 strokes, these aren't anything less than strokes.

21           Some of the other supposedly less  
22 thrombogenic LVADs, for instance, reported by  
23 Frazier, 12 percent. The SynCardia result was 10.5  
24 percent; Banayosy, 20 percent. The Manami, with an  
25 LVAD, 16 percent, and so forth. So, you see

1 certainly it is not higher, and I guess you would  
2 have to say reading this column that it is lower  
3 than every other percentage shown from the  
4 literature that was chosen for us by the FDA to  
5 review.

6 Let's go on to P81, please.

7 [Slide.]

8 Now, this is the multifactorial slide that  
9 looks at various adverse events including  
10 infection, bleeding, and stroke, and it's a  
11 combined stroke and TIA column, so it's a little  
12 higher. This time it's 12.6 instead of 10.5 for  
13 the CardioWest, but let's turn our attention to  
14 bleeding.

15 One of the most recent reports that came  
16 out on one of the least thrombogenic LVADs that is  
17 available today, the bleeding, and this was either  
18 takeback or death, was 51 percent. We had an  
19 incidence of 37 percent total bleeding, and our  
20 takeback was 28 percent. We had 2 deaths. If you  
21 add that together, that is 30 percent. That is  
22 still nowhere near 51 percent.

23 The other numbers, again if you read them  
24 carefully, we are towards the bottom of the pile in  
25 this adverse event for bleeding.

1 DR. HIRSHFELD: I think I agree with  
2 everything that you put up there. I think it is  
3 hard to be certain that there is definitional  
4 comparability across all of those definitions.

5 DR. COPELAND: I can tell you for sure on  
6 the bleeding and death for the LVAD that was just  
7 reported and just passed by this panel, the  
8 bleeding was 51 percent, and that is takeback plus  
9 death. It was quite a surprise to me when I read  
10 the article.

11 DR. TRACY: Dr. Hirshfeld, any other  
12 questions?

13 DR. HIRSHFELD: No.

14 DR. TRACY: Dr. Kato.

15 DR. KATO: I share some of the concerns by  
16 the other panel members today. One of those is  
17 that I think that the idea that this device can be  
18 put in by transplant centers is a recommendation or  
19 as suggested by the company is a little bit too  
20 soft.

21 I think the practical application, at  
22 least what I have seen in the field, unfortunately,  
23 has been situations where even left ventricular  
24 assist devices are being placed in facilities that  
25 do not have transplant capability and oftentimes

1 put in for poor or sometimes even perverted  
2 indications, such as just to avoid a mortality.

3           So, I think that from my perspective, I  
4 would feel much more confident in the company if  
5 the company would say that this device would only  
6 be put in at transplant centers, and not just this  
7 is the intention that it will go in, but it must be  
8 there in print. Again, that is my opinion.

9           Number 2. I am concerned also a little  
10 bit about the distribution of patients primarily  
11 being performed at Tucson, Arizona. I have no  
12 problem obviously with the quality of the surgeons,  
13 but I am a little bit concerned that 60 percent of  
14 the patients who underwent implantation of the  
15 device was the same institution where the device's  
16 technology is originating from.

17           There are four other esteemed transplant  
18 centers that use this device relatively  
19 infrequently. I would like to have some  
20 explanation for that, if possible.

21           DR. COPELAND: In answer to that, I would  
22 say that some of this is based upon history and the  
23 way things happened wasn't exactly in our control,  
24 but it is just the way things happened. To be more  
25 specific, the device was acquired by our hospital,

1 University Medical Center.

2 As you can imagine, they were quite  
3 enthusiastic and it wasn't so much being a case of  
4 enthusiasm as it was they weren't preventing us  
5 from using the device as we saw fit, as many  
6 hospitals do now, as well as insurance companies.

7 We enjoyed a period of time in about the  
8 mid-nineties of use of this device without external  
9 restraint either financial or administrative, that  
10 may not have been enjoyed at other centers, who  
11 were faced with other administrators and other  
12 financial constraints.

13 I think the whole issue of how it happened  
14 is a very complex issue, and that is just part of  
15 the story, but I think it's an important part of  
16 the story, and I think that the other part of the  
17 story is that you need to rely on some of these  
18 other surgeons here and their expertise with  
19 respect to how generalizable the use of this device  
20 can be.

21 I want to ask Dr. Long if he could come  
22 and comment on that at the present time.

23 DR. LONG: I think there are two ways to  
24 look at the expertise that is required to do this  
25 and whether it is reproducible in other centers.

1 One is the hands-on technical side of this, can it  
2 be executed surgically in the operating room.

3 It is my opinion that anybody who can  
4 handle a complex LVAD implantation should well be  
5 able to handle this from a technical point of view  
6 with appropriate training.

7 I think there is a second element of this,  
8 and that is what is demanded of expertise in the  
9 event you made a choice to put an LVAD in, but  
10 really needed a biventricular support device, and  
11 actually could have gotten through the experience  
12 much easier with biventricular support device,  
13 when, in fact, you had an LVAD in place, but then  
14 now have a very complex, difficult management  
15 problem on your hands.

16 I believe the expertise there goes way  
17 beyond just surgical expertise. There is a great  
18 deal that is involved in terms of assessing the  
19 appropriate timing for right ventricular support.  
20 There is a great deal of expertise for timing of  
21 withdrawal of right ventricular support as the  
22 right ventricle recovers, and that expertise is  
23 extreme.

24 Therefore, I think that it is in some way  
25 perhaps counterintuitive, but very possible that

1 the implementation of support with biventricular  
2 support actually makes the course of the patient  
3 going through this experience easier and less  
4 demanding.

5           Therefore, I believe it is no more  
6 demanding to put these technologies in than it is  
7 to be a center that gets good results with a left  
8 ventricular assist device, but I would concur with  
9 the assessment that this really is still high  
10 maintenance technology from both the surgical point  
11 of view, but also a perioperative management point  
12 of view, and have been a proponent of careful,  
13 guarded dissemination of this in the field,  
14 believing that it needs to start with Centers of  
15 Excellence.

16           DR. KATO: I guess my question really  
17 wasn't aimed at questioning how the technology can  
18 be disseminated, but in this day and age of  
19 disclosure and conflicts of interest which we are  
20 reading about in the newspapers every day, you  
21 know, we have heard from the faculty at the  
22 University Medical Center that you do have an  
23 equity interest, on the other hand, Dr. Long at LDS  
24 Hospital does not.

25           So, my question is in follow-up to Dr.

1 Yancy's question before was is there a substantial  
2 equity interest at Loyola, St. Luke's Medical, or  
3 University of Pittsburgh, which could have  
4 influenced the numbers of implants that were  
5 placed.

6 DR. COPELAND: Let me repeat there was no  
7 financial interest in this company, or there wasn't  
8 even a company, SynCardia did not exist until 2002,  
9 when this study was over. So, there was no  
10 conflict of interest existed, because there wasn't  
11 any conflict until 2002 when University Hospital  
12 dropped the technology, and in order to keep it  
13 going, a company had to be founded. So, that is  
14 when the equity part started, but it was after the  
15 study was done.

16 The answer to the rest of that is no, no,  
17 and no, in none of the centers does anyone have any  
18 equity in SynCardia.

19 DR. KATO: Thank you. One final question.  
20 What are you going to do with the patients who say,  
21 gee, you know, they get the artificial heart, and  
22 they are in that small group of patients who kind  
23 of formed a symbiosis with it, actually doing  
24 pretty well, and they go, gee, you know, I don't  
25 want to subject myself to a 10 percent mortality of

1 heart transplant, what are you going to do then?

2 DR. COPELAND: There has never been that  
3 kind of a case in our experience. There has been  
4 one that I know, at least one in Paris, and in  
5 Paris, they have implanted approximately 200 to 250  
6 of these devices. In Bad Oeyenhausen, they have  
7 implanted something like 45, and they just started  
8 a couple of years ago.

9 But in that one case, they just kept the  
10 patient in the room in the hospital and allowed her  
11 to have daily trips out to her hairdresser and the  
12 bakery and the boulangerie, she lived for 623 days  
13 and died of a ruptured mycotic aneurysm.

14 I think that when you put in a total  
15 artificial heart or any artificial device, you have  
16 to have an understanding with the patient before  
17 you do it as to what is going to happen under  
18 various circumstances, what do they want to have  
19 happen, and I think we are able to adapt to just  
20 about anything in these modern times.

21 DR. KATO: Thank you.

22 DR. TRACY: I just have a couple very  
23 quick questions. On your Slide P88 TAH candidate,  
24 one of the criteria that is listed there is  
25 unresuscitatable cardiac arrest. Where I come

1 from, we call them dead people.

2 DR. COPELAND: Slide up, please.

3 DR. TRACY: How do you envision that  
4 working?

5 DR. COPELAND: The English in that could  
6 be a little bit better, couldn't it. It sort of  
7 states the same thing twice. It is somebody that  
8 is still having a cardiac arrest.

9 This scenario has happened many times  
10 actually, has happened many times in the candidate  
11 group, a patient has been selected for transplant,  
12 is deteriorating, comes into the hospital, has a  
13 cardiac arrest.

14 While he is having the arrest, he is put  
15 on an ECMO system or a CPS system, is then taken to  
16 the operating room and has a total artificial heart  
17 implanted. So, this is I think a not too uncommon  
18 indication.

19 DR. TRACY: And neurologic survival in  
20 these people?

21 DR. COPELAND: All of the ones we have  
22 done, to the best of my knowledge, there have been  
23 two deaths. One died who was being resuscitated on  
24 the way to the way to the operating room, still  
25 being resuscitated with cardiac compressions,

1 external compressions.

2           The other is a patient who was  
3 resuscitated with an ECMO pump and had a device put  
4 in, and it was discovered on the first post-op day  
5 that she had a major cerebral hemorrhage, and she  
6 died.

7           The others that I am aware of, and I think  
8 there were something like 15 or 17, and most of  
9 those are those types of scenarios for getting into  
10 the study, did fine.

11           DR. TRACY: Mr. Corbet made an interesting  
12 comment at the beginning that he had a picture of I  
13 believe it was five people that were on the device  
14 at the same time he was, which to me implies five  
15 consoles. Am I correct in that assumption?

16           DR. COPELAND: Yes, it is a picture of a  
17 cluster of consoles.

18           DR. TRACY: Would that be the expectation  
19 that a center that would take on this technology  
20 would have to have more than one console available?

21           DR. COPELAND: Yes, they would have a  
22 minimum of two, and always have a surplus of one.

23           DR. TRACY: The other data that is absent  
24 here is the gender of the recipients, and I take it  
25 I am not a candidate for this device. Is that

1 correct, are they 100 percent male?

2 DR. COPELAND: No, they are not.

3 Please put up B1. I think this has it.

4 [Slide.]

5 You can see that 86 percent of the core  
6 patients were males. So, we did have quite a few  
7 females.

8 DR. TRACY: Just holding the device up  
9 next to my chest, I don't think it would fit. It  
10 is big. I would assume that there are plans to  
11 make it smaller, so that it would have a greater  
12 applicability for a greater diverse size of  
13 patients.

14 DR. COPELAND: There are plans for that.  
15 They are not at the highest priority, but let me  
16 say this. I went to the transplant picnic on  
17 Saturday. I met a lady, Mrs. J., we will call her,  
18 about that tall, a very small, beautiful, pleasant  
19 lady of about 60, who had this total artificial  
20 heart implanted, and I think she had it for around  
21 six months, five or six months, so that it is not  
22 simply body surface area or the diameter of your  
23 chest from anterior to posterior at T10, or the end  
24 diastolic dimension on Echo, or the cardiothoracic  
25 index, it is either how big your heart is inside

1 your chest or how big you are.

2           It is a combination of things that  
3 determines whether or not this device can be  
4 implanted, so smaller people with very large  
5 hearts, such as chronic dilated cardiomyopathies,  
6 who are often slight of body size can actually have  
7 this device implanted.

8           DR. TRACY: Thanks.

9           Dr. Ferguson.

10           DR. FERGUSON: I want to also thank the  
11 sponsors for a beautiful presentation, very clear,  
12 and I only have a comment or two, and some  
13 questions.

14           The comment relates to comparing LVADs to  
15 BiVADs, and BiVADs to this technique. I work, and  
16 I don't do this work anymore, but I work at a small  
17 country clinic in the Midwest, and the difference  
18 between an LVAD, which are hard enough to put in, I  
19 agree with that, and monitor, and so forth, is a  
20 quantum leap from an LVAD to a BiVAD.

21           So, I don't think personally that the  
22 comparisons that are made with the LVAD really are  
23 applicable or should be applicable. The reason I  
24 am saying that and getting to it is because I am  
25 very, very impressed, I think the most impressive