

1 outcome and there were no strokes reported but four
2 of 49 patients had transient ischemic attacks.

3 So we will put the questions up when they
4 are ready.

5 DR. ZUCKERMAN: Dr. Tracy, could we just
6 have clarification, in Question 1, perhaps of Part
7 c. In 1a, the sponsor chose a surrogate variable,
8 closing the hole instead of a primary efficacy
9 outcome of reduction in strokes that was clear.
10 That clearly, perhaps, could be demonstrated.

11 Are there any surrogate variables that the
12 panel might suggest instead of reduction in stroke?

13 DR. TRACY: I have the feeling that
14 reduction in stroke is really critical. I would be
15 interested--Dr. Marler, do you have a comment
16 there?

17 DR. MARLER: I think that the Homus(?)
18 study and the Mas study both bring into question
19 the link in the mechanism between the PFO existence
20 and the occurrence of subsequent strokes, so that I
21 think the usual argument for a surrogate outcome in
22 this case breaks down when those studies are
23 considered. So I think there is enough question
24 there about the link between the occurrence of
25 closure of the PFO or other potential nonclinical

1 outcomes that it would be important that a
2 surrogate would probably be very difficult to find
3 or to justify here.

4 DR. TRACY: The other comment is that I
5 don't think it is fair to any sponsor to have to
6 prove mechanism, but there does need to be
7 comparison. I think that is what is lacking. I
8 think stroke is the critical thing that we are
9 trying to reduce.

10 I don't think that this cohort was a
11 hemodynamic question. I don't think that was the
12 issue here, so I think, no, there isn't another
13 appropriate subgroup.

14 Any other comments on those?

15 DR. COMEROTA: Would it be appropriate,
16 though, to include other events as primary efficacy
17 outcomes, a group of events or the absence of a
18 group of adverse events such as arrhythmias, such
19 as other embolic events besides stroke,
20 procedurally related adverse events versus adverse
21 events occurring in those patients without the
22 procedure.

23 DR. TRACY: Those are good points. I
24 think that, obviously, to look for any--and I do
25 believe they did look for or at least have some

1 screening assessment, whether there were other
2 clinically relevant embolic events. That is
3 obviously something that should be sought.

4 The arrhythmia is a little bit more
5 difficult question because I am not sure how well
6 the screening pre-procedure was carried out to
7 determine whether arrhythmia was part of the
8 pathogenesis. Also, there was a mixture of people
9 where there may have been hemodynamic reasons for
10 development of atrial fibrillation that would not,
11 obviously, be relieved after years of ongoing
12 hemodynamic challenge. So it may be part of the
13 nature of the disease process that these people
14 would develop atrial arrhythmias post-operatively
15 and not necessarily a reflection of a device
16 complication.

17 So I am not sure that sure that--I think
18 it needs to be noted but I don't think it needs to
19 be considered an endpoint.,

20 DR. COMEROTA: One of the obvious problems
21 is that the efficacy endpoints are retrospective
22 and identifying an efficacy endpoint which is
23 retrospective and not having evaluated for it,
24 because these patients were not evaluated for
25 neurologic deficit. If it was reported, that's

1 fine. But we know that in procedures that carry a
2 risk of neurologic events, that, when they are
3 searched for, you are going to find many more than
4 when they are reported by the primary operator.

5 DR. TRACY: So whatever post-procedural
6 screening is done needs to be of the same rigorous
7 nature as the pre-procedural screening for events
8 and clear identification of definite, or as
9 definite as possible, evidence for embolization; is
10 that fair? Okay.

11 We will move on to safety questions. No.
12 2; no prespecified outcome measures were provided
13 for assessment of safety. The primary safety
14 outcome was assessed by evaluating the number of
15 patients who experienced serious, or moderately
16 serious, device implantation or catheterization
17 adverse events.

18 27 percent experienced a serious or
19 moderately serious adverse event. These events
20 were further categorized as related to device,
21 seven of those, or related to the implantation
22 catheterization procedure, six of the
23 complications. There were no patient deaths or
24 strokes during follow up.

25 Question 2a: Please discuss the use of

1 serious and moderately serious adverse events that
2 were definitely, probably or possibly related to
3 the device implantation or catheterization
4 procedure as the primary safety outcome measure for
5 assessment of the clinical benefit versus risk.

6 I think that this is a little bit tied in
7 with the discussion about part a; safety, I think,
8 has to be assessed procedurally and I think that
9 those categorizations are appropriate for
10 procedural safety outcomes and I do believe that
11 the data safety monitoring committee did a good job
12 at looking at those events.

13 However, I think that the committee has
14 expressed concern that the true safety of the
15 device may not be totally evaluated by the
16 procedural outcome.

17 Comments?

18 We will move to 2b, then: Please discuss
19 whether the echocardiographic evaluation and
20 clinical evaluation, including the definitions for
21 occurrence of neurologic events, allow adequate
22 assessment of device-related clinical events.

23 I think you just heard from the panel that
24 the answer to that is no, that more detailed
25 pre-procedural and post-procedural evaluation would

1 have been required. Is that clear enough. Okay.

2 DR. CARABELLO: Also, we had seven
3 patients included for just the closure of the shunt
4 for oxygenation purposes. I think if we are going
5 to continue to have that as a subset of this group
6 of patients, stroke isn't involved here. Rather,
7 hemodynamics are. I think a much more complete
8 analysis of what this does to their hemodynamics is
9 important.

10 DR. TRACY: That is a good point. So
11 hemodynamic assessment, particularly depending on
12 what the initial indication for implantation, a
13 hemodynamic assessment would be critical.

14 2c: Please discuss whether adequate
15 information has been provided to allow assessment
16 of the risk of recurrent cryptogenic stroke versus
17 the risk of device-related neurologic events.

18 I am not sure how to tease those two
19 things apart. Somebody help me.

20 DR. BAILEY: You need more time and you
21 need more events, neither of which are available.

22 DR. TRACY: Okay. Fair enough. Other
23 comments?

24 DR. COMEROTA: This sort of involves the
25 issue of design of a trial. Isn't there precedent

1 for trials that have multiple confounding variables
2 in which you are looking at a specific treatment or
3 a procedure-related outcome, especially, as has
4 been addressed by the representatives or their
5 experts, that treatment tomorrow may be different
6 than treatment today?

7 I think precedents have been set for
8 trials like that. If you offer best medical care
9 plus best medical care in addition to your device,
10 then you will begin to get the answer as to the
11 impact of your device on outcome.

12 So I think that folds into that question.

13 DR. TRACY: That is a good point. So it
14 makes it very difficult to follow the
15 post-procedural neurologic events since treatment,
16 best medical therapy, varied throughout the patient
17 population. So it is not really comparable.

18 Dr. Vetrovec?

19 DR. VETROVEC: One thing that still
20 bothers me is there kind of isn't a matching of the
21 events for a patient that got him into the trial to
22 whether or not--if they had an event after the
23 device was implanted. It still bothers me that
24 four events were called nonsignificant,
25 essentially, when we don't know that they weren't

1 the same events that were called significant to get
2 them into the trial.

3 So I think there needs to be a matching of
4 these events particularly when you have so many
5 small events.

6 DR. TRACY: That's a good point.

7 Question 2d: Please discuss whether
8 adequate information has been provided to
9 characterize the appropriate post-device placement
10 antiplatelet regimen duration and single versus
11 combination therapy or anticoagulation regimen
12 duration and target INR.

13 I think you have heard pretty clearly that
14 no, that wasn't adequately covered.

15 DR. PINA: However, I think that they may
16 have enough data as they continue to collect follow
17 up on these patients that they may be able to
18 figure out what works and what doesn't work and
19 recommend a reasonable plan of either antiplatelet
20 or warfarin follow up.

21 Someone made the good point that there are
22 other agents that will be coming into the market
23 that may be quite valuable and they may want to
24 consider that as they accumulate more follow up.

25 DR. TRACY: I think that is important and

1 that is a difficult piece moving forward since
2 there are other therapies coming out. I think it
3 is just important that some standard be set to
4 attempt to adhere to, and that was not the case
5 here in this protocol.

6 We will move on to Question 3: Please
7 comment on the lack of a prespecified control
8 group, prespecified outcome measures and
9 prespecified sample size.

10 I think it makes it extremely difficult to
11 analyze this device in terms of its comparison to
12 what; to the general population, to people with
13 PFOs, to people who have had surgery. It just is
14 very difficult to know what exactly it is that you
15 are comparing with.

16 I note that it took a long period of time
17 to accrue this number of patients so I don't think
18 we are ever going to have the hundreds of thousands
19 of patients available to get all of the answers
20 that are needed, but I think, with a small group
21 and a well-designed study, you probably could come
22 up with some more definitive answers than I think
23 we have right now.

24 Dr. Marler?

25 DR. MARLER: The lack of a clear

1 inclusion/exclusion criteria that relate to the
2 indication that is being asked for I think was also
3 part of the problem. I don't know if that is part
4 of the answer to the question, but the other
5 questions implied in Question 3 would be much
6 easier to answer if the study population were more
7 clearly defined and that were more closely related
8 to the indication requested.

9 DR. TRACY: Yes. That needs to be stated
10 somewhere that the trial suffers, or the study
11 suffers, from not having clear entry criteria.

12 No. 4: if you believe that the data
13 presented today are inadequate to support safety
14 and effectiveness, please address the following
15 questions.

16 4a: Please clarify if additional analysis
17 of the current dataset could be performed to
18 provide adequate information to support safety and
19 effectiveness.

20 I think not. It is my impression that we
21 will need some additional patients with more
22 clearly defined entry criteria and more clearly
23 defined and probably completely different primary
24 safety-and-effectiveness outcomes. I don't think
25 that additional analysis of the current data,

1 unless there is information--at least, what we have
2 been presented at panel today, I don't think we can
3 come to the answers that we need.

4 Question 4b: Please clarify if the
5 collection of additional data using the current
6 patient selection criteria and outcome measures
7 would be appropriate to support safety and
8 effectiveness. I think, again, similar answer; no,
9 because we are having concerns about what the
10 selection criteria really are and questioning
11 whether the primary outcome endpoints are the
12 correct ones.

13 Question 4c: this is a big one.
14 Alternatively, if you believe that a new trial is
15 required, please address the following
16 clinical-trial-design questions, sub i. Given our
17 current understanding of the causal relationship of
18 the presence of PFO and stroke, presumed
19 paradoxical embolism, please discuss whether a
20 randomized trial is necessary to evaluate safety
21 and effectiveness. If so, can a randomized trial
22 be completed at this time and, part ii, what is the
23 appropriate control group?

24 Let me take a stab at this. I think that
25 the current understanding of the causal

1 relationship with the presence of PFO in stroke is
2 not very well understood, that there is some
3 question about cause and effect here which I do not
4 think a sponsor or corporation needs to answer
5 that. I think what they do need to do is to show
6 tangible comparability of their device with
7 something else and some defined benefit, or benefit
8 to their device, and lack of major adverse outcome
9 related to the use of the device.

10 So, while I think it is not--there have
11 been ethical questions raised whether it is
12 appropriate to randomize people to no device or
13 surgical therapy versus best medical therapy,
14 obviously, you can't do that if you truly believe
15 that people have failed best medical therapy.

16 I am not sure that that is really the
17 concern here. I think the concern is more the
18 definition of how you got into the study and what
19 the endpoints were, so I don't necessarily think
20 that you need to--I don't think that you
21 absolutely necessarily need to go back to a
22 comparative study with a control group.

23 But, there are historic controls that I
24 think would be, perhaps, more appropriate than what
25 was presented here. I would be curious to see if

1 the other panel members agree with that.

2 DR. ZIVIN: I would think that most of us
3 believe that aspirin or warfarin is appropriate
4 therapy for this group of patients and so that the
5 only fair comparison would be that and having a PFO
6 closure device added on, randomized with and
7 without.

8 DR. TRACY: So best medical therapy versus
9 best medical therapy plus device. That is well
10 said.

11 DR. AZIZ: The other thing; I don't know,
12 but, for example, each patient could be his own
13 control if there was a way of documenting, for
14 example, by TCD or so that you were getting hits or
15 blips, whatever therapy you were on before.
16 Whatever reason you intervene, you put the device
17 in and then follow that patient for a period of
18 maybe six months or two or three years.

19 One, obviously, could be that your TIAs
20 and stroke decrease. The other thing, if there was
21 some measurable quantity like hits on TCD--I am not
22 saying that it is--that that changes, so you have
23 something to measure the patients, intervention in
24 the patient against his own standard.

25 DR. TRACY: Okay.

1 DR. BAILEY: It seems to me that a
2 randomized trial here would actually address the
3 causality question once and for all.

4 DR. TRACY: Between a randomized trial of
5 best medical therapy versus best medical therapy
6 plus device?

7 DR. BAILEY: Yes; if you showed an
8 improvement in stroke risk with the hole plugged,
9 it is hard to think of any other explanation.

10 DR. MARLER: I am always doubtful that
11 there isn't, after a trial is done, a way to think
12 past almost any mechanism. So I would continue to
13 focus on the efficacy and, if the clinicians think
14 that they can select a group that is at a high risk
15 of stroke and the PFO is as effective as you would
16 think it would be if the proposed mechanism is
17 true, then it seems that a randomized trial is
18 conceivable and could be practical, depending on
19 the sample size and how that works out.

20 I agree that I think it could be done
21 ethically.

22 DR. WHITE: But could it be done ethically
23 in patients who have not had an event, patients who
24 are discovered to have an asymptomatic PFO, or
25 would you require that the patient have an index

1 symptom for stroke?

2 DR. MARLER: I think that gets back to
3 your initial selection criteria. We are hearing
4 two things. We are hearing that the clinicians
5 think that they can select a high-risk group but it
6 is not really clear to me what that high-risk group
7 is and that that is really who they want to use
8 this procedure in rather than a broader group of
9 patients who have just had a stroke and happen to
10 have a PFO.

11 I don't know if I am answering your
12 question.

13 DR. WHITE: Do you see any role for
14 randomization in an asymptomatic PFO? Is there any
15 role for a device closure to prevent stroke in an
16 asymptomatic PFO?

17 DR. MARLER: No; I don't, not at this
18 time. I would think you would want to go first
19 with the symptomatic. The asymptomatic, the risk
20 is much lower and most preventive therapies have to
21 have a very low risk if they are going to be
22 effective over a decade or more.

23 So I would say, if I understand your
24 question, at least as a first step, I wouldn't take
25 asymptomatic patients because the event rate would

1 be so low.

2 DR. AZIZ: And over 25 percent of patients
3 have PFO.

4 DR. CARABELLO: Right. We have millions
5 of people. We have 20 percent of the people in
6 this room with PFOs. We are not going to--I am not
7 volunteering. The event rate would be so tiny in
8 that group of patients, it would take a huge sample
9 size to prove benefit.

10 DR. LAZAR: For this group, it is high
11 risk, and high risk is defined by the current or
12 previous strokes.

13 DR. WHITE: But, yet, in this population
14 of patients that were asymptomatic, I think
15 asymptomatic patients, or people without strokes,
16 were in the cohort, the primary cohort.

17 DR. MARLER: That's correct. Do you mean
18 with the shunt?

19 DR. WHITE: Is that not true, they all had
20 a stroke?

21 DR. LAZAR: Every patient but one, I
22 think, had a stroke.

23 DR. WHITE: All of the 49 patients had a
24 stroke? Is that right?

25 DR. MARLER: No; seven did not.

1 DR. JENKINS: I think 42 of the 49 had had
2 prior events. They were not all strokes.

3 DR. WHITE: So they could have been a TIA
4 or--

5 DR. JENKINS: That's correct.

6 DR. LASKEY: But, again, let's remember
7 the terminology here. What I heard in answer to my
8 question was this was high-risk for surgical
9 correction, not high risk for recurrence of a CNS
10 event. That is a different issue. Along the lines
11 of that issue, this is a relatively infrequent,
12 unpredictable event.

13 How you would time model that and how you
14 would predict the length of time required for time
15 to a first event, I don't know. I would be
16 interested to hear from some of the biostat people
17 how you would go about planning on looking for the
18 likelihood of a recurrent event given what we know
19 about recurrent events, that they are rare and can
20 occur out to a lengthy time interval. You would be
21 looking for years.

22 DR. TRACY: Dr. Zuckerman?

23 DR. ZUCKERMAN: I guess the problem that
24 the agency and sponsor have is we have heard the
25 benefits of a randomized trial. But, in this

1 patient population presented today, the event rate
2 was still relatively low. So the calculation of a
3 sample size in this type of population is going to
4 be rather large.

5 Is there any panel opinion on how we can
6 better pick this high-risk patient population in
7 order to more clearly show a demonstrated benefit
8 with a reasonable sample size? Who are these
9 patients who we could best demonstrate
10 effectiveness?

11 DR. TRACY: I think that likely there were
12 the right people included here. The problem is
13 that it wasn't the--that term "high risk" has been
14 used in a variety of manners here. It is high risk
15 for surgery.

16 I think that the occurrence of the
17 cryptogenic stroke or multiple neurologic or
18 embolic events is an appropriate entry criterion to
19 this study and I think that if you set the study up
20 correctly, had randomized between best medical
21 therapy versus best medical therapy plus device
22 with a standardized follow-up anticoagulation or
23 antithrombotic regimen, that it would not take--I
24 am am not a statistician, but I don't think that it
25 would take an enormous number of people to achieve

1 an appropriate endpoint.

2 So I can't tell you what that number would
3 be, but maybe Dr. Bailey can, or somebody else.

4 DR. BAILEY: Obviously, it depends on the
5 proportion of these cryptogenic strokes that are
6 due to the PFO.

7 DR. MARLER: The data from the WARSS study
8 indicate that these events are not rare, at least
9 maybe 13 percent is considered rare, but in the
10 stroke world, that is not that rare. Those trials
11 that test aspirin that involve a thousand or more
12 patients are looking for a very small treatment
13 effective. In this case, you have it already
14 established that, I think compared to aspirin, the
15 device intervention, itself, has a little bit--a
16 considerable risk, or it is certainly inconvenient.

17 What you are looking for is a very much
18 larger treatment effect. So, what you are looking
19 at is, in unselected patients with PFO who have
20 previously had a stroke of the so-called
21 cryptogenic variety, 13 percent of them, in two
22 years, should have a stroke.

23 If you include the PFO and you are
24 predicting a very large treatment effect, I don't
25 think the trial comes out in the thousands of

1 patients or certainly not in the hundreds of
2 thousands that I have been hearing about.

3 DR. ZUCKERMAN: Right. The problem,
4 though, is with the WARSS data that you are
5 quoting, I believe the median age is much older
6 than the patients in this cohort today. It is
7 those types of suggestions--

8 DR. MARLER: But, again, the argument I
9 heard from Dr. Futrell others was that these
10 younger patients are at even higher risk.

11 DR. ZUCKERMAN: But we didn't see that in
12 the data presented. We saw relatively low event
13 rates.

14 DR. TRACY: So I think a redesigned trial
15 identifying patients that are at high risk and then
16 comparing them to the endpoint of the study. Part
17 of it in terms of the safety is just a comparison
18 with best medical therapy and that does include the
19 procedural events.

20 I think with screening for appropriate
21 high-risk patients, again, and perhaps that does
22 mean extending it into an older population, I just
23 don't see this taking hundreds of thousands of
24 people.

25 Dr. Pina?

1 DR. PINA: I would like to add to that
2 screening this hypercoagulable state which I agree
3 with the hematologists is very much underestimated.
4 If we are talking about a younger population, it
5 certainly, I think, would pay to screen those
6 patients for hypercoagulable states, at
7 least--where is the hematologist back here? There
8 are, from what I understand, about five blood tests
9 that are the most common of the clotting disorders
10 in these young people that can certainly be used as
11 an additional screening for high-risk individuals
12 in that younger group, aside from the older group
13 that may have a lot of other risk factors like
14 coronary disease or like atrial fibrillation.

15 DR. VETROVEC: It seems to me that Dr.
16 Zuckerman's question was maybe different than what
17 we have been trying to answer. Did you not ask how
18 would you pick a high-risk population that is
19 likely to have an event if you don't do something?
20 Isn't that what you are looking for? Did I
21 understand you correctly?

22 DR. ZUCKERMAN: No. We are talking about
23 the issue of trial design. The panel has suggested
24 that the most appropriate way would be to perform a
25 randomized trial. The sponsor has previously

1 indicated, for a variety of reasons, that the
2 sample size might be very large.

3 But one of the ways to get a reasonable
4 sample size in a randomized trial and show proof of
5 principle is to select the appropriate population
6 with a high event rate such that if the device is
7 effective, it will be clearly seen. We are trying
8 to better discern who those inclusion/exclusion
9 criteria could be such that we could get to the
10 bottom of it.

11 DR. VETROVEC: It seems to me there are
12 some populations that you could look at including
13 the ones with atrial septal aneurysms. That would
14 clearly increase your risk rate. You could take
15 people that had an anticoagulation problem that you
16 couldn't do. You could select out. I think if you
17 stayed under age 55, which has been shown in some
18 of the previous studies to identify the people that
19 are more likely to have strokes related to this
20 problem, then you would be identifying a population
21 that is likely to show you a difference.

22 DR. TRACY: So I think we are getting to
23 an answer. I will let the other members comment
24 briefly, but the answer probably is that there is a
25 way to identify a higher-risk group with, perhaps,

1 a more specific anatomic definition of what the
2 defect looks like, perhaps screening for
3 hypercoagulable states, perhaps moving to a
4 slightly older yet not elderly population for
5 inclusion into the study.

6 Just a couple other brief comments here?

7 DR. BECKER: I was just going to echo, if
8 you really want to show proof of principle, take
9 somebody who is a high risk for DBT with a
10 hypercoagulable state. Those patients should then
11 be at greater risk of paradoxical emboli.

12 In addition, you could take somebody who
13 has already had at least two events which would,
14 theoretically, make them at high risk for a third
15 event.

16 DR. TRACY: Dr. Zivin?

17 DR. ZIVIN: The paper by Mas that you
18 presented to us really provides all of the
19 information that I believe that you are asking for
20 because it is dealing with patients who are between
21 18 and 55. They followed them for a four-year
22 period. They found that patients with both the
23 aneurysm and the PFO had a recurrent stroke-risk
24 rate of 15 percent over that four-year period which
25 is approximately four times higher than the risk

1 rate of people who had PFO alone.

2 When you get up to those types of numbers
3 in a patient group of that age, I think you have a
4 reasonable group which you could use as a basis for
5 the type of study that you are proposing to do.

6 DR. WHITE: Could that data be used as an
7 objective performance criteria so that, instead of
8 a randomized trial, that you could enroll a group
9 of patients comparable to Mas, treat them and look
10 at the outcome and, if you beat them by a certain
11 number, would this panel accept that kind of
12 evidence?

13 DR. ZIVIN: I am always dubious of doing
14 those types of studies. I suppose you could get
15 away with that but, the truth of the matter is,
16 these patients are not that rare. So it would be
17 possible to find a reasonable group and all you
18 would do is cut the cost of your trial in half if
19 you did it the way you suggested.

20 DR. BECKER: I think it is important to
21 point out in the Mas study they also screened for
22 hypercoagulable states so there are probably a set
23 of patients who are even higher risk if they had a
24 hypercoagulable state on top of that.

25 DR. LAZAR: When you say recurrent events,

1 you mean they have had previous cryptogenic stroke?

2 DR. CARABELLO: But, just to reiterate Dr.
3 Aziz' approach, another way around this in terms of
4 handling the sample size is to increase the
5 sensitivity for event rates by using a variety of
6 imaging techniques so that, rather than demanding
7 that, to qualify that the guy can't move his right
8 side, I think that I would--if you showed me a
9 difference in, let's say, the new CT defects or
10 some such surrogate, that that would be pretty good
11 evidence that the thing was working.

12 DR. TRACY: We will move on to the next
13 question which I think we have, in part,
14 anticipated: Please discuss whether adequate trials
15 can be designed with historic controls or objective
16 performance criteria.

17 I think that there needs to be some
18 control within the study of treatment versus
19 something else because historic controls are never
20 going to be quite appropriate to whatever patient
21 population is being studied. I think you have to
22 be comparing apples to apples. I think this can be
23 done appropriately without enlarging the patient
24 population necessary to such an enormous extent.

25 So I don't think we can rely on other

1 types of controls.

2 Based on the type of study design
3 proposed, please address the following issues.

4 Please characterize the appropriate patient
5 population for study enrollment. I think we have
6 had a good deal of discussion on that and I think
7 we have some references that point in the direction
8 of what might define a high-risk patient
9 population.

10 Please discuss the appropriate primary and
11 secondary outcomes measure for evaluation of
12 effectiveness and safety. As part of this
13 discussion, please comment on the use of clinical
14 versus surrogate endpoints.

15 I think we have pretty extensively
16 discussed this already, that the primary and second
17 endpoint outcome measures need to be different from
18 what has been defined here. Looking for embolic
19 events in more sensitive manner would probably be
20 an appropriate outcome.

21 Clinical versus surrogate endpoints. I
22 think we need the clinical events. I don't know
23 how to suggest an appropriate surrogate.

24 DR. ZUCKERMAN: Is there agreement from
25 the neurologists on the panel about Dr. Carabello's

1 last point that the CT scan could be used as a
2 surrogate for neurological events?

3 DR. BECKER: I would increase sensitivity
4 and use an MRI instead as a surrogate. So, if you
5 see new infarcts, then that is a surrogate.

6 DR. LAZAR: There are, at present, no
7 surrogate endpoints for stroke. Period.

8 DR. MARLER: I think you would be getting
9 into a lot of difficulty there because of the
10 short-lived nature of many of the lesions. Most
11 patients who have had stroke have a normal CT
12 scan--many of them have a normal CT scan at three
13 months. So it becomes a question of timing.

14 You would also need pre-scans because,
15 even in a normal population, 20 percent of
16 asymptomatic people with high risk factors will
17 have a stroke even though they have no recollection
18 of the event. So I would be very cautious about
19 building in imaging surrogates.

20 It has been attempted multiple times in
21 stroke. For a small device trial, I think it would
22 be an immense undertaking.

23 DR. BAILEY: Could I make a quick comment,
24 too, on the search for a high-risk population. I
25 like the idea of some of the things, like the

1 hypercoagulable state and the DBTs. But when you
2 get to the anatomy, if you are going to require the
3 aneurysm, if the purpose is to generalize it to
4 people with just a garden-variety PFO, I am nervous
5 about that.

6 DR. TRACY: Okay. Fair enough. I think
7 there is other, perhaps, anatomic variance that
8 might be considered to be of higher risk rather
9 than just aneurysm.

10 Dr. Zuckerman, do you have a comment?

11 DR. ZUCKERMAN: Yes. I don't think the
12 purpose would be to generalize it to the whole PFO
13 universe. Unless the sponsor wants that
14 indication, that would be a different type of
15 trial.

16 DR. ZIVIN: Right. I am assuming that the
17 recommendation to make the inclusion criteria
18 relate to any future indication would be--

19 DR. ZUCKERMAN: That is the usual way that
20 we try to write the indicated label; correct.

21 DR. LASKEY: Am I missing something? Is
22 there some body of data where we can look at the
23 high-risk features or which features confer high
24 risk in patients with PFO? Is there some
25 multivariate analysis that we haven't discussed

1 today?

2 DR. ZIVIN: The Mas paper.

3 DR. LASKEY: I am looking at the Mas
4 paper. There are six events in the septal aneurysm
5 PFO group. I am not sure I want to rely on six
6 events and say that we now have a characterization
7 of the risk profile of patients with PFO.

8 DR. ZIVIN: I would agree that a larger
9 study would be valuable. I certainly would go
10 along with that.

11 DR. TRACY: I think that point was that
12 there probably is a higher risk group than was
13 included here.

14 DR. LASKEY: Which we have not defined.

15 DR. TRACY: Not entirely.

16 DR. LASKEY: Nobody has.

17 DR. TRACY: Nobody has. That is part of
18 the problem.

19 We will move on to: Please discuss the
20 appropriate duration of patient follow up. I think
21 that that is extraordinarily difficult to answer a
22 question like that since events are likely to
23 happen particularly related to device malfunction
24 in multiple years out. I don't think it would be
25 appropriate to require that primary follow up that

1 long, but, certainly, that is the type of issue
2 that can be monitored in a postmarket survival
3 study and that is the type of issue that could be
4 looked for.

5 So I think a duration of two years is
6 probably appropriate.

7 DR. PINA: However, I do think they have a
8 lot of information even though the older two
9 studies are with a different device. I think that,
10 with the great detail that they have gone through
11 to look for adverse events, they will know if
12 events happen early, which may be a reduction in
13 events because of the device, or do events happen
14 later because there is thrombus formation in the
15 device and because of the device.

16 So I think that they can take their body
17 of data and look and see where the duration of
18 follow up would be reasonable.

19 DR. TRACY: Yes; I think that is true. If
20 I am recalling the one graph, there was the late
21 dip that was related to a device, a late device
22 problem. That, I think, is postmarket
23 surveillance, not acute endpoints.

24 DR. ZUCKERMAN: Okay. But, in this study
25 discussed today, the primary efficacy endpoint was

1 measured at six months. Is there any comment on
2 that being too short a time period?

3 DR. TRACY: I would suspect that that
4 probably is too short a time. If you change your
5 outcome definition to stroke, then six months
6 probably is too short.

7 Please comment on what would be a
8 clinically relevant sample size. I think the only
9 thing I can say in terms of what would be an
10 appropriate sample size would be to set the study
11 up so that you have a comparison within it, you
12 will require less than you would otherwise. But I
13 am not sure--I don't know what the event rate is,
14 so maybe somebody who has a better sense of that--

15 DR. BAILEY: The two issues are the event
16 rate and the percent reduction. I think, the event
17 rate, you can try to get up high. The percent
18 reduction becomes a question of what justifies the
19 use of the procedure. How small a difference is it
20 important to detect?

21 DR. ZIVIN: Another way of thinking of
22 that is what we have presented to us is a Phase I
23 trial. What is needed is a Phase II. That hasn't
24 been done yet.

25 DR. BAILEY: Is 30 percent the minimum?

1 Or is it 20, or 10? If this procedure changes your
2 risk by 1 percent, would that be enough?

3 DR. ZIVIN: But we don't know the
4 variability rate, so, until we get there, you are
5 just picking numbers out of the air. We need some
6 data. We don't have enough.

7 DR. TRACY: Yes; we don't have enough even
8 on what the event rate is in the control--

9 DR. MARLER: I would say, for a preventive
10 therapy like this that is going to extend over
11 decades, particularly in younger patients, that the
12 benefit you have to expect has to be in proportion
13 to the risk. To a certain extent, that has been
14 defined, which leads me to believe that you are
15 going to be looking for not a relatively high
16 reduction in the event rate to justify the
17 difference.

18 There is a lot of difference between doing
19 this and taking aspirin in terms of perceived risk,
20 at least to the patient.

21 DR. TRACY: I think, in part, that leads
22 into the next question: Please discuss the criteria
23 for a successful trial. I think that means a trial
24 in which it is demonstrated that the intervention
25 results in decreased events compared to best

1 medical therapy as balanced against the acute
2 procedural complications of the intervention.

3 So I think that you can define endpoints
4 that would be reachable with those criteria.

5 Any comments?

6 No. 6: Please comment on whether
7 adjunctive antithrombotic medication regimens
8 should be left to the operator or prospectively
9 outlined in the protocol.

10 I think it is very clear that that needs
11 to be outlined prospectively in the protocol.
12 Otherwise, it makes it impossible to compare
13 things.

14 Training program: A summary of the
15 physician training program has been provided in
16 Section 5 of the panel package. Please discuss any
17 improvements that could be made to the training
18 program.

19 Maybe one of the primary reviewers. Dr.
20 Vetrovec?

21 DR. VETROVEC: I reviewed the training
22 packet. My observations were that it was not very
23 specific, particularly for the least experienced
24 operators. I would have felt much more comfortable
25 with some established proctoring system and some

1 established number of observed cases or participate
2 in. There are a variety of ways they could do it
3 and I haven't personally done this, so I don't have
4 a feel for what the minimum would be.

5 But I would think that, just because an
6 operator has put stents in a coronary artery, this
7 wouldn't qualify them for an experienced company
8 representative showing them in the coffee room how
9 to do this and they go do one.

10 So I think it needs to be defined. I
11 think people who have experience with it need to
12 help define what that would be, but there has to be
13 some specific observational and probably preceptor
14 training for the least experienced operators.

15 DR. PINA: Dr. Tracy, if, indeed, they go
16 on and do a controlled trial of some sort,
17 particularly with randomization, that can certainly
18 be included in the protocol as investigators are
19 brought in. As other trials have done who are
20 doing things like even exercise testing, there is a
21 whole procedure on teaching the investigators how
22 to do it. So I think that the cohort of people
23 that will learn how to do this will grow the more
24 centers they include.

25 DR. TRACY: Is that adequate? Okay. We

1 will move on to product labeling. One aspect of
2 the premarket evaluation of a new product is the
3 review of labeling. The labeling must indicate
4 which patients are appropriate for treatment,
5 identify potential adverse events with the use of
6 the device and explain how the product should be
7 used to maximize the benefits and minimize adverse
8 events. Please address the following questions as
9 regards the product labeling presented in Section
10 2.

11 Please comment on the Indications for Use
12 section as to whether it identifies the appropriate
13 patient population for treatment with this device.

14 I think I am taking a stab here, but I
15 think as it is stated, it is fair to say that the
16 ultimate goal would be to have a device that would
17 reduce the risk of recurrent cryptogenic stroke or
18 transient ischemic attacks due to presumed
19 pyridoxic embolism through PFO.

20 I had a problem with the word "and,"
21 whether it should be "and/or," based on the initial
22 entry criteria for the study, who are poor
23 candidates for surgery or conventional drug
24 therapy. But I think what we are looking at is a
25 treatment that would be appropriate for that type

1 of patient, at high risk for recurrent
2 embolization.

3 I think, having had an initial event is
4 going to have to be critical to what the indication
5 is. Does that seem to be the consensus, that we
6 need to redefine the indication? Okay.

7 Part b: Please comment on the
8 Contraindications section as to whether there are
9 conditions under which the device should not be
10 used because of risk because the risk of use
11 clearly outweighs any possible benefit.

12 I think that the Contraindications that
13 are stated are based on appropriate criteria. If
14 there is a thrombus or active endocarditis, that is
15 obviously going to be a contraindication. Vascular
16 problems is obviously a contraindication. Patient
17 size that wouldn't permit deployment of the device
18 would be an appropriate contraindication.

19 Patients who are unable to take aspirin,
20 Coumadin or other anticoagulants, that will get in
21 the way of designing a trial of you are going to
22 compare with best medical therapy, so I am not sure
23 what to do with that particular contraindication.
24 But that may, ultimately, be appropriate and,
25 obviously, a patient with endocardiac mass or

1 vegetation would be an appropriate
2 contraindication.

3 I can't think of other contraindications
4 unless Dr. Aziz--

5 DR. AZIZ: If you had an IVC, let's say
6 umbrella or filter, would that be a
7 contraindication? I don't know.

8 DR. WHITE: It depends on the filter a
9 little bit but, for the Greenfield filter, for
10 example, access from below is usually not a
11 problem. Dr. Landzberg is telling us that he has
12 done them also from the jugular access so I think
13 that would be reasonable.

14 DR. AZIZ: Somebody with a tricuspid
15 valve, for a study valve, you could still do it,
16 couldn't you?

17 DR. MARLER: I guess I wanted to say that
18 I think that the question of what is the least
19 burdensome way to demonstrate the potential
20 effectiveness of this is kind of an unstated
21 question here in all of the discussion about the
22 trial. But I just wanted to say I, personally, am
23 not just as a knee-jerk reflex, saying you need to
24 do a clinical trial.

25 I think there is a real concern here based

1 on the evidence from the WARSS trial and the Mas
2 study that an intervention that has a definite risk
3 associated with its insertion could, in the long
4 run, actually not benefit the patient and could
5 even be harmful.

6 So I think that the clinical trial in this
7 case might be the best way to answer that and I
8 doubt there is a very good way to address that
9 without doing some form of randomized and
10 comparison. So I don't want to committee to assume
11 that, because I deal with clinical trials all the
12 time, I am suggesting it. It would be good to find
13 an alternative way to get an answer in this and, in
14 many situations, you probably don't need a clinical
15 trial.

16 But, in this particular case, I think
17 there are enough doubts that that higher standard
18 to establish some benefit to balance the risk is
19 probably necessary.

20 DR. TRACY: I think we had addressed the
21 contraindications as best we can at this point.

22 Please comment on the Warnings and
23 Precautions section as to whether it adequately
24 describes how the device should be used to maximize
25 benefits and minimize adverse events and, unless

1 somebody else has comments, all I see is, "See
2 Warnings and Precautions and final labeling and
3 information for use." So I don't know what they
4 are. So, no; it doesn't adequately state--unless I
5 am missing a piece of the packet.

6 Anybody else see anything more than I see?

7 No? Okay.

8 Part d: Please comment on operators
9 instructions as to whether it adequately describes
10 how the device should be used to maximize benefit
11 and minimize adverse events.

12 Perhaps one of the interventional type of
13 people could answer whether they think that was
14 appropriately described.

15 DR. WHITE: I think it is appropriately
16 described.

17 DR. TRACY: Any other comments on that
18 one?

19 Part e: Please comment on the remainder of
20 the device labeling as to whether it adequately
21 describes how the device should be used to maximize
22 benefits and minimize adverse events. I think that
23 would be hard to answer until we have a better
24 sense of--until we have different outcomes and
25 different endpoints to be looking at. I think we

1 can't really answer that question.

2 So we will move on to the next part,
3 postmarket evaluation. The panel package includes
4 the available data for the STARFlex device in the
5 pivotal cohort. In addition, data were provided
6 from the Clamshell and includes some follow up for
7 out to ten years. Please discuss long-term adverse
8 effects that may be associated with device
9 implantation including late thrombosis formation,
10 the risk of endocarditis, problems with late
11 operation and arrhythmias.

12 Question 7: Based on the clinical data
13 provided in the panel package, do you believe that
14 additional follow-up data or postmarket studies are
15 necessary to evaluate the chronic effects of the
16 implantation of the STARFlex device. If so, how
17 long should patients be followed and what endpoints
18 and adverse events should be measured?

19 I think we don't have long-term follow up
20 on the STARFlex. We have long-term follow up on
21 the predecessor of the STARFlex. We don't know
22 what the long-term fracture will be. I think we
23 need to follow those patients in postmarket
24 surveillance for roughly the equivalent time period
25 as the Clamshell patients have been followed.

1 So I think that all of those mechanical
2 malfunctions and risk of endocarditis, et cetera,
3 should be followed for an extended period of time,
4 something equivalent to what is now available with
5 the Clamshell studies.

6 DR. ZUCKERMAN: Are there any additional
7 comments on what imaging modalities should be used
8 and what other adverse events or clinical scenarios
9 should be looked for?

10 DR. LASKEY: To get at the wire-fracture
11 beast, you would need plane radiography, I would
12 think. I don't think echo is going to do that so,
13 since we still are concerned about wire fractures
14 and their long-term natural history, I think plane
15 chest radiography might work.

16 DR. TRACY: Other comments from the panel
17 members? I believe that was all of
18 the questions that were addressed to the panel from
19 the FDA. At this point, we will briefly go to
20 another open public hearing.

21 **Open Public Hearing**

22 DR. TRACY: If there is any member of the
23 audience that would like to express an opinion at
24 this time, please come forward and identify
25 yourself at this time.

1 If not, we will close the open public
2 hearing.

3 Open Committee Discussion

4 DR. TRACY: I will, at this time, ask the
5 FDA if they have any additional comments or
6 questions before we take our vote.

7 DR. ZUCKERMAN: No; the agency doesn't.

8 DR. TRACY: I would like to ask the
9 sponsor if they have any additional comments or
10 questions at this time.

11 DR. JENKINS: No; we don't.

12 DR. TRACY: I will ask the industry
13 representative if he has any questions or comments.

14 MR. MORTON: No; no comments. Thank you.

15 DR. TRACY: Mr. Dacey? Any questions or
16 comments?

17 MR. DACEY: The only comment I had was on
18 the information for the patient and families. It
19 really assumed much too high a level of patient
20 literacy. When I first looked at it, I felt like I
21 was almost reading a JAMA article. So I would
22 strongly suggest, when the time comes to prepare
23 information for patients and families, that there
24 is a wealth of resources out there on what works
25 and doesn't work.

1 It isn't enough anymore just to keep at at
2 the fifth-grade level. It is a combination of
3 words and pictures and how they are ordered and so
4 forth. So, when the time comes for people who have
5 to confront this issue, they have information that
6 they can capture to the widest possible audience.

7 We know we can't capture everybody but we
8 would let's capture as many people as we can. I
9 guess that is all I have to say at this point.

10 DR. TRACY: Thank you.

11 **Recommendations and Voting**

12 DR. HARVEY: I would like to read into the
13 record the voting options for the panel. The panel
14 recommendation options for premarket approval
15 applications: the Medical Device Amendments to the
16 Federal Food, Drug and Cosmetic Act, the Act, as
17 amended by the Safe Medical Devices Act of 1990,
18 allows this Food and Drug Administration to obtain
19 a recommendation from an expert advisory panel on
20 designated medical device premarket approval
21 applications, or PMAs, that are filed with the
22 agency.

23 The PMA must stand on its own merits and
24 your recommendation must be supported by safety and
25 effectiveness in the application or by applicable

1 publicly available information.

2 Safety is defined in the Act as reasonable
3 assurance based on valid scientific evidence that
4 the probable benefits to health, under conditions
5 on intended use, outweigh any probable risks.

6 Effectiveness is defined as reasonable
7 assurance that, in a significant portion of the
8 population, the use of the device for its intended
9 uses and conditions of use, when labeled, will
10 provide clinically significant results.

11 Your recommendation options for the vote
12 are as follows: number one, approval, if there are
13 no conditions attached; number two, approvable with
14 conditions. That panel may recommend that the PMA
15 be found approvable subject to specified conditions
16 such as physician or patient education, labeling
17 changes or a further analysis of existing data.
18 Prior to voting, all of the conditions should be
19 discussed by the panel.

20 Number 3, not approvable. The panel may
21 recommend that the PMA is not approvable if the
22 data do not provide a reasonable assurance that the
23 device is safe or if a reasonable assurance has not
24 been given that the device is effective under the
25 conditions of use prescribed, recommended or

1 suggested in the proposed labeling.

2 Following the voting, the chair will ask
3 each panel member to present a brief statement
4 outlining the reasons for their vote.

5 DR. TRACY: At this time, I will ask for a
6 motion. Dr. Vetovec, would you care to make a
7 motion regarding this device?

8 DR. VETROVEC: By motion, do you mean that
9 we vote or that we take a stand, what the stand
10 should be?

11 DR. TRACY: I'm sorry.

12 DR. VETROVEC: I don't know what you are
13 asking.

14 DR. TRACY: We need a motion whether the
15 device is approvable, approvable with conditions or
16 not approvable.

17 DR. VETROVEC: I see. I move that it is
18 not approvable.

19 DR. TRACY: Do we have a second on that?

20 DR. COMEROTA: Second.

21 DR. TRACY: Any discussion from the panel?
22 Then, let's take a vote on that. Let's take a hand
23 vote. Those who agree that this is not approvable,
24 please raise your hands.

25 [Show of hands.]

1 DR. HARVEY: The vote is twelve votes for
2 the motion.

3 DR. TRACY: Votes against the motion,
4 which would mean that the device would be
5 approvable, or approvable with conditions?

6 DR. HARVEY: They just voted against that
7 motion.

8 DR. TRACY: Okay.

9 DR. AZIZ: Can I just ask a question, or
10 do I have to make the vote?

11 DR. TRACY: You can ask a question.

12 DR. AZIZ: I was thinking a lot more about
13 this, as obviously the afternoon has gone on. I
14 think that the device has a role to play in
15 patients who are higher risk rather than just
16 high-risk surgery. I am just trying to sort of
17 grapple with the fact that I don't think that it
18 should be used on all PFOs but in this select group
19 of patients in whom surgery really would be a high
20 risk.

21 DR. TRACY: At this point, the vote
22 carries that the device is not approvable and we
23 will ask each member to briefly state their
24 reasoning for their vote.

25 Dr. Carabello?

1 DR. CARABELLO: I believe that the device
2 is safe and I believe it is effective in closing
3 the hole, but I don't believe that that is proof of
4 effectiveness of the device in preventing recurrent
5 strokes.

6 DR. TRACY: Dr. Marler?

7 DR. MARLER: I believe that, in long-term
8 prevention of stroke, safety has to be evaluated in
9 terms of benefit. So I don't think that there is
10 evidence presented that convinces me that it is
11 either safe or that there is evidence to suggest it
12 is effective.

13 DR. TRACY: Dr. Lazar?

14 DR. LAZAR: I agree that the benefits have
15 not been established and more data is needed to be
16 collected with patients whose entry is much more
17 carefully specified so then the indications become
18 clear about how the device should be used in the
19 future.

20 DR. TRACY: Dr. Zivin?

21 DR. ZIVIN: Votes of this type are not
22 about numbers and statistics and epidemiology.
23 They are much more important than that. FDA
24 meetings are fun when I can come and help give the
25 world a new or better form of therapy. They are no

1 pleasure at all when I vote no, and I have only
2 once previously been so unfortunate as to have to
3 do so.

4 We all have, or most of us, have taken the
5 oath of Hippocrates at some or other and that says,
6 amongst other things, to do no harm. Well, we
7 can't believe that because, at a certain level, we
8 must do some harm to some of our patients but it
9 can only be acceptable if it is balanced by some
10 evidence of benefit.

11 Up until this point, the development of
12 this program has shown only harm. Efficacy simply
13 hasn't been tested. If you can find one group of
14 patients that can be helped by this device, I would
15 become a strong advocate of it. Until that
16 happens, I am afraid I have to vote against it.

17 DR. TRACY: Dr. Bailey?

18 DR. BAILEY: I don't have any new reasons.
19 I think they have all been expressed for voting no,
20 and I only hope that this would be a stimulus to
21 developing the data which would enable approval of
22 the device and also, perhaps, answer the scientific
23 question about the role of PFO in stroke.

24 DR. TRACY: Dr. Laskey?

25 DR. LASKEY: I agree with my colleagues

1 here for those reasons and I would just add that it
2 is really very unfortunate that a poorly designed
3 study has gotten this far. I think it has had the
4 expected inevitable outcome.

5 DR. TRACY: Dr. Becker?

6 DR. BECKER: I agree that effectiveness
7 hasn't been shown and I also think that long-term
8 safety has not been shown.

9 DR. TRACY: Dr. Pentecost?

10 DR. PENTECOST: I think the device can be
11 inserted safely. I think it is a pretty slick
12 device. I would think that the measures of
13 effectiveness of this, one would be imaging to
14 prove the hole is closed. That criteria wasn't met
15 for reasons I still don't understand.

16 Secondly, would be clinical effectiveness
17 and to clinically show that you are effective in
18 reducing neurologic episodes. You would think you
19 would have a neurological exam pre- and post. That
20 is also absent.

21 DR. TRACY: Dr. White?

22 DR. WHITE: I vote no for the reasons
23 already enumerated.

24 DR. TRACY: Dr. Vetovec.

25 DR. VETOVEC: I vote no for the reasons

1 stated. I would add that it seems to me that this
2 issue, as I raised earlier, is partly a problem of
3 completeness of data and using standardized
4 criteria for entry and criteria for follow up.
5 That certainly would help in any circumstance in
6 which there is already a lot of confusion.

7 DR. TRACY: Dr. Pina?

8 DR. PINA: I vote no for all the reasons
9 that my colleagues here have said, but I urge the
10 company to take a look at what they have done so
11 far, to learn from their data and to use it to
12 define and design a real trial.

13 DR. TRACY: Dr. Comerato?

14 DR. COMEROTA: I voted no because we have
15 been given a dataset that conflicts with the
16 manufacturer's intention. This does appear to be
17 slick device that will close a PFO but we have had
18 49 patients presented with a medial follow up of
19 6.5 months, 18 percent adverse events in 14 percent
20 of the patients and 27 percent had identified
21 complications.

22 Then we are given a life table probability
23 of freedom from fracture of the device of about 5
24 percent freedom from fracture at about 20 months,
25 which concerns me, especially in very young

1 patients who have many years to live.

2 I think this device will be helpful in
3 patients in the future but it is incumbent upon all
4 of us to identify who those patients are.

5 DR. TRACY: Dr. Aziz?

6 DR. AZIZ: I think I agree, obviously,
7 with a lot of the things that have been said on the
8 panel and I think the study has a lot of
9 deficiencies. My only interest was in the small
10 select patients, group of patients, who are
11 referred to surgeons who have had a PFO
12 demonstrated. It is really a compassionate sort of
13 a feeling and I think that all the deficiencies
14 clearly do exist.

15 I just hope that it would be available on
16 a compassionate basis for that group of higher-risk
17 or high-risk patients.

18 DR. TRACY: Mr. Morton, any comments at
19 this point?

20 Mr. morton: No.

21 DR. TRACY: That concludes this portion of
22 the meeting. We do have another piece of business
23 that wasn't covered yesterday, OSP presentation on
24 the pulmonary-artery rupture following
25 pulmonary-artery catheterization, gender effects.

1 I will ask--I guess it is Dr. Kaczmarek
2 that will be presenting this portion of the
3 meeting.

4 DR. TRACY: For the panel, this is new
5 business that was scheduled to be covered
6 yesterday. If you can remain, that would be very
7 helpful.

8 OSB Presentation

9 Pulmonary-Artery Rupture

10 Following Pulmonary-Artery Catheterization:

11 Gender Effects

12 DR. KACZMAREK: Good afternoon.

13 [Slide.]

14 My presentation is pulmonary-artery
15 rupture following pulmonary-artery catheterization:
16 gender effects. My coauthors are Jenny Liu and Dr.
17 Thomas Gross of the Office of Surveillance and
18 Biometrics.

19 [Slide.]

20 Pulmonary-artery rupture is a recognized
21 rare, but often fatal, complication of
22 pulmonary-artery catheterization. Case reports and
23 case series have described this complication. The
24 primary limitation of the available data is that
25 the cases are generally obtained from a solitary

1 institution. Consequently, the number of cases of
2 pulmonary-artery rupture included is very limited.

3 [Slide.]

4 The purpose of the current study is to
5 improve the understanding of pulmonary-artery
6 rupture following pulmonary-artery catheterization
7 by examining two national databases. First, the
8 FDA's Medical Device Reporting System and,
9 secondly, the Agency for Healthcare Research and
10 Qualities nationwide inpatient sample. Data are
11 obtained from hundreds of hospitals from across the
12 nation in these data-collection systems.

13 [Slide.]

14 Reports were reviewed of
15 medical-device-related adverse events and product
16 problems submitted to FDA's MDR system. This
17 nationwide passive surveillance system received
18 reports from user facilities, manufacturers,
19 healthcare professionals, and the general public.
20 Each year, the FDA receives approximately 90,000
21 reports, 3 percent of which are voluntary.

22 [Slide.]

23 The MAUDE database was examined using the
24 following criteria. Reports coded with
25 flow-directed or pulmonary-artery catheter that

1 were received between January 1 of 1991 and January
2 1 of 2001. A total of 889 reports representing 853
3 adverse events including 55 deaths, 147 injuries
4 and 651 malfunctions were identified and
5 individually reviewed.

6 A total of 71 pulmonary-artery rupture
7 cases were identified from these reports.
8 Pulmonary-artery rupture events were captured using
9 at least one of three inclusion criteria based on
10 the report text: first, hemoptysis, or blood, noted
11 in the endotracheal tube after catheter placement
12 or balloon inflation; secondly, pulmonary-artery
13 rupture in the event description of the report;
14 finally, and most definitively, pulmonary-artery
15 rupture in the autopsy result.

16 [Slide.]

17 The review of the adverse-event reports
18 revealed that a total of 55 deaths were associated
19 with pulmonary-rupture catheter use. These
20 ruptures were associated with 47 deaths and 24
21 injuries accounting for 85 percent of all
22 catheter-related deaths. The remaining 15 percent
23 of the deaths were related to air embolism, 4
24 percent; cardiac tamponade, 2 percent; pleural
25 cavity perforation, 2 percent; and unknown causes,

1 7 percent.

2 [Slide.]

3 Of the 71 pulmonary-artery rupture cases,
4 52 were in women resulting in 39 deaths and 13
5 injuries. Ten of the cases were in men, causing
6 six deaths and four injuries, and nine were gender
7 unreported, two deaths and seven injuries.

8 Overall, women comprised 87 percent of the reported
9 deaths, 39 of 45, among the subset of reports of
10 known gender.

11 [Slide.]

12 Sixty of the pulmonary-artery rupture case
13 reports noted age with a range between 40 in 91
14 years and a mean of 74 years. Elderly females
15 accounting for the majority of reports where age
16 and gender were noted. More cases were noted among
17 women than men in every age group.

18 [Slide.]

19 The nationwide inpatient sample is a
20 massive nationally representative database that is
21 maintained by the Agency for Healthcare Research
22 and Quality. Data are obtained from over 800
23 hospitals from across the nation in this
24 data-collection system. Information is obtained
25 from over 6 million patient discharge summaries.

1 This database was analyzed to obtain nationally
2 representative estimates of the respective
3 proportions of pulmonary rupture catheterizations
4 by gender.

5 [Slide.]

6 Analysis of the 1996 nationwide inpatient
7 sample, with 1996 being the approximate midpoint of
8 the time frame of the study, revealed that the
9 majority of pulmonary rupture catheterizations were
10 actually performed in May. 58 percent were
11 performed in males and only 42 percent were
12 performed in females.

13 [Slide.]

14 This slide examines the age-specific
15 incidence of pulmonary rupture catheterization in
16 the 1996 nationwide inpatient sample. Pulmonary
17 rupture catheterization was performed in a diverse
18 patient population extending from the pediatric
19 population to individuals over 100 years of age.
20 Most importantly, more pulmonary rupture
21 catheterizations were performed in men than women
22 in every age group up to 85 years of age.

23 [Slide.]

24 This is the take-home message from this
25 morning's presentation. There were significantly

1 more cases in women than expected and significantly
2 fewer cases in men than expected. The
3 Mantel-Haenszel common odds-ratio estimate was 5.84
4 with a 95 percent confidence interval ranging from
5 2.97 to 11.46 with a p-value well less than 0.001.

6 [Slide.]

7 Our data highlight the importance of
8 female gender as a risk factor for pulmonary-artery
9 rupture, the data from the nationwide inpatient
10 sample demonstrating that the majority of pulmonary
11 rupture catheterizations occur in male patients
12 argues strongly against the contention that a
13 greater use of pulmonary rupture catheterization
14 among women is responsible for the observed
15 preponderance of case reports occurring among
16 women.

17 Other reports have indicated that females
18 may be at greater risk as well. For example, a
19 case series reported by Mullerworth, et al., noted
20 that all seven of his patients were female.
21 Pulmonary-artery rupture is often fatal. The most
22 likely outcome for the patients in our case-series
23 analysis was death. Mortality following
24 pulmonary-artery rupture in other case series have
25 been very high as well.

1 For example, Kelly, et al., noted that
2 eight of fifteen, or 53 percent, of his reported
3 cases were fatal. The survival that does occur is
4 greatly assisted by the setting of pulmonary
5 rupture catheterization. Essential personnel are
6 immediately available to perform invasive
7 lifesaving emergency procedures.

8 Now, a discussion of the optimum
9 therapeutic measures in response to such rupture is
10 beyond the scope of this afternoon's presentation.
11 However, the authors would submit that the
12 importance of a high index of clinical suspicion
13 for this complication is utterly crucial. The
14 rarity of the complication may result in a given
15 practitioner or even a given healthcare facility
16 not experiencing the complication for extended
17 periods.

18 The failure to experience the complication
19 does not preclude its future recurrence. Patient
20 survival following its occurrence may well depend
21 on rapid recognition and therapy that will be
22 facilitated by a high index of clinical suspicion.

23 [Slide.]

24 A review of the labeling for pulmonary
25 rupture catheters revealed that the risk of

1 pulmonary rupture was noted in the labeling.

2 Gender effects were not addressed.

3 [Slide.]

4 I would like to briefly discuss some of
5 the limitations of the MDR reporting system.
6 First, underreporting is common in passive
7 surveillance systems such as the MDR system. There
8 are several reasons for underreporting including a
9 lack of awareness of the reporting requirement, a
10 reluctance to report complications that had been
11 previously reported in the published literature
12 and, most importantly, medical-legal
13 considerations.

14 Other limitations of the system are the
15 lack of independent verification of the data,
16 missing information and an absence of denominator
17 data--that is, the quantification of device use.

18 [Slide.]

19 Further study of the effect of gender on
20 the risk of pulmonary-artery rupture following
21 pulmonary rupture catheterization is warranted.
22 Such study may pose substantial challenges.
23 Case-control studies can efficiently study the
24 relationship between a potential risk factor and a
25 relatively rare outcome such as pulmonary rupture.

1 Unfortunately, a repository or registry of
2 pulmonary-artery rupture cases is not currently
3 available to provide the cases for study.

4 A cohort study may be relatively costly
5 because the rarity of the complication would
6 require a very large sample size. The challenges
7 posed by more formalized study underscore the
8 importance of case reports. The FDA strongly
9 encourages practitioners and facilities to report
10 such cases.

11 In conclusion, pulmonary-artery rupture is
12 a rare but often fatal when it occurs complication
13 of pulmonary rupture catheterization. The case
14 reports received by the FDA indicate that
15 pulmonary-artery rupture following pulmonary
16 rupture catheterization is a complication worthy of
17 our attention. Clinicians must be aware of the
18 potential for this complication, particularly among
19 female and elderly patients.

20 Thank you.

21 DR. TRACY: Thank you.

22 Any questions from the panel to Dr.
23 Kaczmarek?

24 DR. VETROVEC: Have you got any data on
25 body surface area of the women versus the men or

1 anything else about size that might be helpful out
2 of this data?

3 DR. KACZMAREK: Unfortunately, no. As was
4 indicated earlier, there is a lot of information
5 that, unfortunately, is not reported in case
6 reports. People report what they want to report to
7 the agency. I think, in the context of more
8 formalized study, your suggestions are excellent.

9 DR. TRACY: Dr. Pina?

10 DR. PINA: I have always sensed that the
11 duration of the inflation of the balloon and how
12 far advanced it is-- and Blase is our hemodynamic
13 guru here; he can probably attest to this--will be
14 related to rupture. You do have a trial ongoing.
15 It is called ESCAPE and ESCAPE is an NIH trial
16 randomizing heart-failure patients who are coming
17 in pretty sick to either getting a Swann or not
18 getting a Swann. It would be an ideal place to
19 gather more information because a third of those
20 patients will be women by NIH standards.

21 We will have body size and we will have
22 hemodynamics and we will have everything. That has
23 not been my experience but I would love to hear
24 what Blase says.

25 DR. CARABELLO: We always recommend that

1 the catheter be positioned such that the balloon
2 wedges only when it is fully inflated so that it
3 inflates in the most proximal and presumably
4 strongest part of the pulmonary artery.

5 In women, then, you would guess that,
6 since they are smaller, the balloon would actually
7 plug the--would cause occlusion in the more
8 proximal part of the artery which ought to be
9 better, not worse.

10 So it must have something to do with the
11 fact, though, that one size doesn't fit all and
12 that what winds up--it may be that, therefore, the
13 lack of perfect attention to how this thing is used
14 results in overwedging more frequently in women in
15 a more distal part of the tree where rupture is
16 more likely. That is what I would guess.

17 DR. AZIZ: Do you have any data on the
18 pulmonary pressures in these people?

19 DR. KACZMAREK: Unfortunately, no. But I
20 would like to extend the comments that were made
21 previously, that, if it is correct that the female
22 risk is substantially greater than the male risk,
23 the measures that were suggested just now to reduce
24 the female risk down to the male risk level would
25 substantially reduce the number of pulmonary-artery

1 ruptures.

2 DR. AZIZ: The other thing; do you have
3 any data on how many of these patients were
4 cardiac-surgery patients, and I will tell you why I
5 ask you that question.

6 DR. KACZMAREK: Again, unfortunately, no.
7 The data that we receive under the case-report
8 system is not anywhere near as inclusive as a
9 formalized study, most unfortunately.

10 DR. AZIZ: An actually recognized
11 complication, at least in cardiac-surgery cases,
12 patients who used to be cooled a lot, the
13 anesthesia folks would put their pulmonary rupture
14 catheter in, the patient would be cooled, the
15 catheter tips become stiff. A lot of the time, in
16 manipulating the heart, and this is not an inflated
17 catheter--I, unfortunately, have seen a few, about
18 two or three of these cases and unfortunately all
19 you know is that blood comes out of the ET tube.

20 If you don't recognize it, if you don't
21 think about it--again, it is has got to be dealt
22 with. It would be nice to find out if a number of
23 these patients were women. Again, these are
24 catheters that are really not dilated but the
25 effect of hypothermia.

1 Then, also, patients postoperatively, in
2 the ICU, I think, again, mine, obviously is related
3 to the cardiac-surgery experience, it is
4 important--it is important, particularly a lot of
5 these guys are still sort of anticoagulated or not
6 completely reversed. Again, when people are
7 dilated, a lot of the time, you really don't need
8 the wedge pressure, the PAD. Unless there is
9 pulmonary hypertension, it is sufficient.

10 I have seen, again, two or three patients
11 where inadvertently--or I wouldn't say
12 inadvertently, but I think just the thing that was
13 done, where the patients again were anticoagulated
14 or coagulable. And, again, they bled. Then the
15 management--you could have a whole hour's
16 discussion on that but it doesn't have to be fatal
17 if it is appropriately recognized. You have got to
18 have targeted therapy.

19 DR. KACZMAREK: Right. Let me extend that
20 comment as well. In fact, within the context of
21 our case series, there were 71 cases and 47 deaths.
22 Another goal is for us to present and publish these
23 data in the hopes of increasing the awareness of
24 clinicians to decrease that mortality rate, as you
25 observed.

1 DR. PINA: Dr. Aziz, I disagree with you
2 that you don't need the wedge after surgery since
3 most of the patients that you guys are getting now
4 are patients with sick ventricles where the wedge
5 does not correlate with the PAD.

6 DR. AZIZ: We can talk about that.

7 DR. BAILEY: Crudely, it looked as if,
8 although there is an obvious sex effect, that, in
9 women, there wasn't any age effect; that is, the
10 risk went up with just the number of procedures; is
11 that right?

12 DR. KACZMAREK: No. It was really
13 concentrated in more elderly women.

14 DR. BAILEY: But I mean that more elderly
15 women got the use of it.

16 DR. KACZMAREK: That's true as well; yes.

17 DR. BAILEY: So my question is did you
18 look at whether it was any less in younger women as
19 a proportion of the number of procedures?

20 DR. KACZMAREK: Yes; I believe that the
21 rate was lower among younger women. The proportion
22 was relatively higher among more elderly women.

23 DR. LASKEY: This hazard of Swann-Ganz
24 catheterization has been kicking around for several
25 decades. The usual argument is that sick people

1 wind up getting these procedures. So you really
2 need to factor that into what you apparently can't,
3 your measure of association.

4 Now, it is unlikely that your unadjusted
5 or raw rates are going to be totally adjusted away
6 by confounding features, but I don't see how you
7 are going to get around that issue for publication,
8 that are there different reasons why women are
9 getting these procedures than men. It remains true
10 that women in the hospital tend to have more
11 comorbidities, specifically heart failure, than men
12 for cardiovascular rubrics, anyway. All these are
13 risk factors. I don't know how you are going to
14 get by with just the raw measure of association,
15 striking as it is. It may be completely explained
16 by confounding variables.

17 DR. KACZMAREK: Let me agree with that,
18 that we can't adjust for comorbidities. But what
19 we are attempting to do with the case-report data
20 is to build the case to go forward and do more
21 definitive study where those variables could be
22 addressed, recognizing that it may require
23 considerable resources to do so.

24 But we are getting a signal from the MDR
25 system that really it is worthwhile.

1 DR. LASKEY: The first thing that came to
2 my mind, before you got to the data, was that women
3 tend to have more mitral-valve disease than men and
4 that lead to pulmonary hypertension. That is a
5 setup for this event, that it is more likely to
6 occur, at least by tenfold, in people with
7 pulmonary hypertension than normal pulmonary-artery
8 pressure.

9 There is so much noise in here that you
10 probably do need to dig deeper.

11 DR. KACZMAREK: We would agree entirely.
12 We recognize that we are dealing with case-report
13 data.

14 DR. TRACY: Dr. Marler?

15 DR. MARLER: I was going to suggest that I
16 would find your data more convincing if you looked
17 at comparable procedures and didn't find this
18 difference or even at the whole database as a
19 whole, how many of the complaints, at least as a
20 base for me to begin to compare the effect you see.

21 DR. KACZMAREK: Right. I think what you
22 are suggesting is could gender be related to
23 underreporting and that explain the findings.

24 DR. MARLER: I am suggesting that, if you
25 made it clear that that were not true, it would be

1 more convincing.

2 DR. PINA: This is the kind of thing that
3 committees of the American Heart and committees of
4 the ACC that have to do with invasive procedures
5 and hemodynamic monitoring would love to see
6 because there should be some guidelines--I mean, we
7 have our own guidelines in our hospital but that is
8 because it is set up by us directly.

9 But there should be some guidelines in
10 hospitals for how to measure the wedge and how long
11 to leave the balloon inflated and what do you
12 measure and what kind of curve should it look like
13 when you pull the balloon back. Do you have a PA
14 tracing again and how often do you do it and how
15 much air.

16 All that should be part of it, so that is
17 something that I think that, if you can communicate
18 that to the American Heart or to the ACC, these are
19 the folks that can actually implement it into some
20 kind of a statement or some kind of procedure
21 statement. I have seen this done with other
22 procedures. That is the right venue because that
23 is where the practitioners will actually look at
24 it.

25 DR. ZUCKERMAN: Can you give us an idea of

1 what the sample size is going to be of the ESCAPE
2 trial to see if it is going to be reasonable--

3 DR. PINA: The ESCAPE trial right now has
4 about 360 patients enrolled. We are aiming for
5 more than 500. So we are talking about a pretty
6 sizable group where half will have a Swann and half
7 will not. It is a very sick population because it
8 means they are coming into the hospital because of
9 their heart failure, not sick enough that you have
10 to have a Swann in but sick enough that you are
11 bringing them in and you have reached what we call
12 equipoise so that you can say, "I can manage this
13 patient with a Swann or I can manage them without."

14 As I said, 33 percent of them will be
15 women. Lynn Stevenson is the PI up at the Brigham.
16 I think she would be very interested in hearing
17 these data. I think they are very interesting and
18 almost very alarming in a way. It would be nice to
19 kind of keep track of that in our trial.

20 DR. TRACY: Dr. White.

21 DR. WHITE: I missed it. Did you tell us
22 what duration you collected this data over?

23 DR. KACZMAREK: Over a ten-year span.

24 DR. WHITE: So, in ten years, you had how
25 many deaths?

1 DR. KACZMAREK: There were 47 deaths
2 reported to the agency in 71 cases of
3 pulmonary-artery rupture that were reported to the
4 agency. Again, we have strong reason to believe
5 that, within the context of this reporting system
6 and other passive reporting systems, substantial
7 underreporting does occur.

8 DR. WHITE: I know of a couple.

9 MR. MORTON: It is actually comprehensive
10 of the MAUDE database; is that not right?

11 DR. KACZMAREK: That is correct.

12 MR. MORTON: It is not an arbitrary
13 ten-year window. It is comprehensive.

14 DR. KACZMAREK: Right.

15 DR. TRACY: Any other comments from the
16 panel?

17 DR. VETROVEC: What do you plan to do with
18 this?

19 DR. KACZMAREK: We plan to submit this
20 data for publication. I think it may become a
21 piece of the puzzle on how people treat
22 pulmonary-artery catheters. It is not an answer,
23 in itself, but it may be a useful puzzle piece and
24 it may stimulate further research in the area to
25 address the issues that were brought up earlier

1 that really can only be addressed by more
2 formalized trial.

3 This may provide the basis to go out and
4 do those studies.

5 DR. PINA: But you have got to be careful
6 because the one JAMA paper of about four or five
7 years ago that talked about the risks of Swanns
8 turned everybody against having hemodynamic
9 catheters even in people who needed it, and this
10 may be the fuel for some centers to say, oh, no; we
11 are not doing that, when, in fact, it is a very
12 important procedure and some patients that we
13 really need to manage have done judiciously.

14 So you have to be very cautious about
15 alarming without having something like in a trial
16 like this.

17 DR. TRACY: Any other comments from the
18 panel?

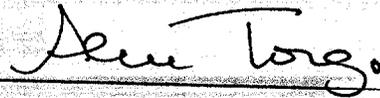
19 I would like to thank everybody for their
20 attention and patience today. We are now
21 adjourned.

22 [Whereupon, at 3:15 p.m., the meeting was
23 adjourned.]

24

CERTIFICATE

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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